A Systematic Review of the Adverse Events of Imatinib Mesylate in the Treatment of Chronic Myeloid Leukaemia

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Summary

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Imatinib mesylate was the first of a generation of tyrosine kinase inhibitors developed for the treatment of cancer. The drug was designed to target the specific molecular abnormality found in the overwhelming majority of patients with chronic myeloid leukaemia. Imatinib was licensed on preliminary clinical data, which showed that it was effective in the treatment of chronic myeloid leukaemia and gastrointestinal stromal tumours, based on surrogate outcome measures.

This study aimed to systematically review the published literature of toxicities related to imatinib mesylate in the treatment of chronic myeloid leukaemia. All literature describing adverse events were sought and assessed on their quality in relation to the question of interest. Two systematic reviews, one randomised controlled trial, 26 uncontrolled clinical trials and 56 case reports/series were included in the study. In addition to the profile of adverse events being presented, the study investigated factors that had the potential to influence the frequency of adverse events, such as the dose of imatinib, the disease stage of the subjects under investigation, the previous treatment history of the patients and the duration of imatinib treatment.

The study found that the most common toxicities observed in clinical trials (controlled and uncontrolled) were gastrointestinal toxicities (nausea, vomiting, diarrhoea), haematologic problems (various cytopenias), musculoskeletal problems such as muscle cramps or musculoskeletal pain, and fluid retention. Case-reports reported dermatological events such as pigment changes and various rashes as the most common toxicities.

The study found that there was no significant influencing factor on the frequency of specific adverse events. A key observation of the thesis was the difficulty in making conclusive findings due to the quality of toxicity reporting by the study authors.

Key words: glivec; tyrosine kinase; drug licensing; evidence-based pharmacotherapy

Dedication

To my mother and father

Acknowledgements

In the name of Allah, the beneficent, the merciful.
Verily, with every difficulty there is relief (Quran 94:5)

I would like to thank all those who helped me throughout the duration of this degree. My heartfelt thanks are extended to my mother and father for always encouraging education, and for their endless sacrifices. Their prayers, emotional and financial support allowed me to achieve my goals. My thanks also go to my dear brothers, Sharjil, Nabil and Sameer for their help, encouragement and their patience.

Thank you to all those at Aston who made this experience worthwhile. To my supervisor Helen in particular, whose professionalism and love of research reminded me of the reason I embarked upon this degree.

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Contents

Abbreviations

***abl*:**	Abelson oncogene
ALL:	acute lymphoblastic leukaemia
AML:	acute myeloblastic leukaemia
Ara-C:	cytosine arabinoside/cytarabine
***arg*:**	abl-related gene
ATM:	ataxia telangiectasia mutated
ATP:	adenosine triphosphate
***bcr*:**	breakpoint cluster region
BMT:	bone marrow transplant
BU:	busulphan
CCR:	complete cytogenetic response
CI:	confidence interval
CLL:	chronic lymphocytic leukaemia
CML:	chronic myeloid leukaemia (also known as chronic myelocytic leukaemia, chronic myelogenous leukaemia)
CR:	cytogenetic response
ECOG:	Eastern Co-operative Oncology Group
EMEA:	The European Agency for the Evaluation of Medicinal Products
ERK:	extracellular signal-regulated kinase
FDA:	Food and Drug Administration (USA)
FISH:	fluorescence *in situ* hybridisation
GAP:	guanosine triphosphatase-activating protein
GEF:	GDP-exchange factor
GIST:	gastrointestinal tumour
Grb-2:	growth factor receptor binding protein
GTPase:	enzyme that binds and hydrolyses GTP (guanosine triphosphate)
GVHD:	graft vs. host disease
HLA:	human leukocyte antigen
HR:	haematological response

HU:	hydroxyurea
IFN-α:	interferon alpha
IRIS:	International Randomised Study of interferon + Ara-C vs. STI571 in CML
ITT:	Intention-to-treat
JAK:	Janus kinase
MAP:	mitogen-activated protein
NCI-CTC:	National Cancer Institute-Common Toxicity Criteria
NICE:	National Institute for Clinical Excellence
PDGF-R:	Platelet-derived growth factor receptor
PEG:	pegylated
PFS:	progression free survival
Ph/Ph1:	Philadelphia chromosome
PKC:	Protein kinase C
QoL:	quality of life
Rac:	Ras-like GTPase
Ras:	protein active in signal transduction mechanisms (name derived from rat sarcoma)
RCT:	randomised controlled trial
Rho:	Ras-like GTPase
SCF:	stem cell factor
SCT:	stem cell transplant
SH:	Src homology domains
Src:	oncogene first found in Rous sarcoma virus which encodes a tyrosine kinase
STATs:	Signal transducers and activators of transcription
STI571:	imatinib mesylate
WBC:	white blood cell

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1.0 Introduction

1.1 Leukaemia

Leukaemias are a group of malignant diseases in which the rate of proliferation of white cells or their precursors is abnormally increased. There are a number of different types of leukaemia which are classified according to their cellular origin and the clinical course of the disease. Leukaemias can either be chronic, in which the disease may progress slowly and continue for a long period, or acute whereby the disease evolves rapidly and exhibits severe symptoms. The disease is also subdivided into either myeloid or lymphatic leukaemia, depending upon the origin of the abnormally proliferating cell. The four major leukaemias are the acute myeloblastic or lymphoblastic leukaemias (AML or ALL) and the chronic myeloid or lymphocytic leukaemias (CML or CLL).

1.2 Epidemiology

Leukaemias represent about 2.5% of all cancers in the UK, with chronic myeloid leukaemia (CML) accounting for about 10% of them, as shown in figure 1.2.1. The incidence of CML affects approximately 1-2 per 100,000 persons per year, with its prevalence relatively consistent in all countries (Brincker, H et al, 1982). The disease is slightly more prevalent amongst males with a male to female ratio of 1.7: 1, and is a rare disease in children, where it does not make up more than 5% of the leukaemias (Castro-Malaspnia, H et al, 1983). The median age at onset is 50-60 years, though CML is seen in all age groups (Lee, S.J et al, 1998).

1.3 Aetiology

The causes of CML remain undetermined although there has been some association between the disease and ionising radiation. This was initially shown in studies following the atomic bomb explosions in the cities of Hiroshima and Nagasaki in 1945, which resulted in the increased incidence of leukaemia thereafter (Heyssel, R et al, 1960; Lange, RD et al, 1954). Evidence of links between therapeutic radiation and CML also emerged some 20 years ago (Moloney, WC et al, 1987). CML does not appear to be an inherited disease; offspring of patients have not shown

to be at a greater risk than the general population, nor is there any correlation in monozygotic twins, suggesting that CML is an acquired disease (Lawler, SD et al, 1977).

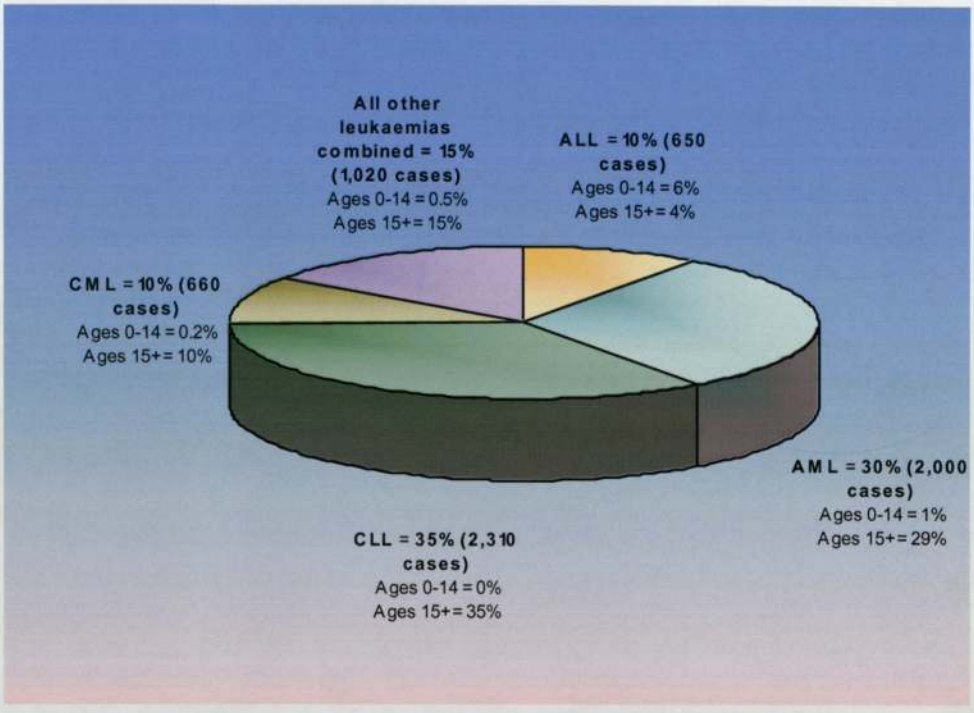

Figure 1.2.1, Numbers and proportions of Leukaemias by type, UK, 1999. ALL – acute lymphoid leukaemia; AML – acute myeloid leukaemia; CLL – chronic lymphoid leukaemia; CML – chronic myeloid leukaemia; all other leukaemias – e.g., hairy cell, prolymphocytic leukaemias etc. Percentages represent proportion of cases out of all leukaemias (*Adapted from Office for National statistics, 2002; Scottish Health Statistics, 2003; Welsh Cancer Intelligence and Surveillance Unit, 2001; Northern Ireland Cancer Registry, 2003)*

1.4 Chronic myeloid leukaemia

Chronic myeloid leukaemia is a haematological cancer affecting the differentiation and proliferation processes of myelocytes. The myeloid lineages in the bone marrow and peripheral blood gradually expand and lose their differentiation capacity, eventually becoming abnormal, immature cells or blasts (Figure 1.4.1). The number of blasts increases as the disease progresses. The result is a reduction of cells of the myeloid lineage (granulocytes, macrophages, platelets, erythrocytes), causing symptoms such as fatigue, bruising or bleeding and an increased susceptibility to infection.

There are usually three phases of CML, the initial chronic phase, the accelerated phase and the blast phase. Some 20% of patients do not experience the accelerated phase and progress directly from the chronic to blast phase (Kantarjian, HM et al, 1993). Progression of the disease typically involves varying levels of clonal evolution, coupled with the increased development and spread of blast cells. Most patients (85%) are diagnosed in the chronic phase of the disease (Faderl, S et al, 1999).

1.4.1 Chronic phase

The chronic phase is a relatively stable phase of CML, which lasts from three to five years (Kantarjian, HM et al, 1988). There are few blast cells in the blood and bone marrow and the malignant progenitor cells retain their ability to differentiate. As the disease progresses, malignant cells begin to lose their differentiation potential.

Chronic phase CML is clinically defined as there being less than 10% blasts and promyelocytes in the peripheral blood and bone marrow by some authors, although others define it as less than 15% blasts or even as stringent as less than 5% blasts (Harris, NL et al, 1999; Kantarjian et al, 2002; Lee, SJ et al 1998). There is an elevated white cell count, together with an elevated platelet count. CML is often described as an indolent disease in its initial stages, which may explain why patients are largely asymptomatic in the chronic phase: about half of all cases are diagnosed by routine blood tests (Faderl, S et al, 1999).

The main clinical observations of a patient in the chronic phase of CML are (Spiers, AS et al, 1977):-

- Fatigue or pale looking due to anaemia
- Splenomegaly or sometimes hepatomegaly
- Pyrexia and night sweats
- Weight loss

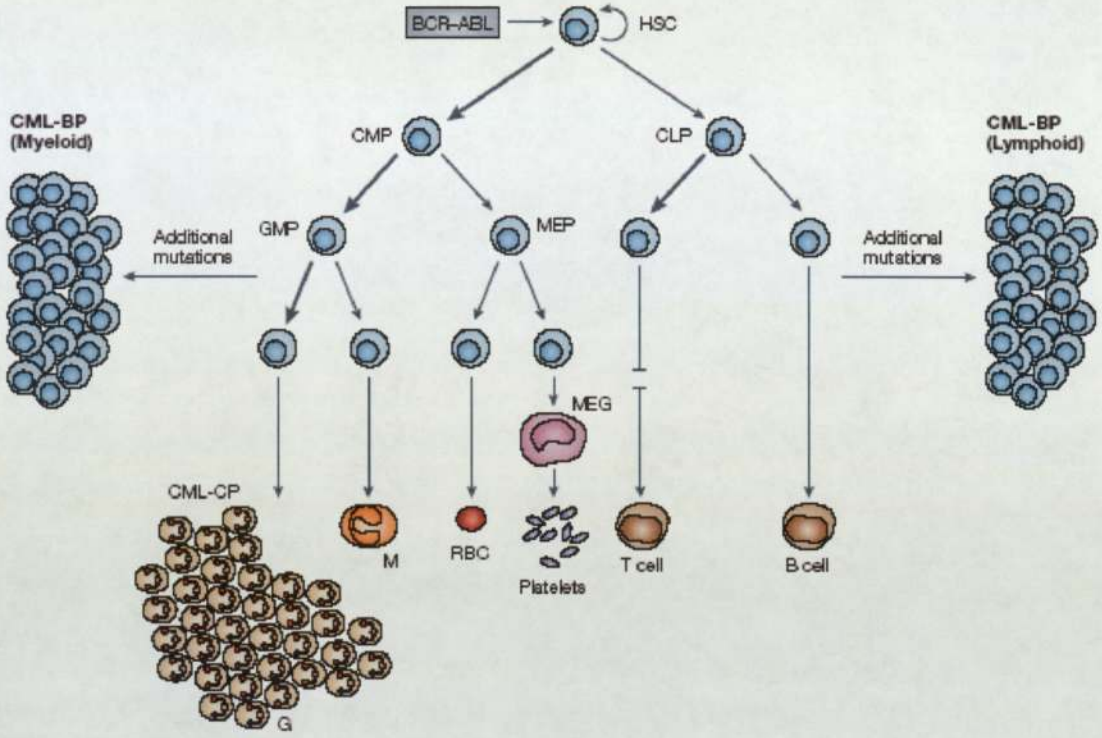

Figure 1.4.1, The development of chronic myelogenous leukaemia. CML is initiated by the presence of the *bcr-abl* fusion gene in self-renewing, haematopoietic stem cells (HSC-s). HSCs can differentiate into common myeloid progenitors (CMP-s), which then give rise to granulocyte/macrophage progenitors (GMPs) and megakaryocyte (MEG)/erythrocyte progenitors (MEPs). HSC-s can also differentiate to CLP-s (common lymphoid progenitors, which develop into lymphocytes such as B and T cells. Acquisition of additional genetic abnormalities is associated with disease progression. Abbreviations; M, macrophages; CML-CP, CML chronic phase; CML-BP, CML blast phase. *(Ren, R 2005)*

1.4.2 Accelerated phase

The definition of the accelerated phase is vague as it is associated with numerous haematologic, cytogenetic and clinical signs and symptoms. It usually lasts from two to 15 months although it generally leads to blast phase within six months.

In some cases, the accelerated phase is clinically defined as greater than 5% blasts in the peripheral blood and marrow but less than 30% in both peripheral blood and bone marrow, although some authors use quite different values (Kantarjian, HM et al, 198815; Sokal, JE et al, 1988; Talpaz, M et al, 2002). Cytogenetic abnormalities, such as trisomy 8 and isochromosome

17, in addition to the Philadelphia chromosome (an abnormally short chromosome 22 arising from the reciprocal translocation of a segment from chromosome 9 found in over 90% of CML patients) also occur, indicating disease progression.

As previously described, 20% of patients do not experience an accelerated phase of CML and progress directly to the blast phase. Patients do not appear to have symptoms specific to the phase and often have the same symptoms as those exhibited in the chronic phase. The accelerated phase is diagnosed by changes in the peripheral blood or bone marrow. Symptoms in the accelerated phase of CML include

- Fatigue due to anemia (reduction of mature erythrocytes)
- Infections (due to reduction of mature granulocytes)
- Bruising or bleeding (due to reduction of mature thrombocytes)
- Progressive splenomegaly

1.4.3 Blast phase

The blast phase is similar to an acute form of leukaemia, and it is usually fatal within three to six months. It is clinically defined as the presence of more than 20% of blast cells in the marrow or the presence of blast cells within the peripheral blood by the World Health Organization, though most authors define the phase as more than 30% blast cells (Harris, NL et al, 1999; Sawyers, CL et al, 2002). The accumulation of multiple characteristic genetic abnormalities (such as trisomy 19 and deletion of chromosome 7) and tumour formation in lymph nodes are also hallmarks of blast phase CML. In a third of blast phase patients, lymphoid structure and lymphoid markers are observed, while two thirds have an acute myeloblastic or an undifferentiated leukaemia-like phenotype (Kantarjian, HM et al, 1987).

The main symptoms observed in the blast phase of CML are:

- Fever, sweats, pain, weight loss
- Hepato-splenomegaly
- Enlarged lymph nodes
- Extramedullary disease (infiltration of blast cells at sites other than the spleen, liver or bone marrow)

1.5 Molecular biology of CML

Over 90% of CML patients have a consistent chromosomal abnormality and it is thought to be related to the pathogenesis of the disease (Nowell, PC et al, 1961; Goh, K et al, 1964). Chromosome 22 is abnormally small and is termed the Philadelphia chromosome (Ph^1) after the city in which it was discovered (Nowell, PC et al, 1960; Hsu, T et al, 1979). It arises from the reciprocal translocation of segments of DNA from chromosome 22 to chromosome 9 – referred to as the t(9:22)-(q34:q11) (Rowley, JD et al, 1973). The result is a chimaeric gene on chromosome 9 which causes an increase in tyrosine kinase activity in haematopoietic cells, and confers a survival advantage over normal haematopoietic cells. The Philadelphia chromosome is also present in around 15-30% of ALL patients, and 2% of patients with newly diagnosed AML (Specchia, G et al, 1995; Kurzrock, R et al, 1988).

In the 1980s, the two genes flanking the translocation breakpoint of the Philadelphia chromosome were identified as the breakpoint cluster region (*BCR*) gene from chromosome 22 and the Abelson (*ABL*) gene from chromosome 9 - the fusion gene was subsequently called the *BCR-ABL* (Bartram, CR et al, 1983; Groffen, J et al, 1984).

1.5.1 The ABL gene

The c-*ABL* gene, normally found on chromosome 9, encodes for a 145-kD protein (Laneuville, P et al, 1995). It is the human homologue of the murine v-*ABL* oncogene (Abelson, HT et al, 1970). The c-Abl protein is a non-receptor tyrosine kinase and possesses a number of diverse functions, ranging from cell cycle regulation and response to genotoxic stress, to integration of signals from intracellular and extracellular sources (Kipreos, ET, et al, 1990; Sawyers, CL et al, 1994; Yuan, ZM et al, 1999; Lewis, JM et al, 1998).

The Abl protein consists of three Src homology (SH) domains (Figure 1.5.1.1) (Deininger, MW et al, 2000). The SH1 domain is positioned in the centre of the protein and contains the Y393 region which is the major site of autophosphorylation and has tyrosine kinase activity. SH2 and SH3 are located upstream of SH1 and participate in interaction with other proteins. A proline rich region downstream of SH1 allows interactions with the SH3 domains of other proteins (van

Etten, RA et al, 1999). The key features of the Abl and Bcr proteins are described in table 1.1 (Faderl, S et al, 1999).

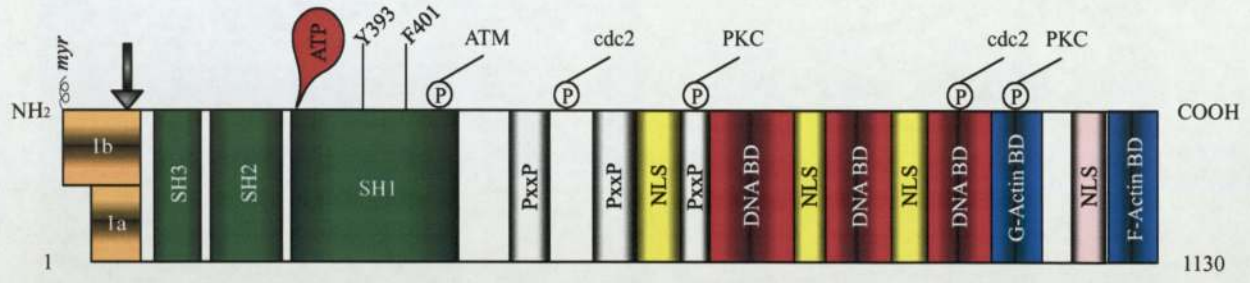

Figure 1.5.1.1, The Abl protein. The arrowhead indicates the position of the breakpoint in the Bcr-Abl fusion protein. Y393 is the major site of autophosphorylation within the kinase domain. Phosphorylation sites by the proteins Atm, cdc2 and PKC are shown. The centre of the protein contains proline-rich regions, and nuclear localisation signals (NLSs). DNA binding and actin binding domains are present towards the carboxy terminal. *(Adapted from Deininger, MW et al, 2000).*

1.5.2 The BCR gene

The *BCR* gene is located on the long arm of chromosome 22. It possesses three distinct regions identified as the m-*bcr* (minor breakpoint cluster region), the M-*bcr* (major breakpoint cluster region) and the µ-*bcr* (micro cluster region) (Melo, JV et al, 1994; van Rhee, F et al, 1996; Pane, F et al, 1996). The M-*bcr* is so named as it has breakpoints clustered within a 5.8 kb area spanning the *bcr* exons b1-b5. This region is thought to be translocated to chromosome 9 in CML patients.

The *BCR* gene encodes a 160 kD protein which has serine/threonine kinase activity and is a GTPase-activating protein for p21 rac (Maru, Y et al, 1991; Diekmann, D et al, 1991) (figure 1.5.2.1). The biological relevance of *BCR* has not been fully determined, although research indicates that it has a role in signal transduction (Ma, G et al, 1997; Liu, J et al, 1996).

Table 1.1, Key functional domains of BCR, ABL and bcr-abl.. SH denotes SRC homology; GEF GDP-GTP exchange factor; GDP guanosine diphosphate; GTP guanosine triphosphate; GAP guanosine triphosphatase-activating protein; and RAC and RHO RAS-like GTPases *(adapted from Faderl, S et al, 1999)*

Protein	Domain	Function
$p145^{Abl}$	Myristoylation site	Localising protein to the nucleus
	SH3 domain	Suppression of the tyrosine kinase function. Negative regulation of transforming activity
	SH2 domain	Interacting with tyrosine-phosphorylated proteins
	SH1 domain	Contains lysine-rich motifs with binding sites for nuclear proteins, DNA and actin
$p160^{Bcr}$	Coiled-coil motif	Required for polymerisation with other proteins
	Catalytic domain	Domain for serine-threonine kinase
	GEF	Control element for members of RAS family. Serves as GDP-GTP exchange for other GTP-binding proteins
	GAP	Control rate of GTP hydrolysis of active RAS proteins to their inactive bound to GDP
$p210^{bcr\text{-}abl}$ (Ph^1 chromosome)	Coiled-coil motif	Polymerisation for activation of other protein functions e.g tyrosine kinase, actin binding
	Tyrosine residue 177	Docking place for adapter proteins
	Serine-threonine kinase	Activating signal-transduction proteins
	SH1 domain	Phosphorylation of various signal and adapter proteins
	Actin-binding domain	Localising to cytoplasm, interfering with focal adhesion

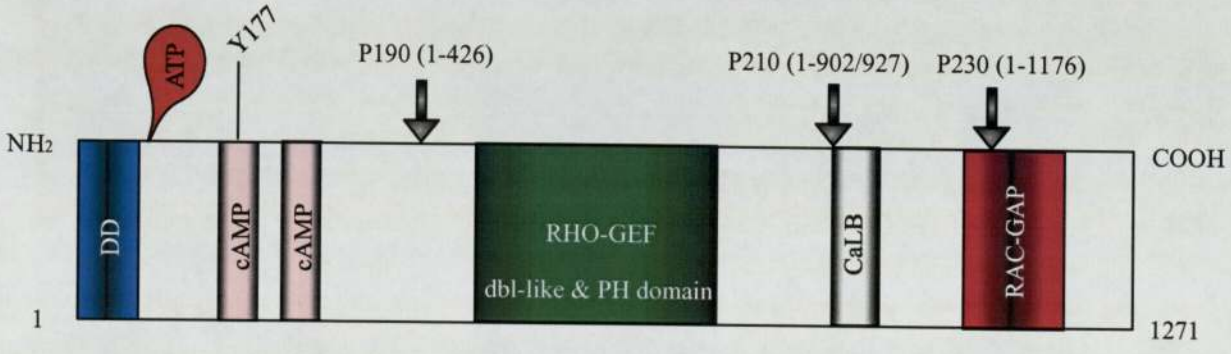

Figure 1.5.2.1, Structure of the Bcr protein. DD denotes the dimerisation domain, cAMP denotes the two cyclic adenosine monophosphate kinase homologous domains at the N terminus. Y177 is the autophophorylation site crucial for binding to Grb-2 (an adapter protein involved in activation of the Ras pathway). The middle of the molecule contains a region homologous to Rho guanidine nucleotide exchange factors (Rho-GEF) as well as dbl-like and pleckstrin homology (PH) domains. The C-terminus has a site for calcium-dependent lipid binding (CaLB) and a domain with activating function for Rac-GTPase (Rac-GAP) are found. Arrowheads show the breakpoint positions in the BCR-ABL fusion protein *(Adapted from Deininger, MW et al, 2000)*

1.5.3 The reciprocal translocation of BCR and ABL

The *bcr-abl* fusion gene is the result of a break at the 3′ end of the *ABL* gene at 9q34, and the fusion of a section of the gene to the 5′ end of the *BCR* gene at chromosome 22q11. The *ABL* gene has 11 exons and the break usually occurs to the 5′ end of exon 2 (Kurzrock, R et al, 1988). It is thought that *ABL* exons 2 to 11 (also known as a2 and a11) are translocated to the M-*bcr* of the *BCR* gene, which lies between exons 12 to 16 (also known as b1 and b5). Interestingly, it was discovered that breakpoints in the *BCR* gene are localised to one of three 'breakpoint cluster regions' (1.5.3.1). In CML patients and about one third of ALL patients, the break occurs in the M-*bcr* region as described above. The *ABL* gene fuses to the b2 or b3 region of *BCR*, forming the b2a2 or b3a2 genes. This results in the most common form of the chimeric gene *bcr-abl*, which encodes a 210-kd protein ($p210^{Bcr\text{-}Abl}$) (Kurzrock, R et al, 1988). In some patients with CML, and the majority of ALL sufferers, alternate splicing causes the fusion of *ABL* to the minor breakpoint cluster region (m-*bcr*) of *BCR* – a region upstream of M-*bcr* between exons e1′ and e2′. The resulting fusion of e1a2 encodes the 190kd protein ($p190^{Bcr\text{-}Abl}$) (Melo, JV et al, 1994; Ravandi, F et al, 1999). A third fusion gene was discovered in the mid 90s. The micro breakpoint cluster region (μ-*bcr*) between exons 19 and 20 (e19 and e20) also fused with *ABL* (e19a2), resulting in a 230kd protein ($p230^{Bcr\text{-}Abl}$), which is thought to be associated with some cases of the Ph-positive chronic neutrophilic leukaemia (Pane, F et al, 1996). Further research into fusion genes has proposed that the *ABL* portion of the chimeric gene carries the leukemia transforming potential since it almost always remains constant, rather than the *BCR* segment which may be responsible for the phenotype of the disease. This theory was supported by Golub and colleagues who showed that the *BCR* moiety may be replaced in principle by other genes, and still cause leukaemia (Golub, TR et al, 1996).

The cause of the translocation remains unknown. The only known risk factor for CML is ionising radiation, which has been proved in vitro and seen in populations exposed to it (Deininger, MW et al, 1998). Ionising radiation causes double strand breakage of DNA. Random joining of base pairs is the most probable cause for translocations or other mutations. It was proposed some years later that translocation could be encouraged by the fact that the *BCR* and *ABL* genes are physically very close to each other. This was observed in human lymphocytes (Kozubek, S et al, 1997; Neves, H et al, 1999).

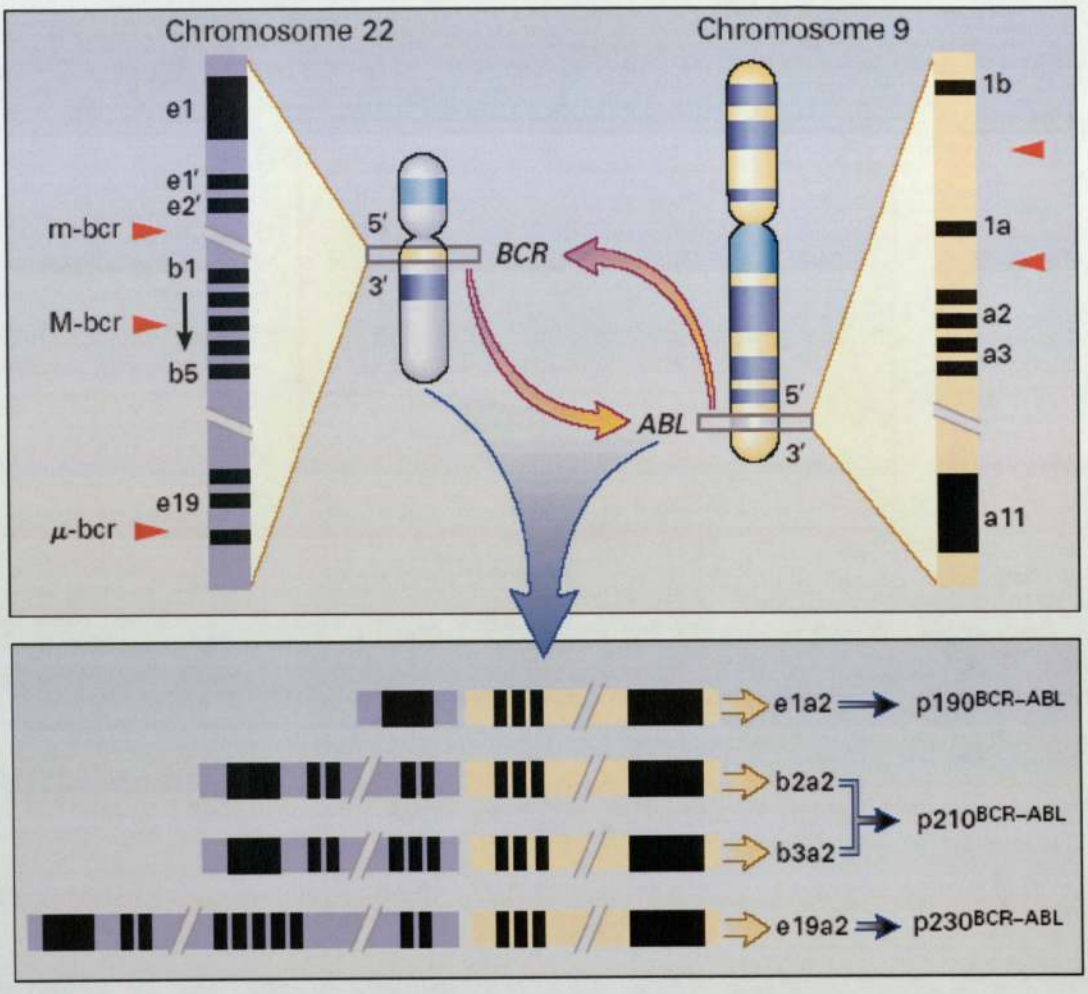

Figure 1.5.3.1, The translocation of t(9;22)(q34;q11) in CML. The Ph chromosome is a shortened chromosome 22 that results from the translocation of 3' ABL segments on chromosome 9 to 5' BCR segments on chromosome 22. Breakpoints (arrowheads) on the ABL gene are located 5' (toward the centromere) of exon a2 in most cases. Depending on which breakpoints are involved, different-sized segments from BCR are fused with the 3' sequences of the ABL gene. This results in fusion messenger RNA molecules (e1a2, b2a2, b3a2, and e19a2) of different lengths that are transcribed into chimeric protein products (p190, p210, and p230) with variable molecular weights and presumably variable function. m-bcr denotes minor breakpoint cluster region, M-bcr major breakpoint cluster region, and μ-bcr a third breakpoint location in the BCR gene that is downstream from the M-bcr region between exons e19 and e20. *(Faderl, S et al, 1999).*

1.5.4 Essential features of the Bcr-Abl fusion protein

The proposed fusion of Bcr-Abl is shown in figure 1.5.4.1 (Faderl, S et al 1999). The combination of the two genes is known to cause the leukaemic transformation of the cell, which is the result of key sites enhancing the tyrosine kinase activity of the protein product. The coiled-coil motif on the N-terminal of Bcr increases the kinase activity, as well as aiding the binding of F-actin by Abl (McWhirter, JR et al, 1993). Segments of Abl are also thought to interfere with focal adhesion – progenitor stem cells would normally be retained in the bone marrow. Bcr-Abl activity has been shown to interfere in this adhesion process allowing these cells to migrate from the marrow into capillaries at an immature stage of development (Sawyers, CL et al, 1992, Di Bacco, A et al, 2000). The serine-threonine kinase domain of Bcr is thought to activate signal transduction proteins (Reuther, GW et al, 1994). A segment of Bcr joins the SH2 domain of Abl, adding a large amino acid segment to the region. Bcr also interferes with the SH3 domain of Abl, which lies next to the SH2 domain. SH3 is known to have a negative regulatory effect on the tyrosine kinase function of Abl, and binding of Bcr is thought to negate this effect and cause Abl to become constitutively active (Pendergast, AM et al, 1991).

The Bcr segment of the fusion protein in particular is largely responsible for the protein-protein interactions required for intracellular signalling. The key adapter protein Grb2 is known to bind to Bcr domains (Puil, L et al, 1994). The GTP-binding protein- Ras is known to be involved in the regulation of cell proliferation and differentiation and is at the heart of key signalling pathways involved in the development of the leukaemic phenotype. It is linked to a conserved tyrosine residue – the Y177 of Bcr through the Grb2 adapter protein which is thought to trigger the signalling cascade (Sawyers, CL et al, 1995).

The *bcr-abl* gene has been implicated in three major processes which together confer the CML phenotype. The cells have a reduced rate of apoptosis, reduced adhesion to stroma in the bone marrow and an increased rate of cellular proliferation (constitutive mitogenic activity). These characteristics are initiated by numerous signalling pathways, which are being studied extensively to further understand the molecular basis of the disease.

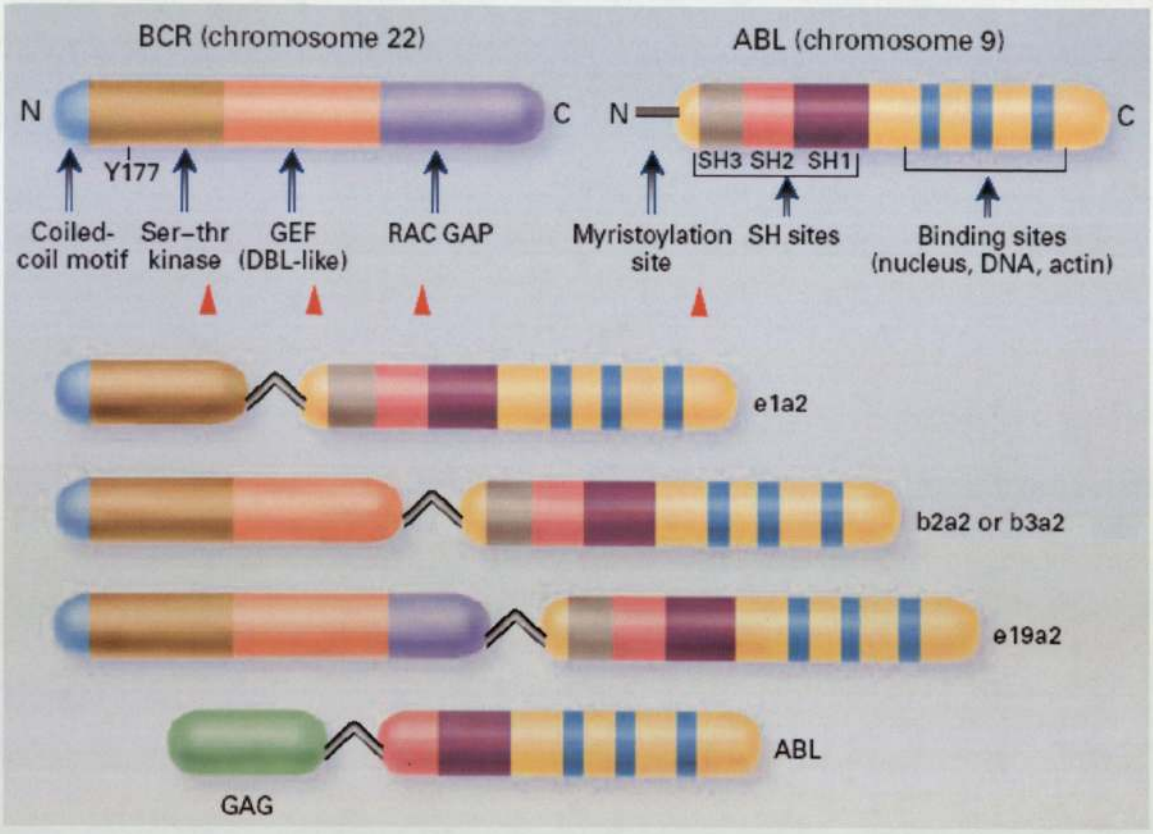

Figure 1.5.4.1, Functional domains of $p160^{Bcr}$, $p145^{Abl}$, and $p210^{Bcr\text{-}Abl}$. Important functional domains of the Bcr and Abl gene products as well as of the different fusion-protein products are shown. Breakpoints are indicated by arrowheads. N denotes N-terminal amino acid sequence, C denotes C-terminal amino acid sequence, Ser-thr serine-threonine, GDP guanosine diphosphate, GTP guanosine triphosphate, GEF GDP-GTP exchange factor, DBL diffuse B-cell lymphoma oncogene. RAC a RAS-like GTPase, GAP guanosine triphophatase-activating function, and SH SRC homology domain. *(Faderl, S et al, 1999).*

1.5.5 The Ras and MAP kinase pathways

Bcr-Abl is known to activate the Ras (name derived from rat sarcoma) pathway through the binding of Grb2 to Bcr domains (Figure 1.5.5.1). This pathway plays a crucial role in the transmission of mitogenic signals from receptor tyrosine kinases (Wood, KW et al, 1992). SHC and Crkl, two other adapter proteins, can also serve as alternative activators of the Ras pathway for haemopoietic transformation (Goga, A et al, 1995; ten Hoeve, J et al, 1994). Pathways downstream of Ras have also been implicated in the leukaemic transformation of the cell, although the evidence for this remains to be confirmed. The MAPK (mitogen-activated protein kinase) pathway seems to play a central role in the activation of signalling pathways. It is

thought to act downstream of Ras and mediate the cascades through Ras and Rac, all of which have some level of mitogenic potential in Ph-positive cells (Marais, R et al, 1995; Cahill, MA et al, 1996).

The main pathways appear to be the JNK (JUN NH-terminal kinase) and the ERK (extracellular signal regulated kinase) pathways, which are both part of the MAPK family (Raitano, AB et al, 1995). Mutations of the cell cycle regulatory proteins c-MYC and cyclin D1 also play a role in malignant transformation from signalling pathways independent of Ras. The proteins have been shown to increase the rate of cellular proliferation and inhibit apoptosis (Afar, DE et al, 1995).

1.5.6 The PI3 kinase pathway

PI3 (phosphatidylinositol 3′) kinase activity has been proven to be important in the proliferation of *bcr-abl* positive cells (Skorski, T et al, 1995). PI3 kinase is activated through the adapter molecules Crk and Crkl. The adapter protein Crkl is involved in integrin-mediated cell adhesion by associating with other focal adhesion proteins (Sattler, M et al, 1996). It is also involved in the regulation of cellular motility which results in the altered adhesion properties associated with Ph-positive cells (Uemura, N et al, 1999). The reduced adhesion properties of CML cells to the stroma seems to allow an enhanced level of cellular proliferation.

The Akt kinase is a substrate of the PI3 signalling cascade and has been associated with an anti-apoptotic effect (Franke, TF et al, 1997). PI3 kinase has been implicated in mitogenesis, cell transformation and apoptosis (Coughlin, SR et al, 1989; Wages, DS et al, 1992).

1.5.7 The JAK-STAT pathway

The JAK-STAT pathway plays an important role in signal transduction from receptors of the cytokine superfamily, and has shown to be involved in the transformation of leukaemic cells (Ilaria, RL et al, 1996). The STAT (signal transducer and activation of transcription) proteins in particular have been reported to directly affect the transcription process in the nucleus and contribute to malignant transformation (de Groot, RP et al, 1999). Bcr-Abl has been shown to constitutively phosphorylate STAT transcription factors. The activation of the STAT proteins appears to inhibit the normal apoptotic process of the cell (Horita, M et al, 2000).

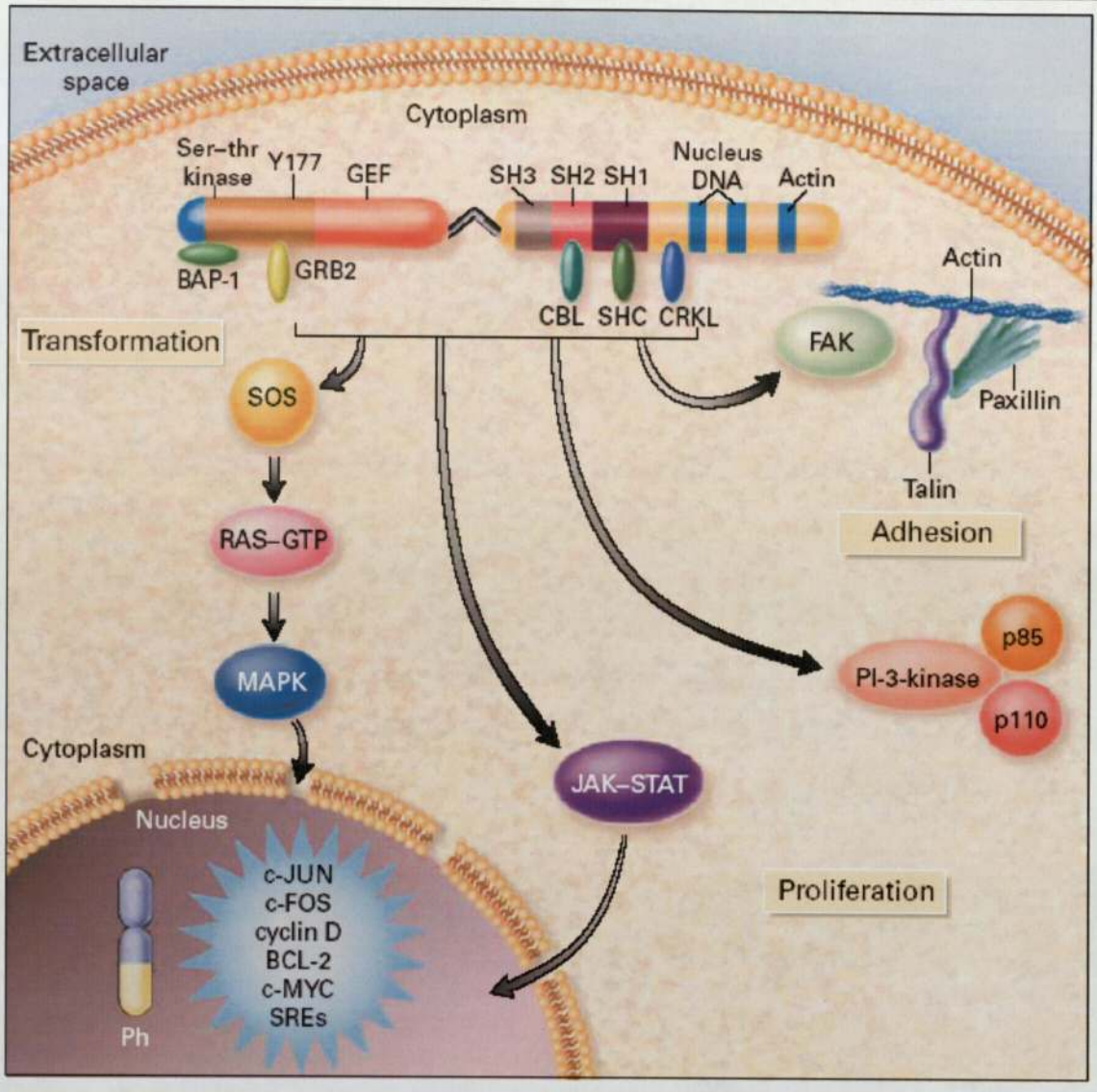

Figure 1.5.5.1, Signalling pathways of p210$^{Bcr-Abl}$. Several regions of Bcr-Abl serve as important control elements for RAS, which is at the centre of the most prominent signalling pathways in CML. Activation of RAS is mediated through a series of adapter proteins, such as GRB2, CBL, SHC and CRKL. Adapter proteins also connect p210 $^{Bcr-Abl}$ to focal adhesion complexes, PI-3 kinases and other messenger systems such as JAK-STAT kinases. Signalling events downstream of RAS are less well characterised. They appear to involve mainly mitogen-activated protein kinases (MAPKs), preferably the JUN kinase (JNK) pathway). BAP-1 denotes BCR-associated protein 1, GRB2 growth factor receptor-bound protein 2, CBL casitas B-lineage lymphoma protein, SHC SRC homology 2-containing protein, CRKL CRK-oncogene-like protein, JAK-STAT Janus kinase-signal transducers and activators of transcription, FAK focal adhesion kinase, SOS son-of-sevenless, GDP guanosine diphosphate, GTP guanosine triphosphate, SRE serum response element, Ser-thr serine-threonine, Y177 a conserved tyrosine residue, GEF GDP-GTP exchange factor, and SH SRC homology domain. *(Faderl, S et al, 1999).*

It is clear that the Bcr-Abl protein uses numerous complex signalling pathways to transform cells and result in the CML phenotype. Much has been done to understand these underlying mechanisms, although unanswered questions such as what the molecular basis of disease progression is and how deregulation of signal transduction leads to a proliferative advantage of the leukaemic cell, need to be addressed to develop better therapies.

1.6 Conventional treatments

1.6.1 Busulphan

Busulphan is an alkylating agent which acts by disrupting DNA formation. By adding an alkyl group to DNA bases, busulphan causes the mispairing of nucleotides. DNA is further fragmented by repair enzymes which attempt to replace the alkylated bases. Busulphan was the first agent to offer a survival benefit to CML patients as it was extremely toxic to stem cells, although it did not bring about cytogenetic or haematologic remissions. Busulphan is less commonly used since hydroxyurea was proved to confer a significant survival advantage over it in a number of randomised controlled trials in the 1990-s (Hehlmann, R et al, 1993; Chronic Myeloid Leukemia Trialists' Collaborative Group, 1997). In addition, busulphan use resulted in more frequent and serious adverse events. Busulphan was associated with irreversible cytopenias, pulmonary, hepatic and cardiac fibrosis (Hehlmann, R et al, 1993; Ohnishi, K et al, 1995).

1.6.2 Hydroxyurea

Hydroxyurea (HU) is a ribonucleotide reductase inhibitor. By inhibiting the conversion of the cytosine nucleotide into the deoxy derivative, DNA synthesis is prevented. DNA formation is further inhibited by hydroxyurea by blocking the incorporation of the thymidine nucleotide into the DNA strand. HU is mainly used to control the levels of white blood cells and platelets, and rarely brings about cytogenetic responses or delays the onset of the advanced stages of CML. For this reason, hydroxyurea serves primarily as a palliative treatment, and is secondary to treatments like allogenic stem cell transplant and IFN-α. HU also has a more favourable tolerability profile to other cytotoxic agents. The main adverse events associated with

hydroxyurea use are nausea, skin atrophy, myelosuppression and fever (The Benelux CML Study Group, 1998; Sandhu, HS et al, 2000).

1.6.3 Cytarabine

Cytarabine is a pyrimidine antagonist and is usually used in combination with interferon-α, since it has little single agent activity. This concomitant therapy increases survival and induces superior rates of cytogenetic response in CML patients compared to interferon-α alone. However this combination also increases toxicity (Guilhot, F et al, 1997; Baccarani, M et al, 2002). A low-dose of cytarabine combined with interferon-alpha is thus recommended, rather than high-dose cytarabine.

1.6.4 Interferon-α

Interferons (IFN) are potent cytokines that possess antiproliferative, antiviral and immunomodulating actions (Baron, S et al, 1992). Purified recombinant human IFN-α induces similar clinical effects in CML as the natural form. The exact mechanism of action remains unknown and its effects vary from one patient to another. IFN-α was found to be an effective treatment for CML after it was shown to inhibit in vivo myeloid colony formation in the early 1980-s (Verma, DS et al, 1979). Unlike previous drug regimens, IFN-α brought about haematologic and cytogenetic remissions in CML patients (Talpaz, M et al, 1986; Talpaz, M et al, 1991). It was also shown to increase the survival of patients and slow disease progression in comparison to other chemotherapeutic agents (Shepherd, PC et al, 1996). IFN-α was shown to induce a haematologic response in up to 80% of CML patients, and around 25% experienced a major cytogenetic response (eradication over 60-65% of Philadelphia positive cells) (Talpaz, M et al, 2001).

Virtually all patients taking IFN-α experience side effects, which vary in severity. Flu like symptoms are the most common observations, such as fever, headache and aching in the joints and muscles. Fatigue and other neurological toxicity is also common among patients taking IFN-α. Studies have shown that the incidence of adverse effects seems to be dose and duration dependent (Vial, T et al, 1994).

1.6.5 Bone Marrow Transplantation

It is still maintained that the only strategies that can cure CML are those that lead to complete and permanent eradication of Ph^1-positive stem cells and the replacement of normal haemopoiesis. Following this theory, allogeneic (based on human leukocyte antigens) bone marrow transplantation is the only treatment known to cure CML. A number of studies have reported long-term survival rates in around 50% to 80% of patients eligible for the treatment (Savage, DG et al, 1997; Hansen, JA et al, 1998).

However, allogenic BMT is only an option for some 40% of patients (Peggs, K et al, 2003). The success of the treatment is largely dependent on the age of the patient, the stage of the disease, the treatment used in preparation for the treatment (i.e. chemotherapy), the availability of a related HLA-matched donor and quite often the experience of the centre providing the service. Younger patients have an increased chance of successful treatment. Patients younger than the age of 20 have the best outcome, with a steady decrease in survival with each successive decade (Clift, RA et al, 1996; Gratwohl, A et al, 1998). Patients in the chronic phase of the disease also fare better than those in the more advanced stages; survival rates after transplantation in the accelerated phase are reduced by 50% and less than 20% of patients treated in the blast crisis survive (Clift, RA et al, 1996; Horowitz, MM et al, 1996). Transplants from non-HLA matched or unrelated donors carry a higher mortality risk, however, related HLA-matched donors are only found for around 30% of CML patients (Clift, RA et al, 1996; Horowitz, MM et al, 1996). The procedure of allogeneic BMT is associated with significant mortality rates, due to the toxicity of the procedure itself and the problem of GVHD (graft versus host disease) post transplantation. Death rates following an allogeneic transplant range between 20%-40% (Silver, RT et al, 1999).

1.7 Prognostic scores

There are two main prognostic scores defined for CML, the Sokal score and the Hasford score (Sokal, JE et al, 1984; Hasford, J et al, 1998). The Sokal score is used to predict prognosis, and takes into account the person's age, percentage of circulating blasts, size of spleen and the number of platelets. The Hasford score is similar, and considers the number of eosinophils and basophils in addition to the components that Sokal describes. (See Appendix 1).

1.8 Imatinib Mesylate

Imatinib mesylate (Glivec®, STI571, Novartis Pharma AG, Basel, Switzerland) was the first of the molecular targeted tyrosine kinase inhibitors to be applied in CML. It has been shown to inhibit a number of protein tyrosine kinases and has led to the successful treatment of patients with chronic myeloid leukaemia and gastrointestinal stromal tumours (GIST). The FDA approved imatinib for the treatment of CML that is refractory to IFN-α in May 2001 and for the treatment of GIST shortly after in February 2002.

1.8.1 History

The story of imatinib began when the *ABL* oncogene was shown to be a therapeutic target for new drugs. *ABL* genes specifically were shown to play an important role in the pathogenesis of human leukaemias (Wang, JY et al, 2000). Following the discovery in the early 1980s that a reciprocal translocation resulted in the fusion of *BCR* and *ABL* gene segments in over 90% of CML patients, the idea of inhibiting the activity of this gene in the hope of treating the disease was adopted (Shtivelman, E et al, 1985; Nowell, PC et al, 1961).

Inhibition of the Abl tyrosine kinase was attempted by several groups, which were unsuccessful, largely due to a lack of selectivity (Geissler, JF et al, 1992; Anafi, M et al, 1993). The Novartis group attempted to identify selective inhibitors of the Abl tyrosine protein kinase in the 1990s. The group was successful in developing a series of compounds of the 2-phenylaminopyrimidine class which showed selectivity for the Abl and PDGF receptor tyrosine kinases (Buchdunger, E et al, 1995; Buchdunger, E et al, 1996). An initial lead compound for targeting the Bcr-Abl tyrosine kinase was found through the process of random screening of compound libraries. The molecule lacked potency and had poor bioavailability, and so the process of optimising the lead compound began. The structure and activity relationship was examined in a variety of assays and a number of alterations were made to obtain the optimal compound (Fig 1.8.1).

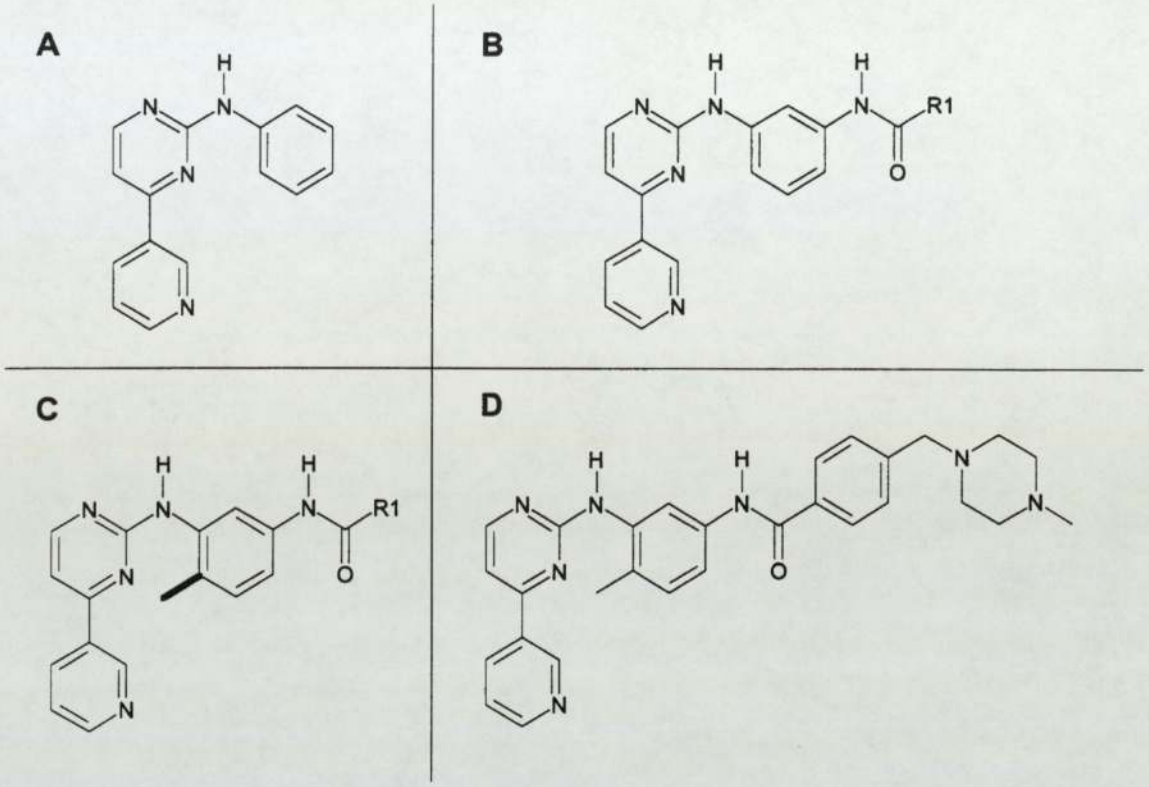

Figure 1.8.1, Optimisation of the phenylamino-pyrimidine lead structure and synthesis of STI571. A – central phenylamino-pyrimidine template;B – methyl substitution of the anilino-phenyl ring at the 6-position led to potent inhibition of the ABL and PDGFR kinases; C – addition of benzamide group at the phenyl ring led to enhanced activity; D – addition of *N*-methyl piperazine group led to an optimal compound CGP 57148 (imatinib mesylate) *(Buchdunger, E et al, 2001)*

1.8.2 Preclinical testing

Imatinib was tested for activity against a variety of protein tyrosine kinases. Preclinical tests showed that imatinib inhibited the autophosphorylation of the protein products of v-Abl, Arg (an Abl-related protein), PDGFR (platelet derived growth factor receptor), and the c-Kit receptor in a number of models (Buchdunger, E et al, 1995; Buchdunger, E et al, 1996; Okuda, K et al, 2001). However, imatinib activity was limited to these kinases and failed to show significant inhibition of targets such as the serine/threonine kinases (Buchdunger, E et al, 2001).

The proof of concept came shortly after when STI571 was shown to suppress the proliferation of Bcr-Abl expressing cells in vitro and in vivo (Druker, BJ et al, 1996). Imatinib caused a 92-98% decrease in the number of Bcr-Abl colonies formed in assays of blood or bone marrow from patients with CML (Druker, BJ et al, 1996). Imatinib also inhibited variant fusions of Abl, such as the *tel-abl* fusion gene found in some patients (Carroll, M et al, 1997; Beran, M et al, 1998).

1.8.3 Mechanism of action

Much work has been done to fully elucidate the mechanism of action of imatinib. It is known to block the tyrosine kinase activity of the receptors by acting as a competitive inhibitor of ATP, thus preventing the constitutive phosphorylation of the kinase (Buchdunger, E et al, 2001). The structural basis of this inhibition was debated, and it was unclear whether imatinib acted by binding to the active or inactive form of the Abl kinase. The group that discovered imatinib initially postulated that imatinib inhibited the active form of the enzyme (Druker, BJ et al, 2000). This proved to be incorrect as the active conformation was very similar to other kinases and did not explain why imatinib was so selective to the specific receptor associated tyrosine kinases it targeted.

Schindler and colleagues used X-ray crystallography to show that imatinib binds the inactive form of the Abl kinase (Schindler, T et al, 2000). The inactive forms of kinases are very different whereas the active forms have a greater similarity (Figure 1.8.2). Since imatinib specifically binds very few kinases, which in their active conformations are quite distinct, it was shown that their similarities lie in their inactive conformations (Schindler, T et al, 2000).

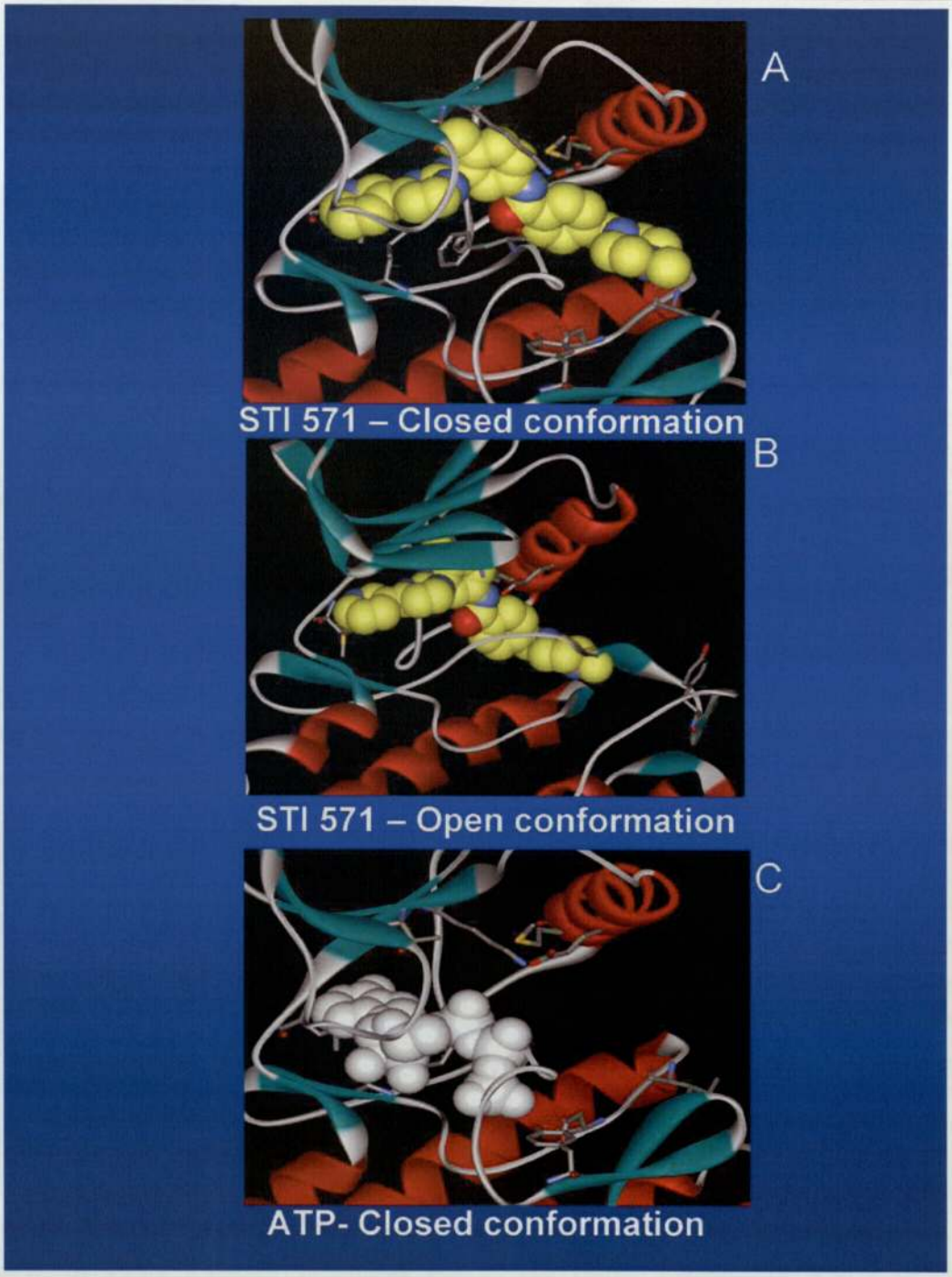

Figure 1.8.2, The structure of imatinib bound to Abl. Imatinib bound to the inactive, closed confirmation of Abl (panel A) in which imatinib straddles the conserved activation loop DFG motif and its acid amine and piperazine (right hand side of inhibitor) pass under helix C. Panel B shows a model of imatinib with Abl in the active confirmation. Note that this binding mode is not allowed due to the orientation of the activation loop. Panel C shows a model of ATP within the inactive confirmation of Abl. Again, this binding mode is not allowed due to the position of the DFG region of the activation *(Lydon, NB et al, 2004)*

1.8.4 Therapeutic implications

As previously described, imatinib has been showed to have significant activity in a variety of different receptor tyrosine kinase targets. This has allowed the use of imatinib in other diseases aside from CML, and has increased the drug's therapeutic value. Although shown to have activity against at least four different tyrosine kinase receptors, imatinib could be functional against other tyrosine kinase receptors not tested and therefore expand its activity in the therapeutic arena.

1.8.5 The c-Kit receptor

The c-Kit receptor is a growth factor receptor with tyrosine kinase activity. c-kit mediates the biochemical effects of stem-cell factor (SCF). c-Kit has a key role in controlling cell proliferation, and its overexpression has been associated with several cancers (Andersson, LC et al, 2002).

A mutated form of c-Kit has been implicated as the major cause of gastrointestinal stromal tumours (GIST). Other mutations of c-Kit have shown to give rise to other tumours, namely mastocytomas and mast cell leukaemias (Andersson, LC et al, 2002). Dysregulation of Kit has also been implicated in the aetiology of a number of cancers in addition to GIST: namely acute myelogenous leukaemia (AML), some lung cancers, gliomas and testicular cancer (Manley, PW et al, 2002).

Imatinib showed activity against c-Kit in preclinical trials and was deemed a suitable therapeutic target for patients with GIST. It was tested for activity in a number of pivotal trials and successfully treated patients with unresectable GIST (van Oosterom, AT et al, 2002; Joensuu, H et al, 2001; Demetri, GD et al, 2002). Abnormalities of c-Kit have been also been observed in conditions such as Ewing's Sarcoma and various melanomas (Merchant, MS et al, 2002). Patients are being recruited for early phase studies of the activity of imatinib with such diseases, although it is only approved for use in CML and GIST patients (U.S. National Institutes of Health, National Library of Medicine, 2005).

1.8.6 The platelet derived growth factor (PDGF) receptor

Platelet-derived growth factor receptor (PDGF-R) tyrosine kinase activity is also selectively inhibited by imatinib. There is a close homology between the kinase domains of PDFG-R and c-Kit (McGary, EC et al, 2002). PDGF-R mediates the biochemical effects of platelet-derived growth factor (PDGF), which normally plays a central role in regulating cell proliferation, chemotaxis and survival in normal cells as well as various disease states such as cancer, atherosclerosis and fibrotic disease. At the same time PDGF promotes cell growth, it may exert a protective effect on cells by inhibiting apoptosis (Buchdunger, ET et al, 2002). The tyrosine kinase domain of PDGFR is involved in activation of several oncogenes. PDGF is a potent mitogen and inhibits apoptosis. It is over-expressed in several cancers including prostate cancer (van der Poel, HG et al, 2004). The PDGF family is composed of dimeric isoforms which exert their effects by differentially binding to two receptor kinases: - PDGFR-α and PDGFR-β. Imatinib inhibits the activity of both of these receptors.

Imatinib is being tested in hypereosinophilic syndrome, prostate cancer, various gliomas and female reproductive cancers (van der Poel, HG et al, 2004; Gleich, GJ et al, 2002; Cools, J et al, 2003). These conditions have been shown to have some type of abnormal PDGF receptor activity, which provides the rationale for treatment with imatinib mesylate.

1.8.7 The Abl and Arg tyrosine kinases

Imatinib achieved its aim in targeting the abnormal Abl protein target in CML patients. It has also successfully targeted the Abl protein in a number of patients with variant forms of leukaemia such as ALL (Druker, BJ et al, 2001). *ARG* is a gene related to *ABL* and has been shown to play a role in some forms of acute myeloid leukaemia (AML). Imatinib was shown to have activity against the Arg tyrosine kinase (Nishimura, N et al, 2003). However, inhibition of the Arg tyrosine kinase by imatinib has only been shown in cell lines from patients and is yet to be proven in a clinical setting.

The multiplicity of therapeutic targets of imatinib has enhanced the profile of imatinib, and certainly merits further investigation. Indeed, imatinib may be capable of inhibiting further targets that, as yet, remain unknown to the scientific community. Completion of current trials investigating the use of imatinib in other cancers will further characterise the potential of the drug.

Imatinib is fast becoming the preferred choice of treatment with its proven efficacy in a number of very different conditions, such as GIST and hypereosinophilic syndrome. The availability of imatinib to vulnerable patient groups has been facilitated by the use of accelerated licensing times and by its classification as an orphan drug.

1.9 The licensing of imatinib mesylate

1.9.1 Imatinib licensing in the USA

The Food and Drug Administration (FDA), similar to other drug regulatory agencies around the globe, has long sought to improve the drug licensing process, in terms of the time taken to approve a new entity and the availability of potentially life-saving drugs to patients. On average, a drug takes about 10-15 years from the time it is discovered in the laboratory until it is used in a clinical setting (Reichert, JM et al, 2003). The resources required, i.e. money and patients, necessary to bring such a drug to the market are huge, and offer little incentive for companies to produce a drug which may only be used in a small population of patients. The effect of this was seen in 2002-2003, when almost 50% fewer applications were submitted to the FDA than in 1996-1997 (Fig 1.9.1.1.). Despite the efforts of pharmaceutical companies to launch new drugs into the market, more than 80% of drugs in development fail to get marketing approval, and about half of all investigated drugs fail to prove successful at phase III (Reichert, JM et al, 2003). The cost of bringing a drug from the discovery stage to phase III can be around 1 billion US dollars; potentially a huge loss if the product is not marketable (Lesko, LJ et al, 2004; DiMasi, JA et al, 2003).

The approval process is relatively fast in comparison with the time taken to prove the safety and efficacy of the drug. The average time from submission of a new drug application (NDA) and its approval by the FDA is around 18.6 months, an increase of about 6 months since 1998 (Reichert, JM et al, 2003). This increase in time has slowed the availability of important and potentially life-saving new therapies to patients with serious conditions, and is against the interests of the sponsor who intends to profit from a commercially available drug.

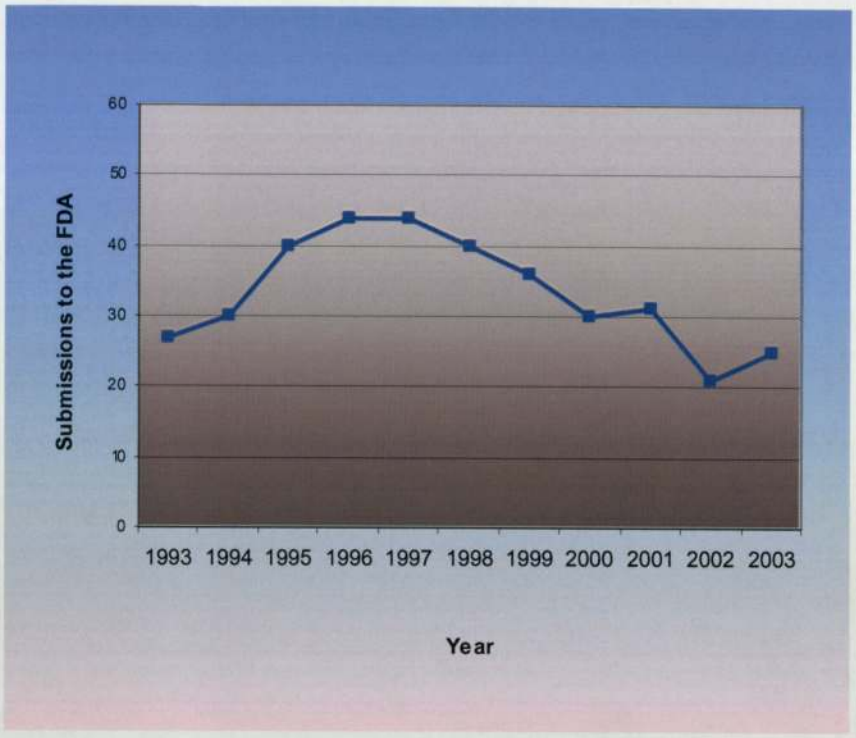

Figure 1.9.1.1, Ten-year trends in major drug product submissions to the FDA. Similar trends have been observed at regulatory agencies worldwide *(Adapted from Innovation Stagnation, FDA, 2004).*

In response to these issues, the FDA has set out a number of initiatives over the last decade, to improve the approval process and allow greater access of new drugs to patients with serious conditions. The main initiatives are the fast-track process, accelerated approval, priority review and orphan drug status. The four processes have similar aims although each is distinct from the others. The fast-track process describes an increased dialogue between the sponsor and the FDA during the development process. Accelerated approval allows an increased input from the FDA in the design of the studies to be undertaken by the sponsor. NDAs given priority review are designated a specific time frame for the review and orphan drug status provides incentive for sponsors to develop drugs used to treat rare conditions. These initiatives are primarily used to develop drugs used to treat rare, serious or life threatening conditions.

The FDA has set out a number of guidelines to define a serious condition (Food and Drug Administration, Guidance for Industry: Fast-track development, 1999). Any condition that affects survival, the day-to-day functioning of a patient, or the probability of the disease to

progress to a serious stage if left untreated is classified as a serious or life-threatening condition. Many diseases fall into this definition such as cancer, heart failure and AIDS. Other illnesses may be well-managed by the treatments available although may have serious outcomes such as asthma and rheumatoid arthritis amongst many others, and are therefore classed as serious also. For a drug to qualify for one of the four increased approval procedures, it must treat a serious aspect of the disease. The drug must meet some or all of the following requirements: -

1. drug must be **therapeutic**, (treat a serious manifestation or symptom)
2. must be **diagnostic** by improving detection or diagnosis
3. **preventive** (prevent serious consequences)
4. lacking in serious adverse events

The drug must also address an 'un-met' medical need to qualify for any of the four initiatives (Food and Drug Administration, Guidance for Industry: Fast-track development, 1999). At least one of the following requirements must be met to qualify for addressing an unmet medical need:

- no existing therapy for the condition
- show an improved effect on serious outcomes of the condition in comparison to current treatments
- affect different outcomes to current therapy
- benefit patients not responding to current therapy
- avoid serious adverse events related to current treatments
- offer improved compliance and convenience in comparison to current therapy

Imatinib was developed in 1996 by Buchdunger and colleagues of Novartis Pharmaceuticals, in an attempt to develop a molecular targeted drug to inhibit the BCR-ABL tyrosine kinase, the hallmark of chronic myeloid leukaemia (CML) (Buchdunger, E et al, 1996). Imatinib was to be the first of such specific inhibitors, and successfully inhibited other tyrosine kinase activities associated with receptors such as c-Kit and PDGFR.

Imatinib proved to be an effective treatment in preclinical studies, showing successful inhibition of the tyrosine kinases investigated, with relatively minimal side effects. Animals treated with

imatinib showed a prolonged survival, although resistance was observed in some cases (Wolff, NC et al, 2001).

The first phase I clinical study began in June of 1998 (Druker, BJ et al, 2001). The encouraging results of this trial, and other phase I studies led to the launch of three pivotal phase II clinical studies, testing the efficacy and safety of imatinib use in the three different phases of CML (Sawyers, CL et al, 2002; Kantarjian, HM et al, 2002; Talpaz, M et al, 2002). These studies began in the latter half of 1999 and the results were published in 2002. The first phase III study was launched in June 2002 and compared imatinib to the standard therapy of interferon-α plus cytarabine (O'Brien, SG et al, 2003). The results of this study were reported in 2003, and confirmed the key findings of previous studies.

FAST-TRACK PROGRAM

The fast-track program is highly beneficial to the sponsor, and to the potential patients, since the drug is likely to go through the approval process more rapidly. A sponsor may request fast-track designation for the investigational new drug application (IND) from the time of filing or any other time during the clinical development of the drug. The FDA will grant designation or non-designation within 60 days, although this fast-track status may be withdrawn at any time of the development process (Food and Drug Administration, Guidance for Industry: Fast-track development, 1999).

Fast-track status enables an enhanced level of communication between the drug sponsor and the FDA. A meeting is usually held before the IND is submitted, with subsequent meetings at the end of phase I and phase II studies. Regular meetings are also held throughout these processes, enabling the FDA to add input into the clinical plans. A meeting is usually held before the sponsor submits the NDA so any formatting of the application is discussed. Together with regular scheduled meetings, the FDA and sponsor often share an increase in written correspondence and often a 'rolling submission' of the NDA is made allowing the FDA to review shorter segments of the report rather than one large package.

Since fast-track approval aims to allow drugs to reach the market sooner, the FDA and sponsor may agree to surrogate endpoints on which to approve the drug. The regular meetings are thus very important to discuss the FDA's requirements of the sponsor, and allows an increased opportunity to resolve any problems that may arise.

Novartis sought fast-track designation for imatinib use in patients with CML. Discussions and meetings were held regularly between the sponsor and FDA and often focussed on the planning and analysis of three important phase II studies looking at imatinib treatment in the 3 phases of CML. The endpoints of the studies were agreed upon, together with key issues such as patient inclusion and exclusion criteria. The three studies were completed in a record two years. The NDA was submitted on the 27th Feb 2001, and the drug was approved on the 10th May of the same year – after only 73 days (FDA approval letter – CML, 2001). Areas that the FDA deemed problematic in these studies, such as the unrandomised study designs, a lack of time-to-events endpoints and a need for the confirmation of the surrogate endpoint were quickly addressed by Novartis launching a phase III randomised, controlled trial comparing imatinib with interferon-alpha plus cytarabine with patients having newly diagnosed and previously untreated chronic phase CML (O'Brien, SG et al, 2003). The trial was designed specifically to assess cytogenetic response and time to disease progression as requested by the FDA.

The efficacy of imatinib was shown to be superior to standard therapy in all three phases of CML and the FDA advised that imatinib was a potential candidate to enter the accelerated approval program for the two trials involving patients with accelerated and blast phase CML. The surrogate outcome measures of haematologic and cytogenetic responses were also confirmed as indicators of survival in patients treated with imatinib.

Correspondence between Novartis and the FDA continued before the approval of imatinib, meetings occurred before the start of phase II trials in the US after completing these studies, before NDA submission and throughout the product labelling and promotional review period. Novartis also presented a rolling submission, which probably speeded the process of approval.

ACCELERATED APPROVAL

Accelerated approval (subpart H approval) was established in 1992 to speed the approval and marketing of promising products for life-threatening diseases (Food and Drug Administration, Guidance for Industry: accelerated approval, 1999). The FDA advises the sponsor regarding the design and analysis of the clinical studies it proposes. To qualify for accelerated approval, the new drug must display some level of efficacy by using either a surrogate endpoint or reliable clinical endpoint other than survival or irreversible morbidity i.e. on the basis of preliminary evidence before the formal demonstration of efficacy and safety in patients.

Sponsors seeking accelerated approval for their product must adhere to specific FDA requirements: -

- completion of studies using a surrogate marker or clinically reliable endpoint, which may allow for provisional approval with written commitment to perform postmarketing clinical studies that show traditional patient benefit
- potential implementation of a restricted distribution plan (i.e. distribution limited to certain facilities or practitioners)
- adherence to more stringent regulations of promotional material, such as submitting all core promotional materials to FDA
- awareness of an increased risk for a more rapid removal from market compared with drugs approved via traditional methods (Food and Drug Administration, Guidance for Industry: accelerated approval, 1999)

The three pivotal trials that formed the basis for imatinib approval were designed using specific surrogate endpoints such as hematologic response and cytogenetic response. The biology of CML has been studied for some time and these endpoints were accepted as markers for disease progression in the treatment of CML with IFN-α (FDA approval letter – CML, 2001). However, these surrogate measures were not validated for imatinib therapy as survival indicators. The role of the FDA in the design of these studies was key to the completion of the phase II studies in the record time of two years. Novartis effectively used the advice of the FDA, managing to adhere to the requirements necessary to gain approval.

PRIORITY REVIEW

The FDA usually classifies submitted NDAs as either priority or standard, indicating the time frame the FDA will use to review the application (Centre for Drug Evaluation and Research; Manual of policies and procedures, 1996). The standard review time is usually about 10 months while drugs given priority are reviewed in an average of six months. Priority review is reserved for drugs which address unmet medical needs and are used to treat serious conditions. Generally drugs that are granted accelerated or fast-track approval are eligible for priority review.

Novartis sought priority review from the FDA at the time of submission of February 27th 2001. The FDA granted the request, and completed the review in 2.5 months, which was largely due to the constant discussion with the sponsor, the efficacy and safety shown by imatinib in clinical trials and the need to make the drug available to patients as soon as possible.

ORPHAN DRUGS

Orphan drugs are defined as drugs used to treat rare diseases which affect fewer than 200,000 patients in the United States (Office of Orphan products development, FDA). The orphan drug act was passed in 1983 and aimed to encourage the research and development of treatments to treat rare conditions.
Orphan drug status benefits a sponsor by providing the following: -

- tax incentives for clinical research
- study design assistance from the Center for Drug Evaluation and Research (CDER)
- exemption from application-filing fees
- possible grant funding for phase I and phase II clinical trials
- seven years of marketing exclusivity after the approval of the drug (Haffner, ME, 2002)

Once drugs receive this status, no changes can occur in their clinical development, and sponsors must still perform traditional studies to demonstrate safety and efficacy unless their products also qualify for accelerated approval. Once the FDA grants orphan status, the designation can be withdrawn only if the original request is found to contain false information or, did not contain

necessary data or that the drug did not satisfy the criteria for orphan drug status at the time of application.

Imatinib was initially approved to treat CML which affected 4,400 patients in the US in 2002 and was therefore granted orphan drug status (Jemal, A et al, 2002). The Office of Orphan Product Development (OOPD) was also involved in the initial review of the NDA. The OOPD does not act by changing the safety and efficacy criteria for a quick approval, but rather as an ombudsman between the sponsor and CDER to aid a quick approval (Haffner, ME et al, 2002). The OOPD may also assist investigators involved in grant programs in setting up and monitoring trials and serve as a liaison between FDA and the investigators.

1.9.2 Imatinib licensing for gastrointestinal stromal tumour (GIST) patients

Imatinib was also licensed for use in patients with c-Kit positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) on the 1st February 2002 following the submission of the NDA on the 15th October 2001 (FDA approval letter – GIST, 2002). Similar to the CML trials, GIST was licensed on surrogate outcome measures, namely objective response rates in GIST and hematologic and cytogenetic response rates in CML, rather than a proven clinical benefit. The license was granted following promising results in three main clinical studies, which investigated the effects of imatinib in a total population of 188 patients with GIST (van Oosterom, et al, 2001; Joensuu, H et al, 2001; Demetri, GD et al, 2002). No controlled trials demonstrating a clinical benefit such as improvement in disease-related symptoms or increased survival were available when the NDA was submitted. Imatinib was granted the four major accelerated procedures for use in GIST which had been allowed for its use in CML patients i.e. the fast-track and accelerated approval, priority review and orphan drug status since GIST only affects some 15,000 people in the US (Office of rare diseases, National Institute of Health, USA).

1.9.3 Imatinib licensing for newly diagnosed and paediatric patients

The FDA approved imatinib for the first-line treatment of patients with CML on the 20th December 2002 (FDA approval letter – newly diagnosed, 2002). Since the drug was initially licensed largely on phase II data, further studies were needed to confirm that imatinib provided an actual clinical benefit such as an increase in survival. Novartis addressed this problem by

initiating the phase III randomised controlled study – IRIS, which compared imatinib to the standard drug regimen of IFN-α and low-dose cytarabine. The study randomised a total of 1106 patients with newly diagnosed CML in the chronic phase to either imatinib or the control group. After a follow-up of a median duration of 14 months, imatinib proved to be significantly better than the control drug in all of the parameters investigated. Although the long-term benefits were not observed in the short follow-up period, the findings showed imatinib to be superior so it was licensed on the preliminary data from the IRIS study for newly diagnosed CML patients.

Imatinib was also approved for use in children whose disease had recurred after stem cell transplant or who were resistant to IFN-α therapy on the 20th May 2003 (FDA approval letter – pediatric patients, 2003). The approval was accelerated based on extrapolation of results from imatinib treated adults with CML together with good responses in a small number of children. The accelerated approval was based on the condition that Novartis was to conduct paediatric studies after the approval to investigate the clinical benefit of imatinib in this patient population.

1.9.4 Imatinib licensing in Europe

Imatinib received marketing authorisation from the European Agency for the Evaluation of Medicinal Products (EMEA) in November 2001 despite the lack of evidence from randomised controlled trials (RCTs) (EMEA, CPMP, EPAR – Glivec, 2001). The license was granted "under exceptional circumstances", as the EMEA stated that "the indications for which the medicinal product in question [imatinib] is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence/data on the quality, safety and efficacy of the medicinal product" (EMEA, CPMP, EPAR – Glivec, 2001). The manufacturer agreed to an identified programme of studies, which would have formed the basis of an annual reassessment of the risk/benefit profile of imatinib.

Imatinib followed a similar pathway in Europe as it did in the US in terms of the licensing procedure. The significant results in the trials to date convinced the EMEA to approve it under exceptional circumstances for the treatment of CML. The EMEA licensed imatinib on the same data as the FDA had awarded the license.

The EMEA designated imatinib an orphan drug on the 14th Feb 2001 (EMEA, COMP – Glivec, 2001). The Committee for Orphan Medicinal Products (COMP) was set up in the year 2000 to consider drugs that pose little financial benefit to pharmaceutical companies as the target population is small. An orphan drug status is granted to products that treat life-threatening or severely debilitating diseases affecting less than 5 in 10,000 residents in the EU and for which no satisfactory alternative is available. As in the USA, companies that develop such drugs are eligible for incentives to support research and development. The period of market exclusivity for drugs with orphan drug status is 10 years in the EU, three years more than in the US (EMEA – 3 years of successful experience on orphan drugs, 2003).

Imatinib was licensed through the centralised procedure, and the process was initiated on the 27th March 2001, when the application was submitted. The Committee for Proprietary Medicinal Products (CPMP), now referred to as the CHMP (Committee for Medicinal Products for Human Use) was the advisory committee to the EMEA for human medicinal products and comprised two delegates from each EU member country (Figure 1.9.4.1). The CPMP agreed to an expedited review when it became evident that the application was of a high quality and that imatinib showed outstanding activity. The design and execution of the studies enabled this expedited review.

Issues raised by the CPMP were addressed by the sponsor, allowing the procedure to progress swiftly. The CPMP subsequently issued a positive opinion for granting a marketing authorisation to imatinib on 26th July 2001 (Figure 1.9.4.2) (EMEA, COMP – Glivec, 2001). The CPMP opinions were forwarded, in all official languages of the EU, to the European Commission, which adopted the corresponding decisions on 11th November 2001. The CPMP recommended the granting of a marketing authorisation 'under exceptional circumstances'. The marketing authorisation holder was requested to submit additional information on clinical aspects of this medicinal product. All additional studies were to be carefully monitored and the results were to be received by the CPMP.

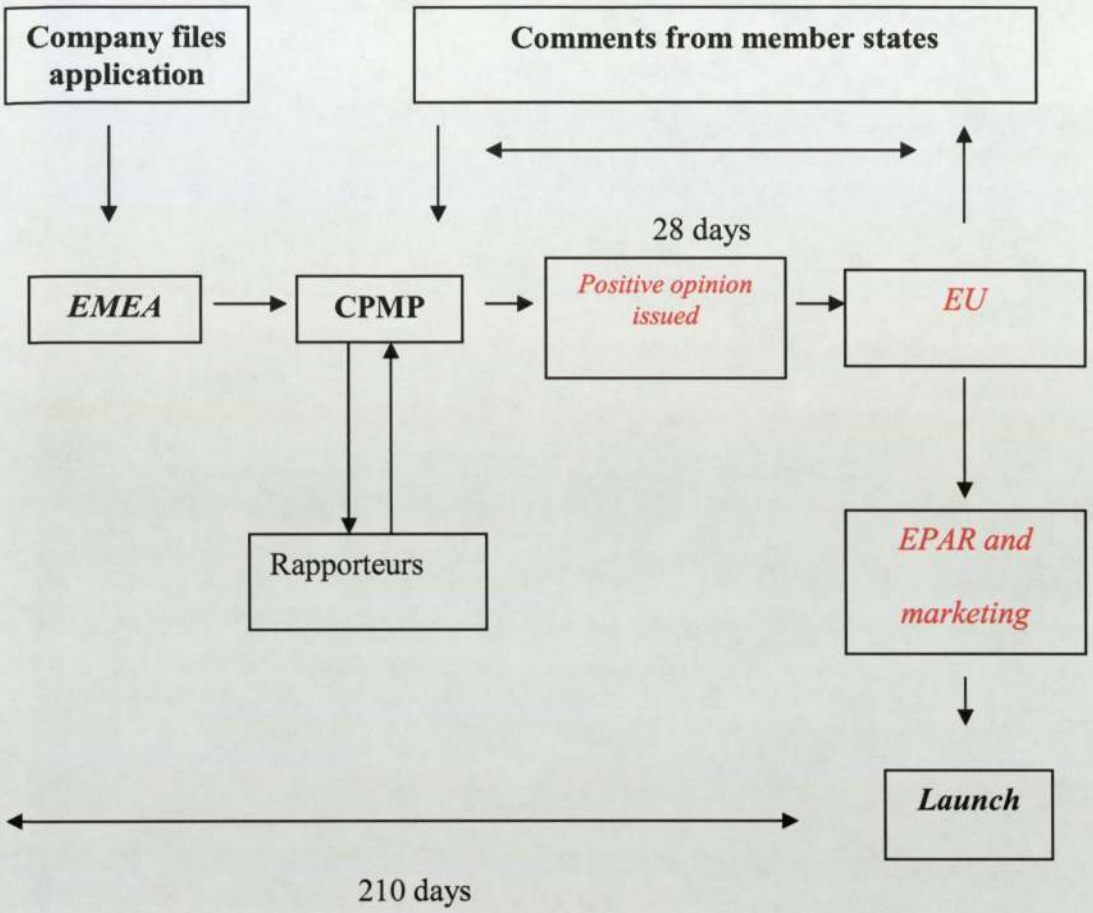

Figure 1.9.4.1. The European Union centralised system for licensing of medicinal products.

CPMP – Committee for Proprietary Medicinal Products; EPAR – European Public Assessment Report; Rapporteurs – representatives from two member states who consider the application, one of which is chosen by the pharmaceutical company . An opinion has to be issued within 210 days of receipt of the application, though the average time is 180 days. Imatinib was approved for use in all stages of CML after IFN-α failure in 119 days. Drugs licensed using the centralised system have a market exclusivity of 10 years, 3 years more than the decentralised system *(Adapted from The licensing of medicines – Aug 2003, NHS).*

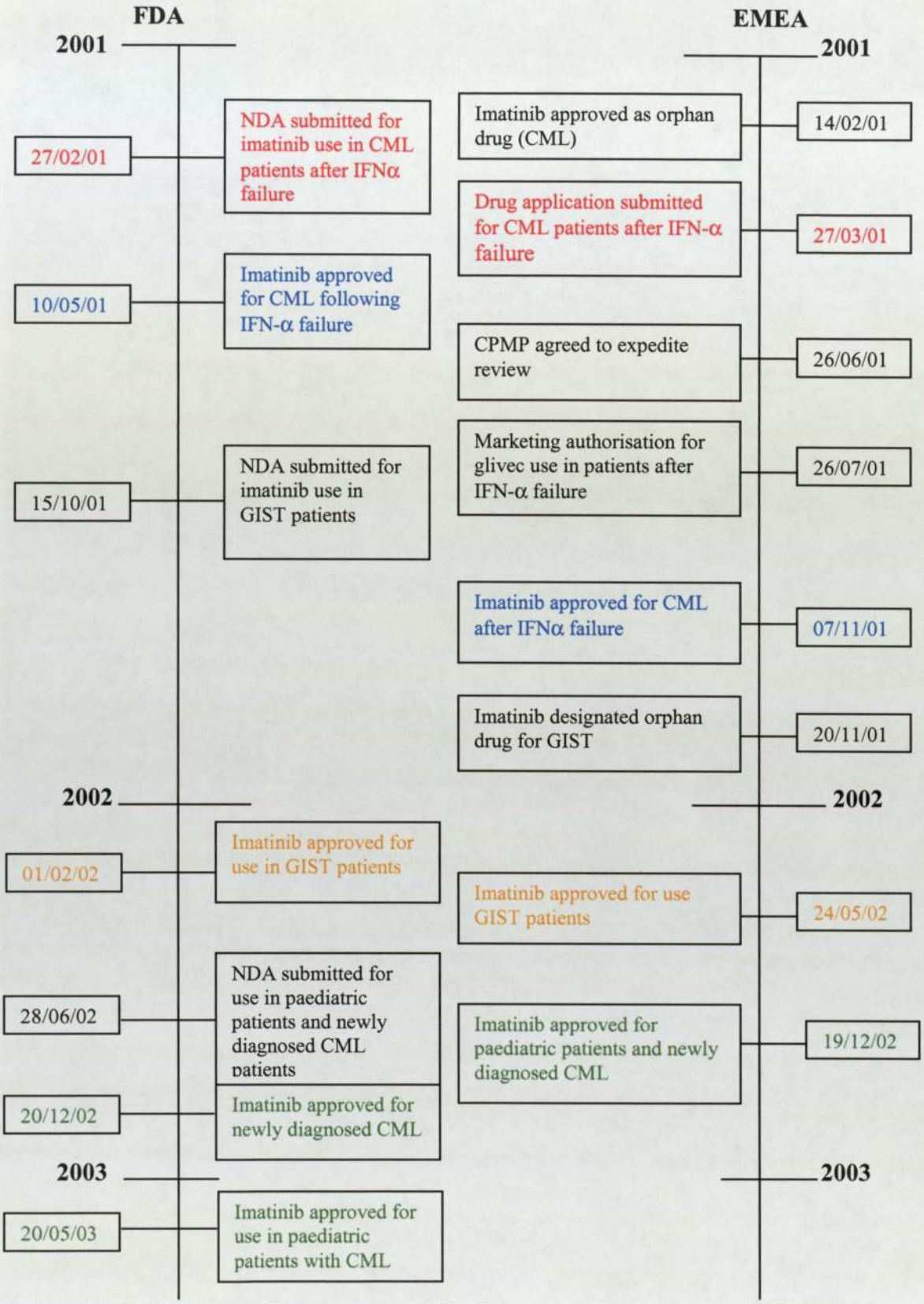

Figure 1.9.4.2, Timeline of key dates in marketing authorisation process of imatinib mesylate

Whilst the accelerated licensing of imatinib through various routes was granted due to proven efficacy for patients with no alternative treatment, there are many drawbacks such as the lack of evidence of proven safety over a prolonged period of time and in different patient populations.

The 'gold-standard' studies upon which licenses are generally granted are RCTs. Such studies have a longer duration and require a large group of patients. In the case of CML, the patient group is generally much smaller (orphan population), and at the time of this review, there was only one published RCT. The largest set of evidence of clinical efficacy at such an early stage post-drug licensing comes from uncontrolled trials (phase 1 and 2), or case-report/series data. There is no general methodology for assessing uncontrolled data, since the data is largely heterogeneous, and poses too much bias for adequate interpretation. Evidence-based pharmacotherapy is a useful tool to apply in situations in which the only available data is too diverse in quality and therefore difficult to interpret.

1.10 Evidence-based medicine

Evidence-based Medicine (EBM) is a relatively old concept, which has been brought to the forefront in the past two decades. It has been defined by Sackett and colleagues as 'the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external evidence from systematic research' (Sackett, DL et al, 1996).

Evidence-based medicine enables the clinician or other professional to make an informed decision about the care of an individual patient. The ultimate goal of EBM is to optimise the treatment given to the patient and subsequently improve the individual's quality of life.

There are a number of reasons for the recent revival of the concepts of EBM (Sackett, DL et al, 2000). Clinicians began to raise a number of concerns regarding patient care, some of which were:-

- need for valid information about diagnosis, prognosis, therapy (Osheroff, JA et al, 1991)

- inadequacy of traditional sources for this information (out-of-date, wrong, ineffective, too overwhelming or too variable) (Antman, EM et al, 1992; Oxman, AD et al, 1993; Davis, DA et al, 1995; Haynes, R et al, 1993)
- disparity between diagnostic skills and clinical judgement (Sackett, DL et al, 1977)
- inability to give sufficient time to patients to assimilate evidence or to pursue reading or study (Sackett, DL et al, 1998; Sackett, DL et al, 1996)

These issues have been addressed in some EBM related developments:-

- development of strategies for efficiently tracking down and appraising evidence (Sackett, DL et al, 2000)
- creation of systematic reviews and concise summaries of the effects of health care
- creation of information systems for bringing the foregoing rapidly
- creation of evidence-based journals of secondary publication
- identification and application of effective strategies for life-long learning and for improving clinical performance (Cochrane Effective Practice and Organisation of Care Group, 1999)

The quality of evidence is highly variable and it has been up to the reader to judge how useful the information of the study is to their question. This problem gave rise to defining the hierarchy of evidence which was an effort by Sackett and colleagues to grade material according to the level at which it reduces bias (Sackett, DL et al, 2000). Studies at the top of the hierarchy are thought to be the most reliable and the highest quality of evidence (Table 1.10.1).

Table 1.10.1, Hierarchy of evidence *(adapted from Jones, C et al 2002)*

- ***Systematic reviews and meta-analyses***
- ***Randomised controlled double blind trials***
- ***Cohort studies***
- ***Case control studies***
- ***Cross sectional surveys***
- ***Case series***
- ***Case reports***

1.10.1 Systematic reviews and meta-analyses

A systematic review is a critical assessment and evaluation of research that attempts to address a focussed clinical question using methods designed to reduce the likelihood of bias (Guyatt, G et al, 2002)

Research findings are often difficult to interpret due to the often contradictory nature across the studies and the varying quality of the evidence. Systematic reviews address this problem to some degree by establishing whether scientific findings are consistent and can be generalised across populations, settings, and treatment variations, or whether findings vary significantly by particular subsets (Mulrow, CD, et al, 1994)

A meta-analysis on the other hand is an overview that incorporates a quantitative strategy for combining the results of several studies into a single pooled or summary estimate. Meta-analysis can increase power and precision of estimates of treatment effects and exposure risks (Guyatt, G et al, 2002; Mulrow, CD, et al, 1994)

1.10.2 Advantages of EBM

The most noticeable attraction of EBM is that it enables the professional to base a decision, with regards to patient care, on relevant and up-to-date information. It is very effective in integrating education with clinical practice in order to deliver the best possible treatment options to the patients. EBM can also be used to involve patients in the decision making process.

EBM also encourages the practitioner to embark on a continuous professional education throughout their career, and therefore maintain an awareness of the most recent research developments. The clinician also obtains valuable skills such as focused, more productive reading habits, as well as data handling techniques. This is highly advantageous for the busy clinician who must have selective reading techniques to cope with the overwhelming literature available.

Another advantage of EBM is that it may be developed into guidelines by practitioners. This could result in more uniformed care for patients, as well as developing team communication amongst professionals to discuss such guidelines.

1.10.3 Limitations of EBM

The major disadvantage of EBM is that it takes a substantial amount of time to learn and master the techniques required for the process. It is also very expensive for a hospital or other resource centre to incorporate the necessary computer software, and subscriptions to the relevant databases.

Another issue concerning practitioners is that EBM exposes gaps in the evidence (Chalmers, I et al, 1992). This may be frustrating for the more inexperienced clinician, but may also be deemed advantageous as it could result in the generation of further research projects (Sheldon, T et al, 1994). The major limitation of EBM is that it is dependent on a primary source of literature, which may not provide sufficient evidence on which to base a valid decision.

2.0 Aims & Objectives

2.1 Study rationale

Imatinib has proven to be more effective than standard treatments for CML patients, and has resulted in remarkable responses in patients. This success enabled the drug to qualify for accelerated approval by licensing authorities without a thorough assessment of the risks that the drug carried. This thesis aims to determine the safety of imatinib in view of the evidence available.

2.2 Study objectives

The primary objective of this study is to systematically review the adverse events associated with the use of imatinib mesylate in CML patients.

The secondary objective of the study is to determine whether the frequency and severity of the observed adverse events is influenced by any identifiable factors. The dose of imatinib, disease stage of the patient, pre-treatment history of the patient and treatment duration with imatinib will be investigated.

3.0 Methods

3.1 Search Strategy for identification of studies

Searching for literature on adverse event data is often highly problematic and time-consuming (Derry, S et al 2001). Since imatinib has only been tested clinically for 7 years at the time of this research, searching by drug name revealed a manageable number (n=2021) of articles, which were then manually searched for toxicity information. Specific adverse events were not sought, since the drug has only been available for a short period and the most appropriate search terms were not known.

All clinical studies of imatinib use in chronic myeloid patients were searched using electronic databases. Both published and unpublished studies were sought.

INTERNET RESOURCES AND DATABASES

The following databases were searched for relevant literature to do the study: -

- Cochrane Library (http://www.cochrane.org/)
- Medline/PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi)
- Embase (http://www.embase.com/)
- Web of Science Proceedings (http://isi22.isiknowledge.com/portal.cgi)
- NLM gateway (http://gateway.nlm.nih.gov/gw/Cmd)
- Current Controlled Trials (http://www.controlled-trials.com/)
- National Cancer Institute inc. clinical trials.gov (http://clinicaltrials.gov/)
- The American Society of Hematology (annual meetings) (http://www.hematology.org/)
- American Society of Clinical Oncology (abstracts) (http://www.asco.org/)
- European Hematology Association (http://www.ehaweb.org/)

ADDITIONAL SITES SEARCHED

- Food and Drug Administration (FDA) (www.fda.gov)
- Novartis (http://www.novartis.com, www.glivec.com, www.gleevec.com)
- European Medicines Evaluation Agency (EMEA) (http://www.emea.eu.int/)
- National Institute of Health/National Cancer Institute US (http://www.nci.nih.gov/)
- National Institute for Clinical Excellence - NICE (http://www.nice.org.uk/)
- Medicines and Healthcare Regulatory Agency (MHRA) (http://www.mca.gov.uk/)

Additional searches of popular haematology journals such as Blood, The British Journal of Haemaology and Leukemia were also undertaken. All databases were searched for clinical studies of imatinib in CML until January 2005. The search process took two months to complete.

SEARCH TERMS

The terms imatinib, gleevec, glivec and STI571 were searched in PubMed. These were combined with CML, chronic myelogenous leukaemia, chronic myeloid leukaemia, chronic granulocytic leukaemia, chronic myelogenous leukemia, chronic myeloid leukemia and chronic granulocytic leukemia to retrieve all studies of imatinib use in CML patients. The search terms were then applied to the other databases used to complete the search.

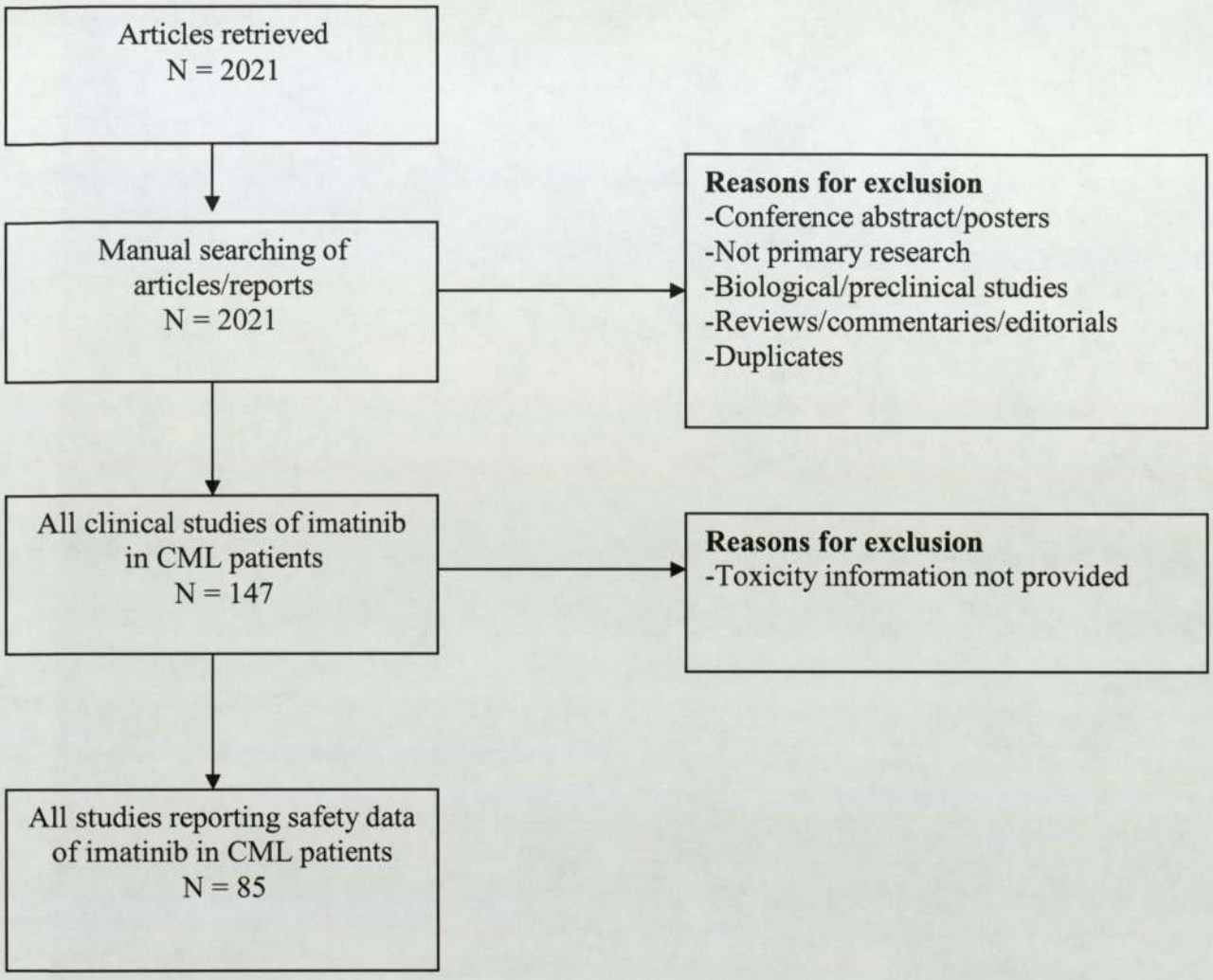

Figure 3.1, Flowchart demonstrating study selection

3.2 Inclusion and Exclusion Criteria

Studies which assessed frequency and type of possible adverse or unintended events occurring with imatinib treatment, irrespective of dose or disease stage were included. RCTs have some limitations such as insufficient information with respect to adverse events (Ioannidis, JP et al 1998; Ernst, E et al 2001). They are generally too small in sample size, and lack the long-term study duration required to determine long-term risks of taking drugs. A thorough review of adverse events therefore needed to go beyond traditional RCTs. As well as RCTs and controlled clinical trials (CCTs), case-control, case-crossover, cohort and case-only studies were also considered for inclusion. However, such studies carry varying levels of bias which should be considered when interpreting information derived from them.

3.3 Data extraction

Baseline characteristics, treatment details, study design and adverse event data on frequency and severity were extracted. In addition, information on the manner in which toxicity was reported was extracted to assess the study quality. Data was then converted to case numbers (from percentages in particular cases) and entered into Excel spreadsheets.

3.4 Quality assessments

Studies were assessed for their quality using recognised criteria. Systematic reviews included in the study were assessed using the Database for Abstracts of Reviews of Effectiveness (DARE) quality criteria (NHS Centre for Reviews and Dissemination, York 2000). The quality of RCTs was assessed using criteria based on CRD report no. 4 (NHS Centre for Reviews and Dissemination, York 2001). Uncontrolled or cohort studies were assessed using the checklists adopted by Crombie, I et al 1996. (See appendix 2 for criteria details).

3.5 Adverse event summaries

Adverse events were organised into categories for reviewing purposes. The National Cancer Institutes Common Toxicity Criteria (NCI-CTC) version 3 was used for categorising toxicities (Cancer Therapy Evaluation Program, 2003). These criteria were also used to assess severity of adverse events, where grade 1 generally describes mild events, with increasing toxicity to grade 5

which describes death due to an adverse event (refer to Appendix 3). The NCI-CTC criteria were used most commonly by the studies selected for the review.

The World Health Organization (WHO) criteria were applied to grade the frequency of adverse events (International drug monitoring, WHO 1972). The definition for frequency is:

- Very common >1/10
- Common >1/100 and <1/10
- Uncommon >1/1,000 and <1/100
- Rare >1/10,000 and <1/1,000
- Very rare <1/10,000

3.6 Data synthesis

Due to a lack of suitable randomised evidence, meta-analyses have not been performed in this review. Meta-analyses require a degree of homogeneity amongst the studies included. Since the studies included in this thesis are largely heterogenous, data are described through narrative and summarised in tables.

4.0 Results

4.1 Introduction and Objectives

The results of this review are divided into two parts. The first section describes all of the adverse events observed in CML patients, using the available literature. Each type of clinical study (i.e, RCT, uncontrolled study, case-report) will be summarised for quality primarily, followed by a summary of the adverse events presented by it.

The second section describes the most common events reported in section one; various factors such as patient populations (e.g, disease stage) and treatment regimes (e.g, dosage) will be investigated to determine whether specific factors influenced the frequency or severity of these events.

4.2 Study Characteristics

A total of 34 clinical trials contained adverse events data relating to imatinib use in CML patients. Excluded trials (n=7) and reasons for exclusion are detailed in Appendix 4.

Of the 27 clinical trials included in the analysis, 26 were uncontrolled clinical trials, 1 was a randomised controlled trial (table 4.2.1). In addition, a total of 56 case reports/series were identified and included in the review. The phases of development of the clinical studies are detailed in figure 4.2.1. Two systematic reviews considered the clinical effectiveness and cost-effectiveness of imatinib for treatment in CML. The reviews analysed preliminary data from individual studies previously identified by the defined search criteria of this thesis. This data was not excluded since systematic reviews provide the most comprehensive approach to searching and disseminating information. The systematic reviews did not identify studies that the review in this thesis did not find. Systematic reviews were examined initially, and those that duplicated individual studies were highlighted. The summaries of the systematic reviews are followed by the summaries of individual study data.

Table 4.2.1, Summary of the studies included in the review for adverse events and the safety of imatinib mesylate. N = total number of studies.

Design	Objectives or type of study			Total
	Incidence of adverse events	Investigating specific aspects of the safety profile	Individual cases of adverse events	
RCT	N = 1	-	-	**N = 1**
Uncontrolled	N = 23	N = 3	-	**N = 26**
Case series	-	-	N = 56	**N = 56**
Total	**N = 24**	**N = 3**	**N = 56**	**N = 83**

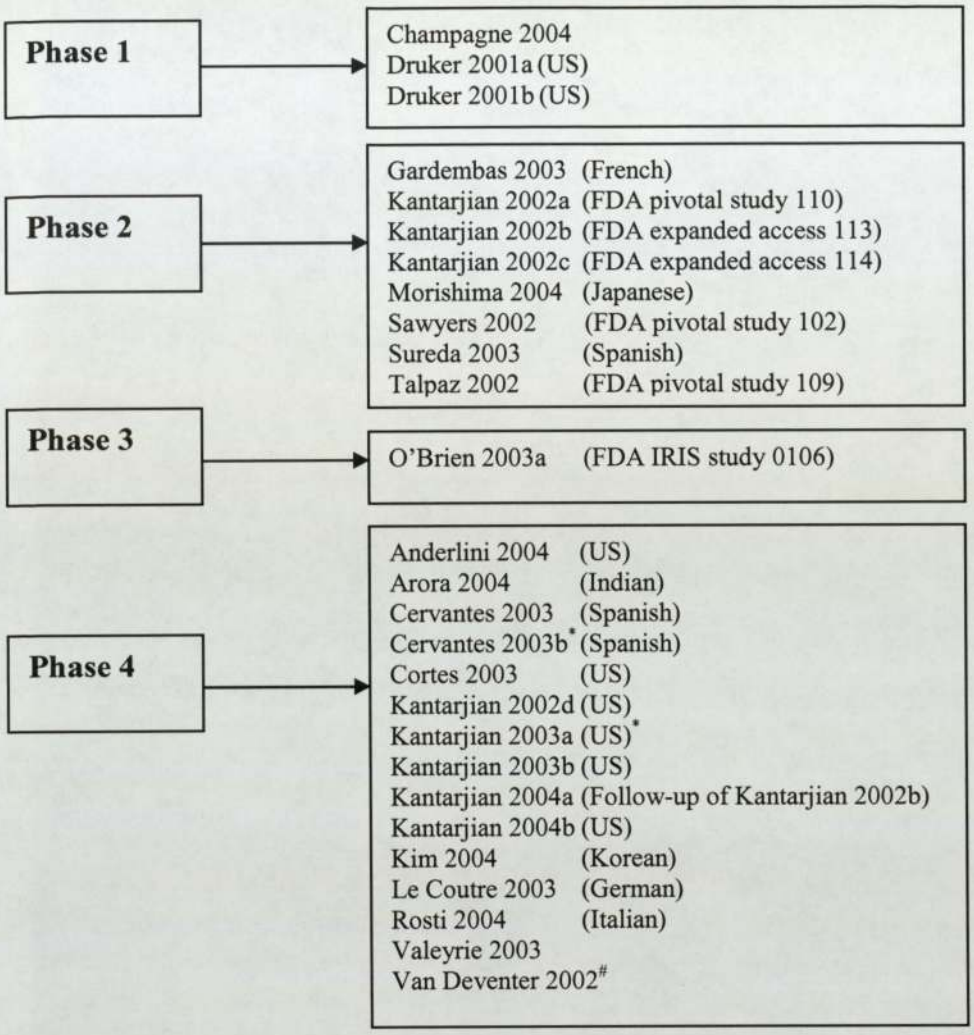

Figure 4.2.1, Studies undertaken during the different phases of development of imatinib

Note: The country in which the study took place is given for informative purposes. Those not indicated took place internationally. *These studies included patients previously treated in the Kantarjian 2002b study. # This study included patients from the Kantarjian 2002c study.

4.3 Systematic reviews

4.3.1 Description of systematic reviews

Two systematic reviews which included data on the adverse events of imatinib in CML were identified. They were both Health Technology Assessments, with the second review updating the first review. The quality of the systematic reviews of effectiveness and/or side-effects have been

assessed using criteria developed for DARE (NHS Centre for Reviews and Dissemination, 2005) (See appendix 6).

4.3.2 Quality of systematic reviews

The primary objective of both reviews was clinical effectiveness and cost-effectiveness rather than risk or harm. The first published systematic review by Garside and colleagues in 2002 was undertaken shortly after the license for imatinib use was granted, and therefore included little clinical data to use for the analysis (Garside, R et al, 2002). The review considered the 3 pivotal phase 2 studies (Kantarjian, H et al, 2002a; Talpaz, M et al, 2002; Sawyers, CL et al, 2002), prior to their publication, and compared these findings with previous studies of IFN-α. No case reports or other material were included as part of the analysis, presumably due to the high level of bias associated with such studies. The review met most of the defined criteria for quality (see appendix 6). The searches were comprehensive for both published and unpublished literature; the studies included were all unpublished at the time of the review. The inclusion and exclusion criteria were applied by one author and checked by another. Similarly, the data extracted was verified by a second author. Validity was described in detail by the author, although it was not clear whether it was synthesised in the interpretation of the findings. Validity was described only in the results section and was not referred to in the discussion or the conclusion of the study findings.

In terms of the adverse events, the review summarised the key finding of the three studies used in the analysis in tabulated form and through narrative. Quantitative synthesis of the incidence of the various side-effects was not undertaken.

The second systematic review (Dalziel, K et al, 2004) updated the first review and had similar aims and objectives to the study by Garside and colleagues. Again, the review was of good quality in terms of the data extraction, validity, exclusion and inclusion criteria. These were all checked independently by secondary authors. The search included only studies that were randomised and therefore only looked at the one RCT available at the time of the review (O'Brien, SG et al, 2003a). The review also allowed the inclusion of observational data. Adverse event data from the RCT was presented in detail and described in tables and in narrative.

Observational data was tabulated and described briefly. The review did not include any phase 2 data. Again, the data was presented qualitatively due to the lack of sufficient trial information.

4.3.3 Adverse events data from systematic reviews of imatinib mesylate

The systematic reviews included preliminary data to a number of studies included in the review undertaken in this thesis. The data provided by the systematic reviews was unpublished at the time of submission of the assessments. This information was assessed independently to avoid duplication of results. The review by Garside and colleagues reported that the main side-effects from imatinib in CML patients were nausea, vomiting and leukopenia or neutropenia (Garside, R et al, 2002). Serious adverse events (grades 3 and 4) as defined by the National Cancer Institute Common Toxicity criteria, that led to drug interruption or discontinuation included haematologic events such as leukopenia, neutropenia, thrombocytopenia and anaemia. Nausea and vomiting were the most common problems, although they were less serious as shown in table 4.3.1. The review showed that imatinib resulted in higher rates of all toxicities with the exception of myalgia/flu symptoms and fatigue/lethargy than IFN-α. Despite these findings, the review concluded than imatinib was better tolerated than the control drug (IFN-α) since a larger proportion of patients withdrew from IFN-α as opposed to imatinib. The study showed that imatinib caused a lower drop-out in all study phases than IFN-α (Table 4.3.2).

Table 4.3.1, Percentage incidence of the most common adverse events in CML patients across different grades of severity. * denotes that this event was only observed in two of the studies. All other adverse events were described in all three pivotal studies *(Garside, R et al, 2002).*

Adverse effect	All grades Median %		Grades 3 and 4 Median % (range)	
	Imatinib	IFN-α	Imatinib	IFN-α
Nausea/vomiting	62%	16.5%	2%	1%
Leukopenia/neutropenia	58%	35%	58%	5%
Oedema	54%	3%	3%	0%
Thrombocytopenia	43%	26%	43%	13%
Anaemia	37%	27%	37%	4%
Diarrhoea	29%	10.5%	0.6%	3%
Dermatological	22%	4.5%	2%	1%
Myalgia/flu symptoms	14%	32.5%	0.6%*	4%
Fatigue/lethargy	9.5%*	30%	0.7%*	2.5%

Table 4.3.2, Withdrawal due to adverse effects on treatments for CML *(Garside, R et al, 2002).*

Study	Number (%) of patients withdrawing due to adverse effects
Chronic phase – imatinib	
Kantarjian 2002a	9/532 (1.7)
Chronic phase – IFN-α	
Alimena 1996	3/114 (3)
Arthur 1993	1/30 (3)
Baccarani 1998	39/218 (18)
Brouset 1992	6/24 (25)
Fernandez-Ranada 1993	6/51 (12)
Freund 1989	2/27 (7)
Giles 1992	3/23 (13)
Guilhot 1997	97/361 (27)
Hehlmann 1994	24/133 (18)
Kantarjian 1991	3/32 (9)
Mahon 1996	5/81 (6)
Mahon 1998	12/116 (10)
O'Brien 1995	7/71 (10)
Sanchez 1992	0/29 (0)
Schofield 1994	0/41 (0)
Talpaz 1987	6/51 (12)
Thaler 1997	16/91 (18)
The Benelux study1998	24/100 (24)
Accelerated/blast phase imatinib	
Sawyers 2002	13/260 (5)
Talpaz 2002	6/235 (3)
Accelerated/blast phase IFN-α	
Kantarjian 1991	4/20 (20)

The second review by Dalziel and colleagues looked at the adverse event profile of RCT and observational data separately (Dalziel, K et al, 2004). It concluded that the most common adverse events from the RCT related to imatinib were gastrointestinal, musculoskeletal and skin events (Table 4.3.3). The table also categorised adverse events under headings such as 'general disorders' and 'investigations'. It is not known what these category of events described since the review did not provide a discussion of such events. Imatinib was shown to be better tolerated than IFN-α. Specifically, the most common adverse events related to imatinib were shown to be nausea, muscle cramps, fatigue and diarrhoea. This review did not include any information with regards to haematologic adverse events unlike the systematic review by Garside and colleagues (Garside, R et al 2002).

Table 4.3.3, Percentage incidence of adverse events in CML patients across different severity grades. (Affecting at least 10% of either treatment group, as indicated by study) *(Dalziel, K et al, 2004).*

Adverse events	All grades %		Grades 3 or 4 (%)	
	Imatinib n = 551	IFN-α + Ara-C n = 553	Imatinib n = 551	IFN-α + Ara-C n = 553
Nausea	42.5	60.8	0.4	5.1
Muscle cramps	33.4	8.6	0.7	0.2
Fatigue	30.7	64.7	1.1	24.0
Diarrhoea	30.3	40.9	1.3	3.2
Headache	28.5	41.8	0.4	3.2
Arthralgia	26.3	38.3	2.2	6.8
Periorbital oedema	25.8	1.1	0.2	0
Myalgia	20.7	38.5	1.5	7.7
Rash	19.8	14.4	1.3	1.1
Nasopharyngitis	19.2	7.7	0	0.2
Oedema peripheral	15.8	3.9	0.2	0
Dyspepsia	15.1	9.0	0	0.8
Pain in limb	14.7	15.0	1.1	2.6
Vomiting	14.7	26.6	0.9	3.4
Back pain	14.5	18.6	0.9	2.4
Pharyngolaryngeal pain	14.2	11.4	0.2	0
Dizziness	13.2	23.1	0.5	3.4
Cough	12.5	21.6	0.2	0.6
Upper respiratory tract infection	12.5	7.9	0.2	0.4
Pyrexia	11.8	38.6	0.5	2.8
Weight increase	11.6	1.5	0.7	0.2
Insomnia	11.4	18.4	0	2.3
Abdominal pain	10.3	10.3	1.1	1.9
Abdominal pain upper	9.6	12.2	0.5	1.5
Depression	8.9	34.7	0.5	12.4
Bone pain	8.0	14.6	0.9	3.0
Constipation	7.6	13.9	0.7	0.2
Rigors	6.9	33.8	0	0.8
Anxiety	6.5	10.9	0.2	2.6
Dyspnoea	6.5	14.4	1.3	1.7
Pruritus	6.5	11.3	0.2	0.2
Influenza-like illness	6.4	18.4	0	1.1
Night sweats	6.4	15.0	0.2	0.4
Anorexia	4.7	31.3	0	2.4
Sweating increase	3.3	14.4	0	0.4
Alopecia	2.2	14.6	0	0.2
Weight decrease	2.2	16.9	0	1.1
Asthenia	1.6	10.9	0	1.9
Dry mouth	1.6	10.3	0	0.2
Mucosal inflammation	0.7	10.1	0	3.2

4.3.4 Summary of findings from systematic reviews of imatinib mesylate

The two published reviews analysed different sets of data that described adverse events associated with imatinib in CML patients (Garside, R et al 2002; Dalziel, K et al). The study by Garside and colleagues concluded that imatinib had a greater frequency of all toxicities with the exception of myalgia/flu symptoms and fatigue/lethargy compared to IFN-α. The study stated that imatinib was better tolerated than the control treatment since patients treated with IFN-α had an increased withdrawal rate from the studies (Garside, R et al 2002). The study by Dalziel and colleagues concluded that imatinib had a better toxicity profile than the comparative treatment; IFN-α. The main adverse events were gastrointestinal, musculoskeletal and skin disorders (table 4.3.4). Haematologic events were not described in this systematic review.

Table 4.3.4, Most frequently reported adverse events associated with imatinib by organ system (affecting more than 15% of either treatment group – IFN-α group not shown) *(Dalziel, K et al, 2004)*

Organ system class	All grades (%)	Grades 3 or 4 (%)
Gastrointestinal disorders	73.3	6.0
Musculoskeletal disorders	71.0	6.5
Skin and subcutaneous disorders	60.8	2.9
General disorders	59.3	3.3
Infections and infestations	55.2	3.6
Nervous system disorders	46.3	3.4
Respiratory/thoracic disorders	40.5	2.0
Eye disorders	30.1	1.3
Psychiatric disorders	25.2	0.9
Investigations	24.7	4.4
Metabolic and nutritional disorders	18.0	1.6
Vascular disorders	11.3	1.8
Any event	**98.0**	**41.0**

The case-reports were reviewed separately and these studies highlighted that oedema and skin reactions were potentially serious adverse events associated with imatinib use (Table 4.3.5).

Table 4.3.5, Summary of adverse reactions related to imatinib in case reports/case-series *(Dalziel, K et al, 2004).*

Study	Adverse events	No. of patients
Etienne 2002	Hair repigmentation	9
Drummond 2003	Rash	8
Milojkovic 2002	Dermatosis	11
Ebnoether 2002	Cerebral oedema	2
Barton 2002	Cardiac tamponade	1
Vidal 2002	Steven-Johnson syndrome	1
Lim 2002	Oral lichenoid reaction	1
Esmaeli 2002	Periorbital oedema	1
Konstantopoulos 2002	Pityriasis rosea	1
Brouard 2001	Cutaneous reaction	1
Ohyashiki 2002	Focal necrosis	1

4.4 Randomised Controlled Trials (RCTs)

4.4.1 Description of RCTs of imatinib

There was one RCT included in this review. The International Randomised Study of interferon + Ara-C vs. STI571 in CML (IRIS) was published in 2003 and was a phase three study comparing imatinib to the standard treatment of IFN-α plus low-dose cytarabine for newly diagnosed CML patients in the chronic phase of the disease (O'Brien, SG et al, 2003a). This is the same study that was included in the systematic review by Dalziel and colleagues (2004). The study was unpublished at the time of its inclusion in the systematic review however. Patients were randomised to receive either imatinib or the control in this prospective, multicentre, open-label, international study. The primary endpoint of the study was disease progression, the secondary endpoints were rates of response, safety and tolerability. Crossover to the alternative treatment arm was permitted in specific circumstances, as defined by the study.

4.4.2 Quality of RCT of imatinib

The IRIS study met most of the quality criteria defined for RCTs, such as randomisation and drug allocation procedures, and comparable inclusion/exclusion criteria etc (see Appendix 6). Novartis benefited greatly from the fast-track and accelerated approval processes of the FDA,

which gave regular feedback regarding the design and conduct of the study. Endpoints, and outcome measures were all agreed upon prior to the study initiation, and were based upon previous studies which validated their use in other CML drugs.

INTERNAL VALIDITY

Sample size

A total of 1106 patients were included in the study. 553 patients were randomised to receive imatinib and 553 were randomised to receive IFN-α plus Ara-c. The sample size was calculated prior to the study, based on projected differences in progression rates. The primary outcome measure was time to progression (with the 5-year progression-free rate on the control arm expected to be 50% compared with 60% for the imatinib group). The authors aimed to detect a relative hazard ratio (ratio between the predicted hazard for imatinib vs control group) of 0.75 for the imatinib group.

Based on this ratio, approximately 822 patients needed to be randomised with an allowance of 10% annual dropout. The target for recruitment was 1032. This was accepted by the FDA as sufficient power for both the primary outcome measure of progression and the secondary outcome measure of major cytogenetic response.

Selection bias

Patients were randomly assigned to receive either imatinib or the control. Individual investigators used a computerised telephone system for randomisation, and no blocking was used. The method used to generate the randomised sequences was not reported. The imatinib and control group had similar baseline characteristics: age, gender, weight, ECOG status, Sokal and Hasford scores were not significantly different. The only significant difference in the base-line characteristics was that more patients in the imatinib group had chromosomal abnormalities in addition to the Philadelphia chromosome than the control group.

Performance bias

Performance bias was difficult to assess since there was little description of the care provided. The study was open-label due to the nature of the drug administration; imatinib was to be administered orally whereas IFN-α plus cytarabine required regular subcutaneous injections of the two drugs. Concurrent treatments were not described in detail.

Detection bias

The outcome measures for the IRIS study were well defined in the protocol, so there was little room for detection bias. The only area likely to be exposed to detection bias were the subjective measures of intolerance and quality of life. Due to the crossover study design, patients and investigators were both likely to have contributed to some level of bias. For instance, assessments of quality of life and intolerance were done at the time of patient crossover. If patients thought that a poor result would enable them to crossover, this would inevitably lead to bias, as would a situation in which the investigator thought crossover would be better for the patient. The study did show that most patients who discontinued after withdrawing consent were in the combination-therapy group and did so when the FDA approved imatinib (May 2001), presumably to receive imatinib outside the confines of the study.

Attrition bias

All of the patients enrolled onto IRIS were accounted for. Withdrawals, treatment discontinuation and crossovers were described. The reasons for treatment discontinuation were also documented. More patients in the control group discontinued treatment. Due to the crossover design, it is likely that there were systematic differences between the two groups who discontinued. Institutions may have been rewarded financially for treating patients with imatinib: IFN-α + Ara-C was provided by healthcare budgets whereas imatinib was funded by its manufacturer Novartis. Due to the significantly higher rate of patient dropout or crossover in the control group, the study was highly prone to attrition bias.

An intention-to-treat (ITT) analysis was undertaken by the authors regardless of whether crossover occurred, which was necessary due to the attrition bias.

Reporting bias

The study reported confidence intervals, survival and point estimates. The data was collected with the use of data-management and statistical-support systems of Novartis. Analysis and interpretation of the data was done by a statistician from Novartis in close collaboration with the investigators.

EXTERNAL VALIDITY

The authors made an effort to make the study generalisable. The inclusion and exclusion criteria were well described and the baseline characteristics were detailed. Patients were recruited from 16 countries in 177 centres. Patients were predominantly from the US. The patients were newly diagnosed and were therefore likely to be at a less advanced stage than other previous studies with the control treatment. As such, the study is generalisable to a newly diagnosed population or patients in the chronic phase of CML.

4.4.3 Adverse events data from RCT of imatinib mesylate

Adverse events were reported for patients who had received at least one dose of either intervention. The imatinib group included 551 patients, and the control group included 553 patients. Adverse events included conditions that worsened from base line or developed during initial treatment in more than 10% of the patients.

Both of the groups experienced adverse events relating to treatment. Imatinib was shown to be better tolerated than IFN-α + Ara-C: there were fewer, less serious events in the imatinib group. The most common adverse events in the imatinib group were haematologic, gastrointestinal, musculoskeletal and skin complications (Table 4.4.1). In the control group, haematologic and gastrointestinal events were also the most commonly observed problems. Within these categories however, the actual frequency of adverse events were quite different in the two groups. For instance, anorexia was nearly 6 times higher in the IFN-α + Ara-C group compared to the imatinib group, whereas weight gain was more common in the imatinib treated patients. There was a greater crossover to the imatinib arm from the control group, indicating a poorer tolerability to IFN-α + ara-C (Table 4.4.2). The most common adverse events in the imatinib group were neutropenia, thrombocytopenia, superficial oedema and anaemia. The group treated with IFN-α + ara-C showed that thrombocytopenia, neutropenia, fatigue and nausea were the most common complications.

Table 4.4.1, Adverse event profile of imatinib in IRIS RCT in newly diagnosed CML patients. *Adverse events included conditions that worsened from baseline or developed during initial treatment in more than 10% of the patients and were graded according to the NCI-CTC *(O'Brien, SG, et al, 2003a)*

Adverse event	All grades (%)		Grades 3 or 4 (%)	
	Imatinib n = 551	IFN-α + Ara-C n = 553	Imatinib n = 551	IFN-α + Ara-C n = 553
Neutropenia	60.8	67.2	14.3	25.0
Thrombocytopenia	56.6	78.6	7.8	16.5
Superficial oedema	55.5	9.2	0.9	0.6
Anemia	44.6	54.8	3.1	4.3
Nausea	43.7	61.4	0.7	5.1
Muscle cramps	38.3	11.1	1.3	0.2
Musculoskeletal pain	36.5	42.0	2.7	8.3
Rash	33.9	25.0	2.0	2.3
Fatigue	34.5	65.5	1.1	24.4
Diarrhoea	32.8	41.7	1.8	3.2
Headache	31.2	42.6	0.4	3.2
Joint pain	28.3	39.6	2.4	7.3
Abdominal pain	27.0	24.6	2.4	3.9
Nasopharyngitis	22.0	8.3	0	0.2
Myalgia	21.4	38.8	1.5	8.1
Haemorrhage	20.9	20.6	0.7	1.5
Vomiting	16.9	27.4	1.5	3.4
Dypepsia	16.2	9.2	0	0.8
Pharyngolaryngeal pain	16.0	13.3	0.2	0.2
Cough	14.5	22.3	0.2	0.6
Dizziness	14.5	23.8	0.9	3.4
Upper respiratory tract infection	14.5	8.3	0.2	0.4
Weight gain	13.4	1.7	1.7	0.2
Pyrexia	13.1	39.2	0.7	2.8
Insomnia	12.2	18.8	0	2.3
Depression	10.2	35.5	0.4	12.8
Constipation	8.5	14.3	0.7	0.2
Anxiety	7.3	11.4	0.2	2.6
Dyspnea	7.3	14.3	1.5	1.5
Pruritus	7.3	11.6	0.2	0.2
Rigors	7.3	33.8	0	0.8
Influenza-like illness	7.1	18.6	0	1.1
Night sweats	7.1	15.6	0.2	0.4
Asthenia	5.6	18.6	0.2	3.9
Anorexia	5.3	31.7	0	2.4
Alopecia	4.4	22.3	0	0.6
Increased sweating	3.6	14.8	0	0.4
Weight loss	3.1	17.1	0.2	1.3
Stomatitis	2.9	12.0	0	0.2
Dry mouth	2.2	10.3	0	0.2
Mucosal inflammation	0.7	10.3	0	3.2

4.4.4 Summary of findings from RCT of imatinib mesylate

The IRIS study was of good quality as defined by the CRD report no. 4 criteria for quality assessment (NHS Centre for Reviews and Dissemination, York 2001), and showed that imatinib was better tolerated than IFN-α + Ara-C. The crossover design of the study may have resulted in bias and should be considered when assessing the toxicity in the two treatment groups.

The findings from IRIS showed that haematologic and gastrointestinal events were the most frequently observed in both the imatinib and the control group of patients. The results were not consistent with those of the systematic reviews undertaken by previous authors. The IRIS study was reviewed in the systematic review by Dalziel and colleagues and showed variations between the values described in the published RCT (Dalziel, K et al 2004; O'Brien, SG et al 2003a). The systematic review did not provide any data or discussion regarding haematologic events, which was a key finding in the published study. The frequency of adverse events was also lower in the unpublished IRIS study assessed in the systematic review, indicating that the data was preliminary (Dalziel, K et al 2004).

Table 4.4.2, Patients' treatment status as of 31/07/2002 in IRIS study *(O'Brien, SG et al, 2003a)*

Variable	Imatinib group (n = 553)	IFN-α + Ara-C (n = 553)
Continued initial treatment	474	60
Discontinued initial treatment	68	175
Adverse events	12	33
Disease progression	18	29
Proceeded to allograft transplantation	8	7
Protocol violation	10	17
Withdrew consent	12	75
Lost to follow-up	2	6
Died	6	2
Crossed over to alternative treatment	11	318
Disease progression		
Increase in white-cell count	2	25
Loss of CHR	3	28
Loss of MCR	1	10
Reason other than disease progression		
Intolerance of treatment	4	136
No CHR at 6 months	0	41
No CHR or MCR at 12 months	1	53
Continued alternative treatment	6	284
Discontinued alternative treatment	5	34

4.5 Uncontrolled Clinical Trials

4.5.1 Description of uncontrolled trials of imatinib mesylate

A total of 26 of the studies which met the inclusion criteria were uncontrolled and were undertaken during different stages of drug development (see table 4.2.2). Some of the reports included patients from other studies, such as those described by Kantarjian, HM et al, 2003a and Cervantes, F et al, 2003b, which enrolled patients treated in the phase 2 study by Kantarjiian, HM et al, 2002a. The patients were treated further, following different protocols. The primary outcome measures and objectives of the studies were different across the studies, with some emphasising toxicity specifically and others investigating efficacy primarily. Some of the studies included patients with different disease conditions (ALL). These studies were included in the systematic review since ALL is phenotypically similar to the blast crisis of CML. None of these studies provided a breakdown of adverse events in this particular population of patients. A detailed description of the uncontrolled trials is given in table 4.5.1.

4.5.2 Quality of uncontrolled studies

As expected, the quality of the uncontrolled clinical trials were varied (see appendix 6). Uncontrolled trials lead to bias since there is no direct comparison for the new treatment, and the clinician is able to decide who may enter the centre at his or her discretion. This results in an increased likelihood of problems such as selection and attrition bias. Any conclusions or interpretations that arise from these studies would be affected by this bias, and flaws in the design of the study must be considered when making assumptions based on such evidence. Nevertheless, it is important to use as much information as possible to make an informed decision with respect to the adverse event profile of the drug. The quality of the 3 pivotal phase 2 studies has been assessed previously in the systematic review by Garside and colleagues (Garside, R et al, 2002). The authors discussed the trials bearing in mind the standard concerns of RCTs, i.e the internal and external validity of the studies.

Table 4.5.1, Identified uncontrolled studies and their characteristics

Study	Outcomes measures	No. of patients	Patient age	Disease	Stage	Daily dose (mg)	Treatment duration/follow-up (days)	Pretreatment status
Anderlini 2004	Efficacy, safety	15	16-69	CML = 8 ALL = 6 AML = 1	NR	100 - 400	365	Patients received imatinib in first 100 days after SCT (allo-SCT, n=14, auto-SCT, n=1). Range of days of imatinib initiation after SCT was 16-37
Arora 2004	Safety	118	NR	CML	CP = 79 AP= 22 BP= 17	400/600	Median 180	NR
Cervantes 2003a	Efficacy, safety	98	NR	CML	CP	400	Median 420	Patients were in two groups, 33 had undergone a previous ASCT & had failed or were intolerant to interferon. Data compared to 65 patients from historical group who were resistant or intolerant to IFN-α without a previous ASCT
Cervantes 2003b	Efficacy, safety	150	16-79 Median 53	CML	CP	400	Median 395	Resistant or intolerant to IFN- α
Champagne 2004	Efficacy, pharmacokinetics, safety	31	3-20 Median 14	CML=20 AML = 1 ALL =10	CP = 14 BP = 6	260 - 570	NR	Two thirds had received multiagent systemic chemotherapy & 13 had prior haematopoietic SCT
Cortes 2003	Efficacy, safety	36	30-75 Median 47	CML	CP	800	Median 480	Failure on IFN-alpha. 13 patients had received other therapies, 4 had CE
Druker 2001a	Efficacy, pharmacokinetics, safety	83	19-76 Median 55	CML	CP	25-1000	Median 310	Patients who had failed IFN-α
Druker 2001b	Efficacy, safety	58	24-76 Median 48	CML, ALL	BP = 38 ALL =20	300-1000	Median 74	16 patients with CML & 7 with ALL had received previous therapy
Gardembas 2003	Efficacy, safety	30	22-81 Median 48	CML	CP	400	Median 365	Patients within 6 months of diagnosis and only been treated with HU
Kantarjian 2002a	Efficacy, safety	532	18-81 Median 57	CML	Late-CP	400	Median 513	Patients who had failed IFN-α
Kantarjian 2002b	Efficacy, safety	261	Age atleast 60 = 34%	CML	CP	400	Median 510	Patients who had failed IFN-α
Kantarjian 2002c	Efficacy, safety	237	18-82 Median 50	CML	AP	400/600	Median 246	Previously treated with IFN-α, with or without cytarabine, ASCT, HHT, HU
Kantarjian 2002d	Efficacy, safety	28	25-64 Median 43	CML	All phases	400-1000	Median 480	Patients who had relapsed after ASCT
Kantarjian 2003a	Efficacy, safety	54	24-77 Median 58	CML	CP	600/800	Median 390	Patients who had failed IFN-α

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; AP, accelerated phase; Ara-C, cytarabine; ASCT, allogenic stem cell transplantation; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; HHT, homoharringtonine; HU, hydroxyurea; NR, not reported; SCT, stem cell transplantation.

Table 4.5.1, Identified uncontrolled studies and their characteristics (continued)

Study	Outcomes measures	No. of patients	Patient age	Disease	Stage	Daily dose (mg)	Treatment duration/follow-up (days)	Pretreatment status
Kantarjian 2003b	Efficacy, safety	50	15-79 Median 48	CML	Early CP	400	Median 270	15 patients had no prior therapy; 35 had received HU and 2 had received IFN-α
Kantarjian 2004a	Efficacy, safety	261	Atleast 60 = 34%	CML	CP	400	Median 1350	Patients who had failed IFN-α
Kantarjian 2004b	Efficacy, safety	114	17-84 Median 48	CML	Early CP	800	Median 450	50 patients had received other therapies (IFN-α and HU)
Kim 2004	Efficacy, safety	13	31-56 Median 33	CML	CP = 7 AP-CE = 6	400	Median 351	Relapse after transplantation
Le Coutre 2003	Efficacy, safety	39	23-80 Mean 56	CML	CP	400	Mean 211	Patients who had failed IFN-α
Morishima 2004	Efficacy, safety	39	23-71 Median 56	CML	CP	400	Median 237	Patients pretreated with IFN-alpha
Rosti 2004	Efficacy, safety	191	NR	CML	Late CP	400	Median 780	Patients who had failed IFN-α. All patients had also received HU. 57 had low-dose arabinosyl cytosine & 13 had busulfan
Sawyers 2002	Efficacy, safety	260	19-81 Median 56	CML	BP	400/600	Median 93	Patients were treated previously for advanced CML
Sureda 2003	Efficacy, safety	30	18-72 Median 50	CML = 24 ALL = 6	CML-BP	600	NR	Previously treated with HU, busulfan, IFN-α
Talpaz 2002	Efficacy, safety	235	22-86 Median 57	CML	AP	400/600	Median 315	Patients who had failed IFN-α
Valeyrie 2003	Safety	54	NR	CML, ALL	All phases	400-800	Mean 126	Patients who had failed IFN-α
Van Deventer 2002	Efficacy, safety	28	Mean 59	CML	AP	600	Median 238	Previously treated for disease – washout periods before imatinib therapy stated

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; AP, accelerated phase; Ara-C, cytarabine; ASCT, allogenic stem cell transplantation; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; HHT, homoharringtonine; HU, hydroxyurea; NR, not reported; SCT, stem cell transplantation.

Table 4.5.2, Key study features of uncontrolled trials

Study	Inclusion/exclusion criteria	Baseline patient characteristics	Treatment regimen
Anderlini 2004	✗	✗	✗
Arora 2004	✗	✗	✓
Cervantes 2003a	✓	✓	✓
Cervantes 2003b	✓	✓	✓
Champagne 2004	✓	✗	✓
Cortes 2003	✓	✓	✓
Druker 2001a	✓	✓	✓
Druker 2001b	✓	✓	✓
Gardembas 2003	✓	✓	✓
Kantarjian 2002a	✓	✓	✓
Kantarjian 2002b	✓	✓	✓
Kantarjian 2002c	✓	✓	✓
Kantarjian 2002d	✓	✓	✓
Kantarjian 2003a	Referenced	✓	✓
Kantarjian 2003b	✓	✓	✓
Kantarjian 2004a	✓	✓	✓
Kantarjian 2004b	✓	✓	✓
Kim 2004	Referenced	✓	✓
Le Coutre 2003	✓	✗	✓
Morishima 2004	✓	✓	✓
Rosti 2004	✓	✗	✓
Sawyers 2002	✓	✓	✓
Sureda 2003	✓	✓	✓
Talpaz 2002	✓	✓	✓
Valeyrie 2003	✗	✗	✓
Van Deventer 2002	✓	✗	✓

✗ indicates information not provided; ✓ indicates information provided

INTERNAL VALIDITY

Selection bias

Details of the selection process of patient entry into the trials were not given for any of the studies. One study stated that imatinib was given entirely at the discretion of their attending physician (Anderlini, P et al, 2004), whilst it is unclear whether eligible patients were invited to participate in all of the other studies. Admittance to a study at the investigators discretion would lead to a bias since it is likely that patients may be selected according to their likelihood of achieving more favourable results. The study by Arora and colleagues did not provide any details about the study design, inclusion or exclusion criteria (Arora, B et al, 2004). Selection bias could not be determined due to a lack of reporting of crucial study features. Two of the pivotal phase 2 studies stated in the exclusion criteria that 'any patients were also excluded from enrollment if they had a history of noncompliance with therapy or if they were considered by the

investigator to be potentially unreliable with respect to compliance' (Sawyers, CL et al, 2002; Talpaz, M et al, 2002). This is a clear indication of selection bias since the investigator may exclude a potential candidate at their own discretion.

Most of the studies did account for all of the patients enrolled onto the study; reasons or numbers for any exclusions or withdrawals were described. The three pivotal phase 2 studies reported that certain patients were not eligible to participate in the study as authors could not confirm the stage of their disease at entry (Kantarjian, HM et al 2002a; Talpaz, M et al 2002; Sawyers, CL et al 2002). A total of 163 out of 1027 were not eligible as their disease stage could not be confirmed. This was despite a strict definition for the disease stages being applied.

Inclusion and exclusion criteria were described in all but 3 studies (Anderlini, P et al 2004; Arora, B et al 2004; Valeyrie, L et al 2003)(see table 4.5.2). It is difficult to ascertain the characteristics of patients in the latter studies and to what extent any bias would have affected the outcomes. It is not clear whether the results published look upon imatinib favourably or not.

Performance bias

Drug dosage: Imatinib was often given at different doses with dose interruptions permitted in certain instances. Most of the studies defined the circumstances in which dose adjustment was permitted, although five studies gave no details about dose changes (Anderlini, P et al 2004; Arora, B et al 2004; Kantarjian, HM et al 2002d; Le Coutre, P et al 2003; Valeyrie, L et al 2003). In the studies that did define the dose adjustment criteria, it is not certain whether the criteria was observed strictly as no further information about patients in whom the dose was changed is provided.

Concomitant drugs: Some of the studies used in the analysis allowed the use of other agents during the trials. The additional therapies were usually hydroxyurea and anagrelide. The procedure of leukopheresis was also permitted in some trials to control the white blood cell count. None of the studies that allowed the use of concomitant agents stated the duration of the treatment or the specific circumstances it was allowed. There was no mention in the studies of specific patients who had received the cytoreductive therapies. Use of these concomitant therapies would have resulted in bias in favour of the efficacy profile of imatinib since their aim

was essentially to reduce white blood cell levels. Studies using concomitant drugs are described in table 4.5.1.

Detection bias

None of the uncontrolled trials were blinded. The adverse events profile may be affected by the fact that patients also knew that they were taking imatinib: this was likely to favour imatinib as patients may have under-reported symptoms in the hope that the new therapy would be effective. Grading and defining adverse events may have been subjective; clinician's definitions of 'mild' or 'moderate' events may differ. Although adverse event criteria were usually described, it is not clear whether they were used to assess each event.

Attrition bias

Reasons for or numbers of patients withdrawing from studies were not described by 9 of the 26 studies in the analysis (Anderlini, P et al 2004; Arora, B et al 2004; Cervantes, F et al 2003a; Champagne, MA et al 2004; Gardembas, M et al 2003; Kantarjian, HM et al 2004b; Le Coutre, P et al 2003; Valeyrie, L et al 2003; van Deventer, HW et al 2002). Of the remaining studies that did make mention of withdrawal, this was rarely clearly described. It is difficult to ascertain whether withdrawal was directly due to imatinib treatment or for other reasons.

EXTERNAL VALIDITY

Due to the variable trial designs and reporting methods, the generalisability of the studies was difficult to establish. Exclusion and inclusion criteria were not described in three studies (Anderlini, P et al, 2004; Arora, B et al 2004; Valeyrie, L et al 2003). The populations of patients were also quite different; the study by Champagne and colleagues assessed imatinib use in a child population (Champagne, MA et al 2004) while the remaining studies investigated imatinib use in adult populations with various stages of disease and different treatment backgrounds. Due to the uncontrolled nature of the studies, bias is likely to be an important factor in the study results and any interpretation of the information must consider these problems.

4.5.3 Adverse events data from uncontrolled studies of imatinib

As expected, the uncontrolled studies of imatinib showed a large spectrum of adverse events. To aid interpretation of the information, adverse events were categorised into the criteria defined by the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0 (Cancer Therapy Evaluation Program, 2003). This criteria was used to define the type and severity of the adverse events in the majority of the studies used in this review. Grade 1 and 2 adverse events are broadly defined as mild and moderate respectively. Grade 3 events are defined as severe and grade 4 events are either life-threatening or disabling events.

Table 4.5.3, Frequency and percentages of adverse events in the 'pain'category in uncontrolled trials of imatinib in CML *denotes grades 3 or 4 events, #denotes grades 1 or 2 events (grades from NCI-CTC criteria)

	n (%)								
	Abdominal pain	Abdominal pain, upper	Arthralgia	Bone ache	Bone pain	Headache	Limb pain	Musculoskeletal pain	Myalgia
Cervantes 2003b n = 150	-	-	6 (4%)	-	-	-	-	-	-
Champagne 2004 n = 31	-	-	1 (1.5%)	-	-	-	-	-	-
Cortes 2003 n= 36	-	-	-	-	15 (42%)	-	-	-	-
Druker 2001a n = 83	-	-	11 (13%)	-	-	-	-	-	34 (41%)
Druker 2001b n = 58	-	-	-	-	-	-	-	-	12 (21%)
Gardembas 2003 n = 30	18 (53%)	-	-	-	-	9 (30%)	-	-	-
Kantarjian 2002a n = 532	99 (19%)	-	100 (19%)	-	-	69 (13%)	-	-	108 (20%)
Kantarjian 2002b n = 261	-	-	-	1 (0.4%)*	-	-	-	-	-
Kantarjian 2002d n = 28	-	-	-	2 (7%)*	-	-	-	-	-
Kantarjian 2004a n = 261	-	-	-	3 (1%)*	-	-	-	-	-
Kantarjian 2004b n = 114	-	-	-	-	3 (3%)*	-	-	-	-
Kim 2004 n = 13	-	-	2 (15%)#	-	-	-	-	-	4 (31%)#
LeCoutre 2003 n = 39	-	-	1 (3%)	-	-	-	-	-	-
Morishima 2004 n = 39	4 (10%)	-	4 (10%)	-	-	-	-	-	4 (10%)
Sawyers 2002 n = 260	27 (10%)	-	21 (8%)	-	-	26 (10%)	-	30 (12%)	15 (6%)
Sureda 2003 n = 30	-	-	4 (13%)	-	-	-	-	2 (7%)	-
Talpaz 2002 n = 235	16 (7%)	24 (10%)	29 (12%)	-	20 (9%)	30 (13%)	27 (11%)	-	30 (13%)

Table 4.5.4, Frequency and percentages of adverse events in the 'musculoskeletal'category in uncontrolled trials of imatinib in CML. *denotes grades 3 or 4 events, #denotes grades 1 or 2 events (grades from NCI-CTC criteria)

	Muscle Cramps n (%)
Cervantes 2003a n = 98	5 (15%)
Cervantes 2003b n = 150	33 (22%)
Gardembas 2003 n = 30	11 (37%)
Kantarjian 2002a n = 532	261 (49%)
Kantarjian 2002c n = 237	17 (7%)
Kantarjian 2002d n = 28	1 (4%)*
Kantarjian 2003b n = 50	1 (2%)*
LeCoutre 2003 n = 39	10 (26%)
Morishima 2004 n = 39	6 (15%)
Sawyers 2002 n = 260	65 (25%)
Talpaz 2002 n = 235	75 (32%)

Pain was a frequent occurrence in the studies investigating imatinib use. Of particular interest were those associated with the musculoskeletal system such as myalgia, arthralgias and bone aches (Table 4.5.3). Muscle cramps occurred in many of the studies (n=11) – although this event fell into musculoskeletal category (Table 4.5.4). There was an overlap in reporting e.g. bone pain, ache, limb pain etc. Muscle cramps are noted as characteristic of imatinib use in published reviews (Deininger, MW et al 2003). The evidence suggests that imatinib does result in muscle cramps in certain subjects, although in some cases the incidence is greater than others. For instance, in the study by Kantarjian, HM et al 2002a, nearly half of all patients suffered from muscle cramps, whereas other studies showed lower levels of muscle cramps (Kantarjian, HM et al 2002d; Kantarjian, HM et al 2003b).

The study by Kim et al reported a higher proportion of arthralgia and myalgia (15% and 31% respectively) than many of the other studies, bearing in mind that only grades 1 and 2 of the events were described (Kim, YJ et al 2004).

Bone pain was also observed in nearly half of the patients (42%), in the study by Cortes, J et al, 2003, which was proportionally much higher than in the other studies.

Headaches were observed in the Gardembas study which may have been the result of adding cytarabine to imatinib treatment (Gardembas, M et al 2003). Further study of patients treated with imatinib in combination with cytarabine may confirm or disprove this phenomenon. Similarly, abdominal pain was proportionally high in this study. Abdominal pain was more prevalent in the studies on which imatinib was licensed, i.e. the studies by Kantarjian, HM et al 2002a; Sawyers, CL et al 2002; Talpaz, M et al 2002.

Table 4.5.5, Frequency and percentages of adverse events in the 'renal'category in uncontrolled trials of imatinib in CML

	Renal Failure n (%)
Cervantes 2003b n = 150	2 (1%)
Druker 2001b n = 58	1 (2%)
Sawyers 2002 n = 260	1 (0.4%)

Table 4.5.6, Frequency and percentages of adverse events in the 'syndromes' category in uncontrolled trials of imatinib in CML

	Budd-Chiari Syndrome n (%)
Talpaz 2002 n = 235	1 (0.4%)

Table 4.5.7, Frequency and percentages of adverse events in the 'vascular' category in uncontrolled trials of imatinib in CML

	Digital Ischemia n (%)	Numbness n (%)
Cervantes 2003b n = 150	1 (1%)	-
Cortes 2003 n = 36	-	1 (3%)

Table 4.5.8, Frequency and percentages of 'miscellaneous' adverse events in uncontrolled clinical trials of imatinib in CML

	Bronchogenic Carcinoma n (%)	GVHD n (%)
Kim 2004 n = 13	-	2 (15%)
Rosti 2004 n = 191	1 (0.5%)	-

Renal failure, syndromes, vascular problems, secondary malignancies and neurological symptoms were also observed in patients treated with imatinib (tables 4.5.5-8). These events observed were proportionally lower than other adverse events.

Neurological symptoms were observed in a small minority of patients. Two studies classified them under the broad heading of neurological symptoms, rather than the individual event names (Gardembas, M et al 2003; Kantarjian, HM et al 2004a). Depression, stroke, dizziness and seizures occurred in less than 5% of patients assessed. (Table 4.5.9)

Table 4.5.9, Frequency and percentages of 'neurology' events in uncontrolled trials of imatinib in CML. *denotes grades 3 or 4 events (grades from NCI-CTC criteria)

	Cerebrovascular accident n (%)	Depression n (%)	Dizziness n (%)	Neurological symptoms n (%)	Seizures n (%)
Champagne 2004 n = 31	-	-	-	-	1 (1%)
Cortes 2003 n = 36	-	1 (3%)	-	-	-
Gardembas 2003 n = 30	-	-	-	1 (3%)	-
Kantarjian 2002a n = 532	1 (0.2%)	-	-	-	-
Kantarjian 2002b n = 261	-	2 (0.8%)*	-	-	-
Kantarjian 2004a n = 261	-	-	-	2 (0.8%)*	-
LeCoutre 2003 n = 39	-	-	1 (3%)	-	-

Table 4.5.10, Frequency and percentages of 'lymphatics' adverse events in uncontrolled clinical trials of imatinib in CML. *denotes grades 3 or 4 events, #denotes grades 1 or 2 events (grades from NCI-CTC criteria)

	Oedema n (%)	Fluid Retention n (%)	Periorbital Oedema N (%)	Superficial Oedema n (%)
Anderlini 2004 n = 15	-	-	1 (7%)	-
Arora 2004 n = 118	-	-	-	57 (48%)
Cervantes 2003a n = 98	-	-	-	7 (21%)
Cervantes 2003b n = 150	33 (22%)	-	-	-
Champagne 2004 n = 31	1 (1%)	-	-	-
Cortes 2003 n = 36	-	18 (50%)	-	-
Druker 2001a n = 83	32 (39%)	-	-	-
Druker 2001b n = 58	24 (41%)	-	-	-
Gardembas 2003 n = 30	-	-	-	15 (50%)
Kantarjian 2002a n = 532	-	-	-	318 (60%)
Kantarjian 2002c n = 237	-	7 (3%)	-	-
Kantarjian 2002d n = 28	-	3 (10%)*	-	-
Kantarjian 2004b n = 114	-	1 (1%)*	-	-
Kim 2004 n = 13	8 (62%)#	-	-	-
LeCoutre 2003 n = 39	-	-	-	18 (46%)
Morishima 2004 n = 39	25 (64%)	-	-	-
Sawyers 2002 n = 260	-	24 (9%)	-	144 (55%)
Sureda 2003 n = 30	-	12 (40%)	-	-
Talpaz 2002 n = 235	150 (64%)	-	-	-
Valeyrie 2003 n = 54	35 (65%)	-	-	-

Oedema was one of the most commonly observed problems associated with imatinib use – a total of 20 studies reported this event (table 4.5.10). Some authors preferred to describe the event as fluid retention or assign it to a particular region of the body, such as periorbital oedema (Anderlini, P et al 2004; Sawyers, CL et al 2002).

The studies by Valeyrie, L et al 2003; Kim, YJ et al 2004; Morishima, Y et al 2004; and Talpaz, M et al 2002, reported the highest proportions of oedema (65%, 62%, 64%, 64% respectively). These proportions were higher than some of the other studies, for instance, Anderlini, P et al 2004, and Kantarjian, HM et al 2002c reported much fewer cases of oedema (7% and 3% respectively). Again, the study by Kim, YJ et al 2004 only reported a proportion of the adverse events seen so the true figure is likely to be higher still.

Table 4.5.11, Frequency and percentages of 'infection' adverse events in uncontrolled clinical trials of imatinib in CML. *denotes grades 3 or 4 events, (grades from NCI-CTC criteria)

	Febrile Episodes n (%)	Herpes Zoster n (%)	Infection n (%)	Nasopharyngitis n (%)
Cervantes 2003b n = 150	-	-	6 (4%)	-
Champagne 2004 n = 31	-	-	1 (1%)	-
Gardembas 2003 n = 30	-	-	-	8 (27%)
Kantarjian 2002c n = 237	30 (13%)	-	17 (7%)	-
Kantarjian 2002d n = 28	-	-	1 (4%)*	-
Morishima 2004 n = 39	-	1 (3%)	-	-

Various kinds of infection occurred in patients (table 4.5.11). Some infections were defined, such as herpes zoster, whereas most of the incidences are classified under the general heading of infection as they were not described separately. Febrile episodes were a common occurrence in the study by Kantarjian, HM et al 2002c (13%) – often the result of extensive neutropenia. Nasopharyngitis was proportionally higher in only one study – the study by Gardembas reported that 27% of all patients suffered from the infection (Gardembas, M et al 2003).

Table 4.5.12, Frequency and percentages of 'hepatobiliary' adverse events in uncontrolled clinical trials of imatinib in CML. *denotes grades 3 or 4 events (grades from NCI-CTC criteria)

	Liver toxicity n (%)
Cervantes 2003a n = 98	1 (3%)
Cervantes 2003b n = 150	3 (2%)
Champagne 2004 n = 31	2 (6.7%)
Cortes 2003 n = 36	7 (19%)
Druker 2001b n = 58	1 (2%)
Kantarjian 2002a n = 532	4 (1%)
Kantarjian 2002b n = 261	3 (1%)*
Kantarjian 2002c n = 237	12 (5%)
Kantarjian 2002d n = 28	5 (18%)*
Kantarjian 2003b n = 50	2 (4%)*
Kantarjian 2004a n = 261	6 (2%)*
Kantarjian 2004b n = 114	8 (7%)*
Morishima 2004 n = 39	2 (5%)
Rosti 2004 n = 191	2(1%)
Sawyers 2002 n = 260	21 (8%)
Sureda 2003 n = 30	6 (20%)
Talpaz 2002 n = 235	16 (7%)

Liver toxicity was described in most of the studies. It was usually termed as abnormal elevations of liver enzymes, such as aspartate aminotransferase (AST) or alanine aminotransferase (ALT), although the level of increase was rarely given. Often, liver toxicity was described briefly, and not alongside other adverse events. The true extent of liver toxicity is difficult to determine for this reason. The study by Sureda and colleagues, which assessed imatinib use in advanced stages of CML, reported the highest levels (20%) of liver toxicity (table 4.5.12) (Sureda, A et al 2003). Kantarjian, HM et al 2002d also reported a higher proportion of hepatotoxicity than other studies at 18% - only the most severe cases (grades 3 and 4) were reported.

Table 4.5.13, Frequency and percentages of 'haemorrhage' adverse events in uncontrolled clinical trials of imatinib in CML

	n (%)					
	Cerebral haemorrhage	Haemorrhage	Hemothorax	Intestinal haemorrhage	Intracranial haemorrhage	Subarachnoid haemorrhage
Cervantes 2003b n = 150	-	-	-	1 (1%)	-	-
Champagne 2004 n = 31	-	-	-	-	1 (1%)	-
Druker 2001b n = 58	-	1 (2%)	-	-	-	-
Kantarjian 2002a n = 532	1 (0.2%)	-	-	-	-	1 (0.2%)
Kantarjian 2002c n = 237	-	1 (0.4%)	-	-	-	-
Rosti 2004 n = 191	-	1 (0.5%)	-	-	-	-
Sawyers 2002 n = 260	-	27 (10%)	1 (0.4%)	-	-	-
Talpaz 2002 n = 235	-	29 (12%)	-	-	-	-
Van Deventer 2003 n = 28	-	1 (4%)	-	-	-	-

The problem of haemorrhage was observed in a number of studies, though with a low incidence. It was categorised into the different locations of the haemorrhage by some authors, whereas others categorised them under the general heading of haemorrhage. Kantarjian, HM et al 2002a described two cases of haemorrhage though described them as subarachnoid and cerebral depending on the site of occurrence (table 4.5.13).

The studies by Sawyers, CL et al 2002 and Talpaz, M et al 2002 observed the highest proportions of haemorrhage, at 10% and 12% respectively. The remaining studies recorded haemorrhage in one patient only.

Table 4.5.14, Frequency and percentages of 'haematologic' adverse events in uncontrolled clinical trials of imatinib in CML. *denotes grades 3 or 4 events (grades from NCI-CTC criteria)

	n (%)					
	Anaemia	*Granulocytopenia*	*Leukopenia*	*Neutropenia*	*Pancytopenia*	*Thromb-ocytopenia*
Anderlini 2004 n = 15	-	-	-	10 (67%)*	-	7 (47%)*
Cervantes 2003a n = 98	4 (12%)	11 (33%)*	-	-	-	9 (27%)*
Cervantes 2003b n = 150	9 (6%)*	49 (33%)*	-	-	-	24 (16%)*
Cortes 2003 n = 36	29 (81%)	-	-	28 (78%)	-	14 (39%)
Druker 2001a n = 83	4 (5%)*	-	-	12 (14%)	-	13 (16%)
Druker 2001b n = 58	-	-	-	38 (66%)*	1 (2%)	40 (69%)*
Gardembas 2003 n = 30	3 (10%)	-	-	16 (53%)	-	15 (50%)
Kantarjian 2002a n = 532	36 (7%)*	-	124 (23%)*	186 (35%)*	-	106 (20%)*
Kantarjian 2002b n = 261	18 (7%)*	106 (41%)*	-	41 (36%)*	-	47 (18%)*
Kantarjian 2002c n = 237	-	40 (17%)*	-	-	-	30 (13%)*
Kantarjian 2002d n = 28	-	6 (21%)*	-	-	-	4 (14%)*
Kantarjian 2003a n = 54	-	-	-	-	13 (24%)	-
Kantarjian 2003b n = 50	4 (8%)*	10 (20%)*	-	-	-	4 (8%)*
Kantarjian 2004a n = 261	37 (14%)*	163 (62%)*	-	-	-	59 (23%)*
Kantarjian 2004b n = 114	11 (10%)*	-	-	-	-	29 (25%)*
Kim 2004 n = 13	-	6 (46%)*	-	-	-	-
LeCoutre 2003 n = 39	5 (13%)	-	4 (10%)	3 (8%)	-	16 (41%)
Morishima 2004 n = 39	6 (15%)	-	13 (33%)	14 (36%)	-	15 (39%)
Rosti 2004 n = 191	-	-	-	-	-	2 (1%)
Sawyers 2002 n = 260	135 (52%)*	-	-	165 (63%)*	-	160 (62%)*
Sureda 2003 n = 30	-	-	17 (57%)	-	-	13 (43%)
Talpaz 2002 n = 235	92 (39%)*	-	111 (47%)*	137 (58%)*	-	102 (43%)*
Van Deventer 2003 n = 28	-	-	-	5 (19%)*	-	11 (40.7%)

Haematologic events were described in all but three of the studies (Arora, B et al 2004; Champagne, MA et al 2004 and Valeyrie, L et al 2003). Abnormal peripheral blood cell levels are characteristic of CML – as the disease stage progresses, cell numbers increase or deplete dramatically across different populations. The studies showed that imatinib may have contributed to this effect, although the extent of myelosuppression caused by the drug remains unclear due to the nature of the underlying condition.

The most common reported haematologic events were thrombocytopenia and neutropenia (table 4.5.14). Most of the studies only described the most severe grades of myelosuppression – the true figure is likely to be much higher. The highest levels of thrombocytopenia were seen in patients with an advanced disease stage, such as the studies by Druker 2001b and Sawyers, CL et al 2002 which assessed imatinib use in the blast crisis. A significant proportion of patients were affected by thrombocytopenia in the study by Anderlini, P et al 2004 (47%). This study was carried out in patients treated with imatinib within 100 days of a stem cell transplantation.
Neutropenia was also a common occurrence. Significant proportions of patients experienced the problem. Individual data was not reported in all of the studies, however, despite the majority of CML patients experiencing some level of neutropenia as described in the text.
Anaemia was reported in 14 studies, although the frequency of this event was lower than thrombocytopenia and neutropenia. The highest levels were seen in the study by Cortes, J et al 2003 (81%).

Reduction in white blood cells and platelets generally increase the susceptibility to infection and haemorrhage respectively. There was no clear correlation between infection and a reduction in white blood cells – six studies described various infections whereas 21 studies described a reduction in white blood cells. Similarly, thrombocytopenia was seen in 21 studies; nine of which also described haemorrhage. The studies with the highest frequencies of haemorrhage (Talpaz, M et al 2002 and Sawyers, CL et al 2002) did however show significant levels of grades 3-4 thrombocytopenia (43% and 62% respectively).

Table 4.5.15, Frequency and percentages of 'constitutional symptoms' adverse events in uncontrolled clinical trials of imatinib in CML. *denotes grades 3 or 4 events (grades from NCI-CTC criteria)

	Asthenia n (%)	Fatigue n (%)	Fever n (%)	Weight gain n (%)
Champagne 2004 n = 31	-	1 (3.5%)	-	-
Cortes 2003 n = 36	-	8 (22%)	-	-
Druker 2001a n = 83	-	17 (20%)	-	-
Druker 2001b n = 58	-	6 (10%)	-	-
Gardembas 2003 n = 30	21 (70%)	-	-	-
Kantarjian 2002a n = 532	-	95 (18%)	-	137 (26%)
Kantarjian 2002b n = 261	-	1 (0.4%)	1 (0.4%)*	-
Kantarjian 2002c n = 237	-	17 (7%)	-	2 (1%)
Kantarjian 2002d n = 28	-	-	1 (4%)*	1 (4%)*
Kantarjian 2003b n = 50	-	1 (2%)*	-	-
Kantarjian 2004a n = 261	-	1 (0.4%)*	4 (1.5%)*	-
Kantarjian 2004b n = 114	-	1 (1%)*	-	-
LeCoutre 2003 n = 39	-	-	-	5 (13%)
Morishima 2004 n = 39	-	8 (21%)	-	-
Rosti 2004 n = 191	-	-	1 (0.5%)	-
Sawyers 2002 n = 260	-	20 (8%)	-	-
Sureda 2003 n = 30	-	11 (37%)	-	-
Talpaz 2002 n = 235	-	25 (11%)	-	27 (11%)

Patient fatigue was described in the majority of the studies (n=14) (table 4.5.15). It was observed in varying frequencies (range = 0.4 -37%) across studies of patients with different disease stages. The highest occurrence (37%) was in the study by Sureda, A et al 2003, which was a study in the blast crisis of CML. Fever was reported in four studies. It is not clear whether the fever was neutropenic, where the underlying disease would have contributed to its presence, or fever directly as a result of imatinib use. The Gardembas study showed that asthenia was a common occurrence in patients following a treatment of imatinib and cytarabine (Gardembas, M et al 2003). Asthenia was not observed in any of the other studies that investigated the use of imatinib alone.

Weight gain was a problem in certain studies with the study by Kantarjian, HM et al 2002a showing the highest level. The study observed that 137 patients out of 532 had a weight gain following imatinib treatment. The severity of the gain is not described however, and other studies may not have recorded slight gains.

Table 4.5.16, Frequency and percentages of 'dermatology' adverse events in uncontrolled clinical trials of imatinib in CML. *denotes grades 3 or 4 events (grades from NCI-CTC criteria)

	n (%)											
	Cheilitis	*Cutaneous Dryness*	*De pigmentation*	*Dermatitis*	*Eczema*	*Hair darkening*	*Hyper pigmentaion*	*Photosensitivity*	*Prolonged wound healing*	*Pruritus*	*Rash*	*SJS*
Arora 2004 (532)	-	-	48 (40.9%)	-	-	-	4 (3.6%)	-	-	-	15 (12.7%)	-
Cervantes 2003a (98)	-	-	-	-	-	-	-	-	-	-	1 (3%)	-
Cervantes 2003b (150)	-	-	-	-	-	-	-	-	-	-	13 (9%)	-
Cortes 2003 (36)	-	-	-	-	-	-	-	-	-	-	13 (36%)	-
Druker 2001a (83)	-	-	-	-	-	-	-	-	-	-	16 (19%)	-
Druker 2001b (58)	-	-	-	1 (2%)	-	-	-	-	-	-	10 (17%)	-
Gardembas 2003 (30)	-	-	-	-	-	-	-	-	-	4 (13%)	7 (23%)	-
Kantarjian 2002a (532)	-	-	-	-	-	-	-	-	-	46 (9%)	171 (32%)	-
Kantarjian 2002b (261)	-	-	-	-	-	-	-	-	-	-	6 (2%)*	-
Kantarjian 2002c (237)	-	-	-	-	-	-	-	-	-	-	9 (4%)	-
Kantarjian 2002d (28)	-	-	-	-	-	-	-	-	-	-	11 (39%)	-
Kantarjian 2003b (50)	-	-	-	-	-	-	-	-	-	-	3 (6%)*	-
Kantarjian 2004a (261)	-	-	-	-	-	-	-	-	-	-	6 (2%)*	-
Kantarjian 2004b (114)	-	-	-	-	-	-	-	-	-	-	7 (6%)*	-
LeCoutre 2003 (39)	-	-	-	-	5 (13%)	-	-	-	1 (3%)	-	6 (15%)	-
Morishima 2004 (39)	-	-	-	18 (46%)	-	-	-	-	-	-	-	-
Rosti 2004 (191)	-	-	-	-	-	-	-	-	-	-	1 (0.5%)	-
Sawyers 2002 (260)	-	-	-	59 (23%)	-	-	-	-	-	-	-	-
Sureda 2003 (30)	-	-	-	-	-	-	-	-	-	-	1 (3%)	1 (3%)
Talpaz 2002 (235)	-	-	-	52 (22%)	-	-	-	-	-	20 (9%)	-	-
Valeyrie 2003 (54)	4 (7%)	17 (31%)	7 (13%)	-	-	8 (15%)	1 (2%)	4 (7%)	-	22 (41%)	36 (67%)	-

Table 4.5.17, Frequency and percentages of 'gastrointestinal' adverse events in uncontrolled clinical trials of imatinib in CML. *denotes grades 3 or 4 events, #denotes grades 1 or 2 events (grades from NCI-CTC criteria)

	n (%)							
	Anorexia	Diarrhoea	Dyspepsia	GI Symptoms	Mucositis	Nausea	Taste disturbance	Vomiting
Cervantes 2003a n = 98	-	-	-	6 (18%)	-	-	-	-
Cervantes 2003b n = 150	-	-	-	18 (12%)	-	-	-	-
Champagne 2004 n = 31	-	1 (2.7%)	-	-	-	1 (4%)	-	1 (3.5%)
Cortes 2003 n = 36	-	7 (19%)	-	-	-	7 (19%)	-	-
Druker 2001a n = 83	-	21 (25%)	15 (18%)	-	-	36 (43%)	-	15 (18%)
Druker 2001b n = 58	6 (10%)	10 (17%)	-	-	-	32 (55%)	-	24 (41%)
Gardembas 2003 n = 30	4 (13%)	12 (40%)	-	-	4 (13%)	25 (83%)	-	19 (63%)
Kantarjian 2002a n = 532	-	152 (29%)	93 (17%)	-	-	293 (55%)	-	125 (23%)
Kantarjian 2002b n = 261	-	1 (0.4%)*	-	-	-	-	-	-
Kantarjian 2002c n = 237	-	5 (2%)	-	-	-	2 (1%)	-	-
Kantarjian 2002d n = 28	-	-	-	-	-	1 (4%)*	-	-
Kantarjian 2004a n = 261	-	1 (0.4%)*	-	-	-	-	-	-
Kantarjian 2004b n = 114	-	1 (1%)	-	-	-	1 (1%)*	-	-
Kim 2004 n = 13	-	1 (8%)#	-	-	-	-	-	-
LeCoutre 2003 n = 39	-		-	-	-	2 (5%)	-	-
Morishima 2004 n = 39	-	8 (21%)	-	-	-	17 (44%)	5 (13%)	6 (15%)
Sawyers 2002 n = 260	-	62 (24%)	18 (7%)	2 (0.8%)	-	164 (63%)	-	114 (44%)
Sureda 2003 n = 30	-	7 (23%)	-	-	-	10 (33%)	-	7 (23%)
Talpaz 2002 n = 235	18 (8%)	88 (37%)	38 (16%)	-	-	153 (65%)	-	114 (49%)

Dermatological events were unexpected problems associated with imatinib use, of which the most common was rash and was reported in 18 studies. Two of the studies (Arora, B et al 2004 and Valeyrie, L et al 2003) focussed specifically on dermatologic events and reported high levels of skin rash. The study by Valeyrie et al 2003 reported 67% of patients experiencing rash following treatment with imatinib – far greater a proportion than that observed in other studies (table 4.5.16). The study by Druker, BJ et al 2001b described dermatitis as well as rash – by definition the two events are the same and it is unclear what the author meant by using the two definitions. The study by Morishima, Y et al 2003 was a phase 2 study in Japanese patients; in this study nearly half of all patients experienced dermatitis – a substantially higher proportion than in the other studies.

Pigment changes also occurred in patients treated with imatinib. The study by Arora et al reported the highest level of depigmentation associated with imatinib use than any of the other studies (Arora, B et al 2004). Hyperpigmentation was also observed in this patient group too. A smaller proportion experienced this phenomenon compared with depigmentation.

Pruritus was also observed in some of the studies. The highest proportion was seen in the study by Valeyrie, L et al 2003 (41%), followed by the study by Gardembas M et al 2003 (13%).
The study by Valeyrie, L et al 2003 showed many more dermatological events than the other studies - cheilitis, depigmentation, hair darkening, hyperpigmentation and photosensitivity were seen in small proportions of patients. Cutaneous dryness (which may have resulted in rash), pruritus and rash were seen in higher proportions of patients. The severity of these conditions was unclear, largely due to the inconsistent reporting of the results. This study was the only one to report cheilitis, cutaneous dryness, hair darkening and photosensitivity.

Gastrointestinal symptoms such as nausea and diarrhoea were a problem in many patients treated with imatinib. Initially, imatinib was given to patients on an empty stomach which resulted in nausea and vomiting. This was later changed and imatinib was administered to patients with a meal. The levels of nausea and vomiting were reduced in later studies. Mucositis occurred in the Gardembas study alone (Gardembas, M et al 2003)(table 4.5.17). Diarrhoea was also a common adverse event (15 studies). The Gardembas study reported the highest proportion of diarrhoea (40%), and patients with more advanced disease stages also saw increases of the event (Gardembas, M et al 2003; Sawyers, CL et al 2002; Sureda, A et al 2003; Talpaz, M et al 2002).

4.5.4 Severity of adverse events in uncontrolled studies

Many of the studies presented certain grades of adverse event rather than all of the events. Other studies separated them by grades 1 - 2, and grades 3 - 4 to determine the significance of problems associated with imatinib.

Prevalence of grades 1-2 and 3-4 toxicities

Seven studies described grade 1 - 2 adverse events; 23 described grade 3 - 4 events (Table 4.5.18). All of the studies that reported grades 1 - 2, also reported grade 3 - 4 events. Many of the studies that reported grade 3 - 4 events, either did not observe grade 1 - 2 or did not report or define them as separate events. It may be assumed that all other adverse events mentioned aside from grades 3 - 4 would be grades 1 - 2. Unless a grade 1 - 2 event was not mentioned explicitly, it was not included in the table. This understandably corrupts the true findings of the assessment, however it also protects the data from one's own assumption which cannot be verified.

Grade 3 - 4 events were reported on a larger scale than grade 1 - 2 events. The general trend showed that of the grade 1 - 2 events that were reported, they were higher in proportion to the same grade 3 - 4 event in the study. For example, 12% of patients experienced grades 1- 2 arthralgia, compared to 1% experiencing the same event at grade 3 - 4 in the Druker, BJ et al 2001a study. Similarly, the study by Druker, BJ et al 2001b study reported that 14% of patients had a grade 1 – 2 rash, compared to 3% of patients experiencing it at the more severe grades. One of the exceptions to this trend was that of haematologic events. In the study by Druker, BJ et al 2001a, neutropenia and thrombocytopenia was slightly higher at grades 3 - 4 compared to grades 1 – 2 (11% vs 4% and 9% vs 6% respectively). The only other study to report haematologic events at all grades was the study by Sureda, A et al 2003. This study however reported higher levels of leukopenia and thrombocytopenia at grades 1 - 2 (37% vs 20%, 23% vs 20% respectively).

The study by Champagne, MA et al 2004 reported almost twice as many cases of liver toxicity at grades 3 - 4 compared to grades 1 and 2 (13% compared to 6.7%). The study reported two events

at the severe grades (liver toxicity and vomiting). All other events (n=7) were reported at grades 1 - 2.

The adverse events appeared to be similar across the studies at the same grade. Anaemia occurred in between 5-15% of patients at grades 3 - 4 in all of the studies that reported it. The exceptions to this trend were the studies by Sawyers, CL et al 2002 and Talpaz, M et al 2002 which reported significantly higher proportions of this event (52 and 39% respectively). No more than 3% of patients experienced grades 3 - 4 diarrhoea or fatigue in any of the studies. The values were relatively consistent across the studies.

The highest reported values were the haematologic events (granulocytopenia, leukopenia, neutropenia and thrombocytopenia) at all severity grades. Oedema was also a commonly reported problem within studies, with the highest frequencies reported at grades 1 – 2.

Table 4.5.18, Percentage frequency of reported grades (severity) of adverse events in uncontrolled clinical trials

	Frequency (%)													
Toxicity	*Anderlini 2004 n = 15*	*Cervantes2003a n=33*	*Cervantes2003b n=150*	*Champagne2004 n =31*	*Cortes2003 n=36*	*Druker2001a n=83*	*Druker2001b n = 58*	*Gardembas2003 n=30*	*Kantarjian2002a n=532*	*Kantarjian2002b n=261*	*Kantarjian2002c n=237*			
Grade	**3/4**	**3/4**	**3/4**	**1/2**	**3/4**	**3/4**	**1/2**	**3/4**	**1/2**	**3/4**	**3/4**	**3/4**	**3/4**	**3/4**
Abdominal pain	-	-	-	-	-	-	-	-	-	-	10	-	-	-
Anaemia	-	12	6	-	-	8	-	5	-	-	7	7	7	-
Anorexia	-	-	-	-	-	-	-	-	10	-	-	-	-	-
Arthralgia	-	-	-	1.5	-	-	12	1	-	-	-	0.8	-	-
Bone pain	-	-	-	-	-	3	-	-	-	-	-	-	-	-
Dermatitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diarrhoea	-	-	-	2.7	-	-	23	1	17	-	-	0.9	0.4	2
Dyspepsia	-	-	-	-	-	-	18	-	-	-	-	-	-	-
Fatigue	-	-	-	3.5	-	3	19	1	10	-	-	0.4	0.4	7
Granulocytopenia	-	33	33	-	-	-	-	-	-	-	-	-	41	17
Haemorrhage	-	-	-	-	-	-	-	-	-	-	-	-	-	0.4
Headache	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Leukopenia	-	-	-	-	-	-	-	-	-	-	-	23	-	-
Liver toxicity	-	-	-	6.7	13	3	-	-	-	-	-	-	1	5
Muscle cramps	-	-	-	-	-	-	-	-	-	-	-	0.9	-	7
Myalgia	-	-	-	-	-	-	35	6	21	-	-	0.2	-	-
Nausea	-	-	-	4	-	-	43	-	45	10	-	1.5	-	1
Neutropenia	67	-	-	-	-	31	4	11	-	66	27	35	-	-
Oedema	-	-	-	1	-	-	35	2	34	7	-	1.1	-	3
Pruritus	-	-	-	-	-	-	-	-	-	-	-	0.4	-	-
Rash	-	-	-	-	-	8	18	1	14	3	-	3	2	4
Thrombocytopenia	47	27	16	-	-	22	6	9	-	69	37	20	18	13
Vomiting	-	-	-	3.5	3	-	17	-	34	7	13	0.6	-	-
Weight gain	-	-	-	-	-	-	-	-	-	-	-	4	-	1

Table 4.5.18, Percentage frequency of reported grades (severity) of adverse events in uncontrolled clinical trials (continued)

	Frequency (%)															
Toxicity	*Kantarjian2002d n=28*	*Kantarjian2003b n=50*	*Kantarjian2004a n=261*	*Kantarjian2004b n=114*	*Kim2004 n=13*		*Le Coutre2003 n=39*		*Morishima2004 n=39*	*Sawyers2002 n=260*	*Sureda2003 n=30*		*Talpaz2002 n=235*	*Valeyrie2003 n=54*		*van Deventer2003 n=27*
Grade	**3/4**	**3/4**	**3/4**	**3/4**	**1/2**	**3/4**	**1/2**	**3/4**	**3/4**	**3/4**	**1/2**	**3/4**	**3/4**	**1/2**	**3/4**	**3/4**
Abdominal pain	-	-	-	-	-	-	-	-	-	0.8	-	-	0.9	-	-	-
Anaemia	-	8	14	10	-	-	13	-	8	52	-	-	39	-	-	-
Anorexia	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-
Arthralgia	-	-	-	-	15	-	3	-	-	1.2	13	-	3	-	-	-
Bone pain	-	-	-	3	-	-	-	-	-	-	-	-	0.4	-	-	-
Dermatitis	-	-	-	-	-	-	-	-	18	4.2	-	-	1	-	-	-
Diarrhoea	-	-	0.4	1	8	-	-	-	-	0.8	23	-	0.4	-	-	-
Dyspepsia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fatigue	-	2	0.4	1	-	-	-	-	-	1.5	37	-	3	-	-	-
Granulocytopenia	21	20	62	-	-	46	-	-	-	-	-	-	-	-	-	-
Haemorrhage	-	-	-	-	-	-	-	-	-	2.3	-	-	2	-	-	-
Headache	-	-	-	-	-	-	-	-	-	0.8	-	-	1	-	-	-
Leukopenia	-	-	-	-	-	-	10	-	31	-	37	20	47	-	-	-
Liver toxicity	18	4	2	7	-	-	-	-	-	-	14	6	-	-	-	-
Muscle cramps	4	2	-	-	-	-	26	-	-	0.8	-	-	0.4	-	-	-
Myalgia	-	-	-	-	31	-	-	-	2.6	-	-	-	1	-	-	-
Nausea	4	-	-	1	-	-	5	-	-	1.9	30	3	3	-	-	-
Neutropenia	-	-	-	36	-	-	8	-	36	63	-	-	58	-	-	19
Oedema	10	-	-	1	62	-	46	-	-	6.5	40	-	3	44	17	-
Pruritus	-	-	-	-	-	-	-	-	-	-	-	-	0.4	35	4	-
Rash	39	6	2	6	-	-	15	3	-	-	-	3	-	57	9	-
Thrombocytopenia	14	8	23	25	-	-	41	-	31	62	23	20	43	-	-	-
Vomiting	-	-	-	-	-	-	-	-	5	1.2	23	-	1	-	-	-
Weight gain	4	-	-	-	-	-	13	-	-	-	-	-	1	-	-	-

4.5.5 Summary of findings from uncontrolled studies of imatinib

The uncontrolled studies showed that the most common toxicities observed were gastrointestinal toxicities (nausea, vomiting, diarrhoea), haematologic problems (various cytopenias), musculoskeletal problems such as muscle cramps or musculoskeletal pain, and fluid retention.

4.6 Case reports and case series

A total of 56 case-reports/case-series were identified for this review. Case-reports or case-series that reported toxicity to imatinib in CML patients were included (See Appendix 5 for case-report details and excluded reports). Dermatologic events, such as exfoliative dermatitis, Sweet syndrome and lichenoid cutaneous reactions were commonly reported and were attributed to the drug in most cases. Conditions related to disease progression such as extramedullary CNS disease were also reported (table 4.6.1). Potentially life-threatening conditions such as respiratory failure and pleural-pericardic effusion were also recorded in case-reports. Many of these cases described a favourable response to imatinib initially, followed by a sudden and unexpected deterioration in the health of the patient.

The case-reports confirmed the findings of clinical trials that imatinib caused dermatological toxicities in patients. The case-reports also highlighted that disease progression and serious adverse events of other body systems (hepatobiliary, respiratory, cardiac etc) may arise from the use of imatinib.

Table 4.6.1, Summary of case reports/case series of adverse events associated with imatinib

Type of side-effect	Number of people	Reference
Acute hepatitis	2	James, C et al. 2003
Acute renal failure	1	Pou, M et al. 2003
AGEP	2	Schwarz, M et al. 2002
Anaemia & abdominal tumour	1	Lowe, EJ et al. 2004
Blast mantle cell lymphoma	1	Rodler, E et al. 2004.
Carcinoma	Unknown	Baskaynak, G et al. 2003
Cardiac morbidity	Unknown	Sohn, SK et al. 2003
Cardiac tamponade	1	Barton, JC et al. 2002
Cerebral oedema	2	Ebnoether, M et al. 2002
CNS and cutaneous involvement	2	Abruzzese, E et al. 2003
CNS blast crisis	1	Bornhauser, M et al. 2004
CNS relapse	2	Bujassoum, S et al. 2004.
CNS relapse	2	Rytting, ME et al. 2004
Contemporaneous pulmonary sarcoidosis	Unknown	Pavithran, K et al. 2004
Depigmentation	1	Raanani, P et al. 2002
Dermatological	Unknown	Burton, C et al. 2002
Erythema	Unknown	Duncan, E et al. 2003
Exfoliative dermatitis	Unknown	Banka, N et al. 2003
Extramedullary relapse	1	Smaradottir, A et al.. 2004
Fibrous dysplasia	1	Hon, C et al. 2003
Follicular mucinosis	1	Yanagi, T et al. 2004
Hepato-toxicity	1	Ohyashiki, K et al. 2002.
Hypersensitivity pneumonitis	1	Bergeron, A et al. 2002
Hypopigmentation	1	Grossman, WJ et al. 2004
Hypopigmentation	6	Tsao, AS et al. 2003
Interstitial pneumonia	1	Yokovama, T et al. 2004
Interstitial pneumonitis	1	Isshiki, I et al. 2004
Interstitial pneumonitis	Unknown	Ma, CX et al. 2003
Interstitial pneumonitis	1	Rosado, MF et al. 2003
Intramuscular oedema	1	Shimazaki, C et al. 2003
Lichenoid cutaneous reaction	1	Roux, C et al. 2004
Maculopapular rash	Unknown	Dogra, S et al. 2003
Myelodysplastic syndrome	1	Chee, YL et al. 2003
Ocular side-effects	Unknown	Fraunfelder, FW et al. 2003
Oral lichenoid reaction	1	Lim, DS et al. 2002
Pancytopenia	1	Sumi, M et al. 2002
Panniculitis	1	Ugurel, S et al. 2003
Periorbital oedema	1	Esmaeli, B et al. 2002
Periorbital oedema	1	Ramar, K et al. 2003
Periorbital oedema	Unknown	Antin, JH. 2003
Pityriasis rosea	1	Konstantopoulos, K et al. 2002
Pleural effusions	3	Goldsby, R et al. 2002
Porphyria cutanea tarda	1	Breccia, M et al. 2004
Porphyria cutanea tarda	Unknown	Ho, AY et al. 2003
Pulmonary alveolar proteinosis	1	Wagner, U et al. 2003
Pulmonary nocardiosis	Unknown	Lin, JT et al. 2004
Renal failure	1	Kitivakara, C et al. 2002
Hair repigmentation	9	Etienne, G et al 2002
Rash	8	Drummond, A et al 2003
Dermatosis	11	Milojkovic, D et al 2002
Cutaneous reaction	1	Brouard, M et al 2001
Severe hepatitis	1	Kikuchi, S et al. 2004
Stevens-Johnson syndrome	Unknown	Hsiao, LT et al. 2002
Stevens-Johnson syndrome	1	Vidal, D et al. 2002
Sweet's syndrome	1	Liu, D et al. 2004
Tumour lysis syndrome	1	Vora, A et al. 2002

Abbreviations: CNS, central nervous system; AGEP, acute generalized exanthematous pustulosis

4.7 Influencing factors

The following section aims to determine factors that influence the frequency of adverse events associated with imatinib mesylate in CML patients. The dose of imatinib, disease stage of patients, duration of treatment with imatinib, and pre-treatment status are investigated.
Very common adverse events (as defined by the WHO criteria) are those that occur in more than 10% of patients (International drug monitoring, WHO 1972). Such adverse events that occur in three or more studies, to allow a comparison, have been reviewed further.

The studies from each of the potential risk factors identified have been grouped together and presented in tables. Key findings have then been summarised for the purpose of the study. The following tables will highlight the key variables across the studies. Quantitative analyses have not been undertaken due to the lack of homogeneity of the studies included in the review.

4.7.1 Dose

The effect of the dose of imatinib on the frequency of the common adverse events is shown in Table 4.7.1. 15 studies assessed imatinib use at doses 400/600 mg daily, 2 assessed imatinib at 600mg once daily and 2 further assessed imatinib use at 800 mg daily. The studies generally showed that doses of 400/600 mg resulted in higher frequencies in most of the adverse events assessed. One of the two studies assessing imatinib at 800 mg was a study focussing on dermatological events alone (Valeyrie, L et al 2003). This study reported the highest levels of rash and pruritus. Some adverse events were only observed in the 400/600 mg group of patients, for instance, abdominal pain, anorexia, arthralgia, dermatitis, dyspepsia, GI symptoms (as classified by the authors), headache, leukopenia, myalgia, and vomiting.

Table 4.7.1.1, Percentage of CML patients experiencing toxicities following treatment with imatinib mesylate at doses ranging from 400 mg to 800 mg daily. *denotes grades 3 and 4 only; # denotes grades 1 and 2 only

	Studies assessing imatinib at 400/600 mg															Studies assessing imatinib at 600mg		Studies assessing imatinib at 800mg	
	Anderlini2004 n = 15	*Arora2004 n = 118*	*Cervantes 2003a n = 98*	*Cervantes 2003b n = 150*	*Gardembas 2003 n = 30*	*Kantarjian 2002a n = 532*	*Kantarjian 2002b n = 261*	*Kantarjian 2003b n = 50*	*Kantarjian 2004a n = 261*	*Kim2004 n = 13*	*Le Coutre2003 n = 39*	*Morishima2004 n = 39*	*Rosti2004 n = 191*	*Sawyers2002 n = 260*	*Talpaz2002 n = 235*	*Kantarjian 2002c n = 237*	*van Deventer 2003 n = 28*	*Kantarjian 2004b n = 114*	*Valeyrie 2003 n = 54*
Abdominal pain	-	-	-	-	53	19	-	-	-	-	-	10	-	10	17	-	-	-	-
Anaemia	-	-	12*	6*	10	7*	7*	8*	14*	-	13	15	-	52*	39*	-	-	10*	-
Anorexia	-	-	-	-	13	-	-	-	-	-	-	-	-	-	8	-	-	-	-
Arthralgia	-	-	-	4	-	19	-	-	-	15#	3	10	-	8	12	-	-	-	-
Bone pain	-	-	-	-	-	-	-	-	-	-	-	-	-	-	9	-	-	3*	-
Dermatitis	-	-	-	-	-	-	-	-	-	-	-	46	-	23	22	-	-	-	-
Diarrhea	-	-	-	-	40	29	0.4*	-	0.4*	8#	-	21	-	24	37	2	-	1*	-
Dyspepsia	-	-	-	-	-	17	-	-	-	-	-	-	-	7	16	-	-	-	-
Fatigue	-	-	-	-	-	18	0.4*	2*	0.4*	-	-	21	-	8	11	7	-	1*	-
GI symptoms	-	-	18	12	-	-	-	-	-	-	-	-	-	0.8	-	-	-	-	-
Granulocytopenia	-	-	33*	33*	-	-	41*	20*	62*	46*	-	-	-	-	-	17*	-	-	-
Haemorrhage	-	-	-	1	-	0.4	-	-	-	-	-	-	0.5	11	12	-	4	-	-
Headache	-	-	-	-	30	13	-	-	-	-	-	-	-	10	13	-	-	-	-
Leukopenia	-	-	-	-	-	23*	-	-	-	-	10	33	-	-	47*	-	-	-	-
Liver toxicity	-	-	3	2	-	1	1*	4*	2*	-	-	5	1	8	7	5	-	7*	-
Muscle cramps	-	-	15	22	37	49	-	2*	-	-	26	15	-	25	32	7	-	-	-
Myalgia	-	-	-	-	-	20	-	-	-	31#	-	10	-	6	13	-	-	-	-
Nausea	-	-	-	-	83	55	-	-	-	-	5	44	-	63	65	1	-	1*	-
Neutropenia	67*	-	-	-	53	35*	-	-	-	-	8	36	-	63*	58*	-	19*	36*	-
Oedema*	7	48	21	22	50	60	-	-	-	62#	46	64	-	65	64	3	-	1*	65
Pruritus	-	-	-	-	13	9	-	-	-	-	-	-	-	-	9	-	-	-	41
Rash	-	12.7	3	9	23	32	2*	6*	2*	-	15	-	0.5	-	-	4	-	6*	67
Thrombocytopenia	47*	-	27*	16*	50	20*	18*	8*	23*	-	41	39	1	62*	43*	13*	40.7	25*	-
Vomiting	-	-	-	-	63	23	-	-	-	-	-	15	-	44	49	-	-	-	-
Weight gain	-	-	-	-	-	26	-	-	-	-	13	-	-	-	11	1	-	-	-

4.7.2 Disease Stage

Imatinib was investigated in each of the three disease stages of CML. Two of the studies assessed imatinib use in patients in the blast crisis of their disease, three of the studies were in accelerated phase and 13 studies were in the chronic phase of CML (Tables 4.7.2.1-2). Anorexia, bone pain, GI symptoms, granulocytopenia, pruritus and weight gain were not described or observed in the blast crisis studies. Conversely, all other adverse events, with the exception of haemorrhage, were observed in patients in the chronic phase of CML. The number of haemorrhages in advanced disease stages remains low, at below 5%. All of the adverse events, with the exception of GI symptoms (as classified by the study authors), occurred in the accelerated phase of CML also.

Table 4.7.2.1, Percentage of patients with very common toxicities in the chronic phase of CML following imatinib treatment. *denotes grades 3 or 4 events (grades from NCI-CTC criteria)

	Cervantes 2003a n = 98	Cervantes 2003b n = 150	Cortes2003 n = 36	Druker 2001a n = 83	Gardembas2003 n = 30	Kantarjian2002a n = 532	Kantarjian2002b n = 261	Kantarjian2003b n = 50	Kantarjian2004a n = 261	Kantarjian2004b n = 114	Le Coutre2003 n = 39	Morishima2004 n = 39	Rosti2004 n = 191
Abdominal pain	-	-	-	-	53	19	-	-	-	-	-	10	-
Anaemia	12*	6*	81	5*	10	7*	7*	8*	14*	10*	13	15	-
Anorexia	-	-	-	-	13	-	-	-	-	-	3	10	-
Arthralgia	-	4	-	13	-	19	-	-	-	-	-	-	-
Bone pain	-	-	42	-	-	-	-	-	-	3*	-	-	-
Dermatitis	-	-	-	-	-	-	-	-	-	-	-	46	-
Diarrhoea	-	-	19	25	40	29	0.4*	-	0.4*	1*	-	21	-
Dyspepsia	-	-	-	18	-	17	-	-	-	-	-	-	-
Fatigue	-	-	22	20	-	18	0.4*	2*	0.4*	1*	-	21	-
GI symptoms	18	12	-	-	-	-	-	-	-	-	-	-	-
Granulocytopenia	33*	33*	-	-	-	-	41*	20*	62*	-	-	-	-
Haemorrhage	-	1	-	-	-	0.4	-	-	-	-	-	-	0.5
Headache	-	-	-	-	30	13	-	-	-	-	-	-	-
Leukopenia	-	-	-	-	-	23*	-	-	-	-	10	33	-
Liver toxicity	3	2	19	-	-	1	1*	4*	2*	7*	-	5	1
Muscle cramps	15	22	-	-	37	49	-	2*	-	-	26	15	-
Myalgia	-	-	-	41	-	20	-	-	-	-	-	10	-
Nausea	-	-	19	43	83	55	-	-	-	1*	5	44	-
Neutropenia	-	-	78	14	53	35*	-	-	-	36*	8	36	-
Oedema	21	22	50	39	50	60	-	-	-	1*	46	64	-
Pruritus	-	-	-	-	13	9	-	-	-	-	-	-	-
Rash	3	9	36	19	23	32	2*	6*	2*	6*	15	-	0.5
Thrombocytopenia	27*	16*	39	16	50	20*	18*	8*	23*	25*	41	39	1
Vomiting	-	-	-	18	63	23	-	-	-	-	-	15	-
Weight gain	-	-	-	-	-	26	-	-	-	-	13	-	-

Table 4.7.2.2, Percentage of patients with very common toxicities in the accelerated and blast phases of CML following imatinib treatment. *denotes grades 3-4 events

	Studies assessing imatinib use in the accelerated phase			Studies assessing imatinib use in the blast crisis	
	Kantarjian 2002c *n = 237*	*Talpaz 2002* *n = 235*	*vanDeventer 2003* *n = 28*	*Sawyers 2002* *n = 260*	*Sureda 2003* *n = 30*
Abdominal pain	-	17	-	10	-
Anaemia	-	39*	-	52*	-
Anorexia	-	8	-	-	-
Arthralgia	-	12	-	8	13
Bone pain	-	9	-	-	-
Dermatitis	-	22	-	23	-
Diarrhoea	2	37	-	24	23
Dyspepsia	-	16	-	7	-
Fatigue	7	11	-	8	37
GI symptoms	-	-	-	0.8	-
Granulocytopenia	17*	-	-	-	-
Haemorrhage	0.4	12	4	11	-
Headache	-	13	-	10	-
Leukopenia	-	47*	-	-	57
Liver toxicity	5	7	-	8	20
Muscle cramps	7	32	-	25	-
Myalgia	-	13	-	6	-
Nausea	1	65	-	63	33
Neutropenia	-	58*	19*	63*	-
Oedema	3	64	-	65	40
Pruritus	-	9	-	-	-
Rash	4	-	-	-	3
Thrombocytopenia	13*	43*	40.7	62*	43
Vomiting	-	49	-	44	23
Weight gain	1	11	-	-	-

4.7.3 Pre-treatment history

There is no apparent association of adverse drug reactions with the pretreatment status of patients. 16 studies investigated imatinib use in patients who had failed standard treatments (IFN-alpha), 3 studies investigated imatinib use in newly diagnosed patients and 4 investigated its use post allogeneic stem cell transplantation (tables 4.7.3.1-2). Patients in the ASCT group generally experienced fewer adverse events than the other two groups compared to it. Newly diagnosed patients did not appear to experience as broad a spectrum of adverse events as the group that failed on standard therapies; the group that failed on previous treatments experienced all of the adverse events defined as common, whereas the newly diagnosed group did not experience arthralgia, dermatitis, dyspepsia, GI symptoms (as classified by the authors), haemorrhages, leukopenia, myalgia and weight gain. Of the adverse events described in this group, the frequency was variable; adverse events were higher in newly diagnosed patients than the patient group that failed on standard drug regimens as in the case of abdominal toxicity, and lower in other toxicities, for instance oedema.

Table 4.7.3.1, Percentage frequency of adverse events following imatinib therapy in CML patients refractory to drug therapy. *denotes grades 3-4 events

	Cervantes 2003b n = 150	Champagne 2004 n = 31	Cortes 2003 n = 36	Druker 2001a n = 83	Druker 2001b n = 58	Kantarjian 2002a n = 532	Kantarjian 2002b n = 261	Kantarjian 2002c n = 237	Kantarjian 2004a n = 261	LeCoutre 2003 n = 39	Rosti 2004 n = 191	Sawyers 2002 n = 260	Sureda 2003 n = 30	Talpaz 2002 n = 235	Valeyrie 2003 n = 54	van Deventer 2003 n = 28
Abdominal pain	-	-	-	-	-	19	-	-	-	-	-	10	-	17	-	-
Anaemia	6*	-	81	5*	-	7*	7*	-	14*	13	-	52*	-	39*	-	-
Anorexia	-	-	-	-	10	-	-	-	-	3	-	-	-	8	-	-
Arthralgia	4	1.5	-	13	-	19	-	-	-	-	-	8	13	12	-	-
Bone pain	-	-	42	-	-	-	-	-	-	-	-	-	-	9	-	-
Dermatitis	-	-	-	-	2	-	-	-	-	-	-	23	-	22	-	-
Diarrhoea	-	2.7	19	25	17	29	0.4*	2	0.4*	-	-	24	23	37	-	-
Dyspepsia	-	-	-	18	-	17	-	-	-	-	-	7	-	16	-	-
Fatigue	-	3.5	22	20	10	18	0.4*	7	0.4*	-	-	8	37	11	-	-
GI symptoms	12	-	-	-	-	-	-	-	-	-	-	0.8	-	-	-	-
Granulocytopenia	33*	-	-	-	-	-	41*	17*	62*	-	-	-	-	-	-	-
Haemorrhage	1	1	-	-	2	0.4	-	0.4	-	-	0.5	11	-	12	-	4
Headache	-	-	-	-	-	13	-	-	-	-	-	10	-	13	-	-
Leukopenia	-	-	-	-	-	23*	-	-	-	10	-	-	57	47*	-	-
Liver toxicity	2	6.7	19	-	2	1	1*	5	2*	-	1	8	20	7	-	-
Muscle cramps	22	-	-	-	-	49	-	7	-	26	-	25	-	32	-	-
Myalgia	-	-	-	41	21	20	-	-	-	-	-	6	-	13	-	-
Nausea	-	4	19	43	55	55	-	1	-	5	-	63	33	65	-	-
Neutropenia	-	-	78	14	66*	35*	-	-	-	8	-	63*	-	58*	-	19*
Oedema	22	-	50	39	41	60	-	3	-	46	-	65	40	64	65	-
Pruritus	-	-	-	-	-	9	-	-	-	-	-	-	-	9	41	-
Rash	9	-	36	19	17	32	2*	4	2*	15	0.5	-	3	-	67	-
Thrombocytopenia	16*	-	39	16	69*	20*	18*	13*	23*	41	1	62*	43	43*	-	40.7
Vomiting	-	3.5	-	18	41	23	-	-	-	-	-	44	23	49	-	-
Weight gain	-	-	-	-	-	26	-	1	-	13	-	-	-	11	-	-

Table 4.7.3.2, Percentage frequency of adverse events to imatinib in newly diagnosed CML patients and those who have relapsed post stem cell transplantation. #denotes grades 1 -2 events; *denotes grades 3-4 events

	Newly diagnosed patients			Post-Stem cell transplantation			
	Gardembas2003 n = 30	*Kantarjian2003b n = 50*	*Kantarjian2004b n = 114*	*Anderlini2004 n = 15*	*Cervantes2003a n = 98*	*Kantarjian2002d n = 28*	*Kim2004 n = 13*
Abdominal pain	53	-	-	-	-	-	-
Anaemia	10	8*	10*	-	12*	-	-
Anorexia	13	-	-	-	-	-	-
Arthralgia	-	-	-	-	-	-	15#
Bone pain	-	-	3*	-	-	-	-
Dermatitis	-	-	-	-	-	-	-
Diarrhoea	40	-	1*	-	-	-	8#
Dyspepsia	-	-	-	-	-	-	-
Fatigue	-	2*	1*	-	-	-	-
GI symptoms	-	-	-	-	18	-	-
Granulocytopenia	-	20*	-	-	33*	21*	46*
Haemorrhage	-	-	-	-	-	-	-
Headache	30	-	-	-	-	-	-
Leukopenia	-	-	-	-	-	-	-
Liver toxicity	-	4*	7*	-	3	18*	-
Muscle cramps	37	2*	-	-	15	4*	-
Myalgia	-	-	-	-	-	-	31#
Nausea	83	-	1*	-	-	4*	-
Neutropenia	53	-	36*	67*	-	-	-
Oedema	50	-	1*	7	21	10*	62#
Pruritus	13	-	-	-	-	-	-
Rash	23	6*	6*	-	3	39	-
Thrombocytopenia	50	8*	25*	47*	27*	14*	-
Vomiting	63	-	-	-	-	-	-
Weight gain	-	-	-	-	-	4*	-

4.7.4 Treatment duration

Table 4.7.4.1 describes the duration of imatinib treatment and its effect on the frequency of adverse events. The table presents all of the studies that detailed a median study duration period (in days); from left to right, the duration of imatinib treatment increases. The first study by Druker, BJ et al 2001b had a median follow-up of 74 days, while the last study by Kantarjian, HM et al 2004a had a median follow-up of 1350 days.

All of the adverse events vary in frequency, with no consistent pattern according to study duration. For example, anaemia is not described in the studies of short duration; it shows a high frequency of over 50% in the Sawyers study (Sawyers, CL 2002). It then remains substantially lower (mostly below 20%) in the studies that follow. Anaemia is at its highest frequency in the study by Cortes, J et al 2003, which had a median study duration of 480 days. Granulocytopenia was at its highest frequency in the study with the longest median study duration of 1350 days (Kantarjian 2004a). There were four recorded events of leukopenia, the highest recorded frequency was just below 50% in the study by Talpaz, M et al 2002, which had a median follow-up of 315 days. Eleven studies treated patients for a longer duration than this study, with one reporting leukopenia. Thrombocytopenia and neutropenia both had varying frequencies as the follow-up period increased. The highest level of neutropenia was in the study by Cortes, F et al 2003, at 480 days. The highest reported frequency of thrombocytopenia was in the study by Druker, BJ et al 2001b which had a median follow-up of 74 days – study with the shortest study period.

Muscle cramps were described in eleven studies, with varying frequencies over time. The highest frequency was 49% in the study by Kantarjian, HM et al 2002a (median follow-up 513 days). This was the longest study period that recorded muscle cramps. All other events occurred in varying frequencies. Headaches were higher in the study by Gardembas, M et al 2003, which had a median follow-up of one year. Bone pain was recorded in three studies, two of which had a median follow-up of greater than 450 days. The studies with the longest follow-up period (Rosti, G et al 2004 and Kantarjian, HM et al 2004a (780 and 1350 days respectively) did not report any adverse events which fell into the pain category.

Studies with the longest study duration (Rosti, G et al 2004; Kantarjian, HM et al 2004a) show low frequencies of the adverse events reported. Many other studies also show low frequencies of GI and hepatobiliary events. The broad category of GI symptoms (which could include any of the other symptoms recorded in this category such as nausea/vomiting) is reported by the two Cervantes studies, post one year of treatment (Cervantes, F et al 2003a and b).

The level of oedema remained relatively constant over the duration of the studies; levels of over 40% were commonly reported. Rash was variable and no trend was observed with duration of follow-up.

Table 4.7.4.1, Percentage frequency of adverse events at median study duration periods (study duration time increases from left to right)

	Druker 2001b (74 days)	Sawyers 2002 (93 days)	Valeyrie 2003 (126 days)	Arora 2004 (180 days)	LeCoutre 2003 (211 days)	Morishima 2004 (237 days)	van eventer 2003 (238 days)	Kantarjian 2002c (246 days)	Kantarjian 2003b (270 days)	Druker 2001a (310 days)	Talpaz 2002 (315 days)	Kim 2004 (351 days)	Anderlini 2004 (365 days)	Gardembas 2003 (365 days)	Cervantes 2003b (395 days)	Cervantes 2003a (420 days)	Kantarjian 2004b (450 days)	Cortes 2003 (480 days)	Kantarjian 2002d (480 days)	Kantarjian 2002b (510 days)	Kantarjian 2002a (513 days)	Rosti 2004 (780 days)	Kantarjian 2004a (1350 days)
Abdominal pain	-	10	-	-	-	10	-	-	-	-	17	-	-	53	-	-	-	-	-	-	19	-	-
Anaemia	-	52*	-	-	13	15	-	-	8*	5*	39*	-	-	10	6*	12*	10*	81	-	7*	7*	-	14*
Anorexia	10	-	-	-	3	10	-	-	-	-	8	-	-	13	-	-	-	-	-	-	-	-	-
Arthralgia	-	8	-	-	-	-	-	-	-	13	12	15#	-	-	4	-	-	-	-	-	19	-	-
Bone pain	-	-	-	-	-	-	-	-	-	-	9	-	-	-	-	-	3*	42	-	-	-	-	-
Dermatitis	2	23	-	-	-	46	-	-	-	-	22	-	-	-	-	-	-	-	-	-	-	-	-
Diarrhea	17	24	-	-	-	21	-	2	-	25	37	8#	-	40	-	-	1*	19	-	0.4*	29	-	0.4*
Dyspepsia	-	7	-	-	-	-	-	-	-	18	16	-	-	-	-	-	-	-	-	-	17	-	-
Fatigue	10	8	-	-	-	21	-	7	2*	20	11	-	-	-	-	-	1*	22	-	0.4*	18	-	0.4*
GI symptoms	-	0.8	-	-	-	-	-	-	-	-	-	-	-	-	12	18	-	-	-	-	-	-	-
Granulocytopenia	-	-	-	-	-	-	-	17*	20*	-	-	46*	-	-	33*	33*	-	-	21*	41*	-	-	62*
Haemorrhage	2	10	-	-	-	-	4	0.4	-	-	12	-	-	-	1	-	-	-	-	-	0.4	0.5	-
Headache	-	10	-	-	-	-	-	-	-	-	13	-	-	30	-	-	-	-	-	-	13	-	-
Leukopenia	-	-	-	-	10	33	-	-	-	-	47*	-	-	-	-	-	-	-	-	-	23*	-	-
Liver toxicity	2	8	-	-	-	5	-	5	4*	-	7	-	-	-	2	3	7*	19	18*	1*	1	1	2*
Muscle cramps	-	25	-	-	26	15	-	7	2*	-	32	-	-	37	22	15	-	-	4*	-	49	-	-
Myalgia	21	6	-	-	-	10	-	-	-	41	13	31#	-	-	-	-	-	-	-	-	20	-	-
Nausea	55	63	-	-	5	44	-	1	-	43	65	-	-	83	-	-	1*	19	4*	-	55	-	-
Neutropenia	66*	63*	-	-	8	36	19*	-	-	14	58*	-	67*	53	-	-	36*	78	-	-	35*	-	-
Oedema	41	64	65	48	46	64	-	3	-	39	64	62#	7	50	22	21	1*	50	10*	-	60	-	-
Pruritus	-	-	41	-	-	-	-	-	-	-	9	-	-	13	-	-	-	-	-	-	9	-	-
Rash	17	-	67	12.7	15	-	-	4	6*	19	-	-	-	23	9	3	6*	36	39	2*	32	0.5	2*
Thrombocytopenia	69*	62*	-	-	41	39	40.7	13*	8*	16	43*	-	47*	50	16*	27*	25*	39	14*	18*	20*	1	23*
Vomiting	41	44	-	-	-	15	-	-	-	18	49	-	-	63	-	-	-	-	-	-	23	-	-
Weight gain	-	-	-	-	13	-	-	1	-	-	11	-	-	-	-	-	-	-	4*	-	26	-	-

#denotes grades 1 -2 events; *denotes grades 3-4 events

5.0 Discussion

The aim of this review was to assess the adverse event profile and factors that may influence the frequency of these events following treatment with the tyrosine kinase inhibitor imatinib mesylate for CML. Imatinib was the first of a generation of tyrosine kinase inhibitors and was designed to inhibit the molecular abnormality found in over 90% of CML patients.

Imatinib was licensed on preliminary data since it produced such remarkable responses in patients with CML, and was generally well tolerated. Licensing imatinib at such an early stage enabled patients with a terminal illness to be treated with a promising agent. At the time of licensing however, the long-term effects and overall safety of imatinib, remained to be determined.

This thesis has assessed all of the published studies of imatinib mesylate use in CML that described toxicity data. Uncontrolled studies of different phases, case reports and randomised controlled studies were reviewed for their overall quality and the information they provided. Some of the information was previously described and this thesis has overlapped such data. The aim of this review is to provide a more comprehensive and up-to-date profile of the adverse events associated with imatinib mesylate in CML patients.

THE PROBLEMS OF REVIEWING ADVERSE EVENTS

Searching

Conducting any type of systematic review of adverse events is often highly problematic due to the vast and variable information available. The initial problem arises in the first stage of searching for the literature and trying to determine a suitable strategy that will capture all of the information required (Derry, S et al, 2001; Bagett, R et al, 1999). When investigating the adverse event profile of a particular drug, as in the case of this review, it appears best to search the literature for the drug name – both generic and brand name. Manual searches are extremely tedious and are open to error, although they are the optimum searching methods when trying to obtain adverse event data. In the case of imatinib, the searches were over the five year period,

since the drug was launched. Manual searches would be highly impractical for drugs which have been in the market for much longer than this period.

Evidence/literature

Upon deciding on a focussed research question, the next step is to identify the literature needed to achieve the aim of the study. The main considerations in conducting any systematic review are the amount and type of evidence available to the researcher, noting that adverse events are reported in observational studies, RCTs and non-randomised studies. The strengths and weaknesses of the different types of evidence must be considered when making assessments from the studies (Figure 5.1).

Systematic reviews generally incorporate RCTs, considering they are the 'gold standard' of clinical trials as there is a control group which is compared to the new therapeutic arm. This approach is most certainly appropriate when assessing efficacy or response to the new agent, although in the case of adverse events or 'risk' to the treatment it poses its own problems. Firstly, to include only RCT data would dismiss a wealth of information from other types of evidence (i.e., case reports, uncontrolled/cohort studies). This approach would perhaps be suitable if comparing two agents, for example, if one were to compare the safety of imatinib and IFN-alpha, it would be wise to use studies in which the two were compared in a randomised controlled manner. Assessing a single drug profile would be best achieved by investigating its use in all settings. This would allow the findings of the review to be more generalisable.

RCTs also lack long-term toxicity data, which is often obtained through prolonged use of drugs. RCTs often have too short a study period and an unusually idealised patient population to gain a true reflection of the risk of a therapeutic intervention. Adverse events are often reported in observational studies, some of which may focus on a particular type of adverse event, or a particular patient group. Nevertheless, it gives a wider picture of the toxicity profile of a drug to be used in the targeted patients. It must be highlighted that the use of case reports in a systematic review presents a significant bias to interpretation. However, a review of adverse events would be incomplete without mention of individual cases of severe problems possibly associated with the drug. It is important to assess these findings in the context of the entire review and give

weight to each piece of evidence based on its quality and generalisability. This review was unique in that the literature base was unusually small and consisted of mainly uncontrolled and consequently highly biased data.

Table 5.1, Strengths and weaknesses of studies included in systematic reviews of harmful effects *(Jefferson, T et al 2003)*

Study design	Strengths	Weaknesses
Case report	Early warning	Bias, differing case definitions, lack of comparators
Case crossover and case based studies	No need for independent controls	Lack of wide acceptance, bias, differing case definition
Case-control study	Can test hypotheses, especially rare events	Confounding, bias, differing case definitions
Cohort study	Powerful, cheap (if retrospective)	Confounding, bias (especially attrition), differing case definitions
Historical control study	Powerful, cheap	Bias, differing case definitions, difficulty in interpretation, differing case definitions
Randomised and clinically controlled studies	Powerful, minimisation of all biases	Short follow up, limited power, differing case definitions

The size of the studies is also an important aspect to consider. The sample size of a study is particularly important since a sample size that is small will carry with it an unacceptable risk of accepting a null hypothesis when it is in fact false. A sample size that is larger than required is wasteful of resources and may reveal a statistically significant difference, which is of no practical significance. It is not clear whether studies with smaller sample sizes would have recognised rare adverse events.

REPORTING

The literature used for this assessment was diverse in study design and the information provided with regards to toxicity. Even when studies reported that their outcome measures included toxicity, adverse event data was often erratic and gave a selected profile of the findings. Missing or unexplained findings were a frequent problem. Such a lack of homogeneity amongst the studies created difficulties in drawing valid interpretations or conclusions. There appears to be a

lack of useful guidelines to the way in which toxicity information should be reported for reviewers to be able to make use of the data.

One of the unfortunate failings of studies recording adverse events is the lack of background information on the patients and the way the study was undertaken. In order for reviewers to make use of the toxicity data, baseline characteristics would be useful, as well as dose information, pretreatment status and concomitant therapy. In this assessment, these were often poorly described. Vital information was not given making it difficult to assess whether events were attributable to the drug rather than an underlying recurrent condition. Studies also failed to mention other key features of the treatment regimen, such as dose reductions/temporary discontinuation, and durations of adverse events etc.

Although many of the studies stated that the primary aim of the study was to assess toxicity, reporting showed that this may not have been the case since the information was inadequate. Often, the most commonly occurring and severe events were described, rather than all of the toxicity data. Studies that did not declare toxicity assessments as the main aims of the study usually reported few adverse events. Even when it appeared that all of the toxicity data was provided, further inspection of preliminary work submitted to regulatory agencies such as the FDA showed that only events seen in more than 5 or 10% of patients was given in the published studies (Sawyers, CL et al, 2002; Talpaz, M et al, 2002).

Studies reported adverse event data in different ways; some authors preferred to declare the number of events while others may have reported the number of patients experiencing the event as the study by Rosti and colleagues did (Rosti, G et al 2004). It was often unclear which of the two methods were used since authors neglected to mention what they were reporting – this review assumed that all studies reported the number of events unless otherwise stated. This would inevitably mislead readers trying to obtain a picture of the adverse event profile of a drug.

Authors tend to follow a particular style of reporting and disseminating information. A number of authors conducted multiple studies of imatinib, for example, Kantarjian, HM et al published eight studies, and Cervantes, F et al and Druker, BJ et al published two studies. Cervantes was the only author to use the term GI symptoms in both of the studies rather than define what this

term meant. The study also used the term granulocytopenia in isolation (no mention of neutropenia – although none may have been observed).

Adverse event reporting was often erratic. The general trend was to present data in tables, although the text would often report further toxicities. It was unclear on occasions whether the author was elaborating on an event described in a table, or whether this was a separate event entirely. It is not clear therefore whether all events were reported. Other studies reported data in the text alone, without any tables or graphs to reflect the findings. Withdrawals, when described, were usually described in the text. It was often unclear whether patients withdrew from the study due to adverse events or other reasons. Information on withdrawal should be a key consideration in a systematic review as a marker for the overall safety of a treatment. Similarly, mortality associated with imatinib was very rarely described in sufficient detail.

Adverse events were also defined differently across studies. For example, authors used terms interchangeably - rash and dermatitis were commonly described as the same event; some authors would use the term oedema, while others defined the same event as fluid retention. The term was elaborated on further in some studies by stating its location, such as periorbital oedema. Similarly, haemorrhages were separated according to the region in which they occurred. Of particular concern are descriptions such as liver failure. Some authors chose to describe this occurrence by describing abnormal levels of liver enzymes and not using the term liver failure. Others did the contrary – stating that liver failure occurred but not defining it by abnormal laboratory tests.

A frequent problem observed in CML patients treated with imatinib was haematologic toxicity. The results from the studies may have been slightly misleading due to the terms that authors chose to use, as neutrophils are a type of granulocyte, and granulocytes are types of leukocytes. Common haematologic problems were a reduction in the levels of these cells (neutropenia, granulocytopenia, and leukopenia). Some of the studies stated granulocytopenia, without mention of whether this included neutropenia and vice versa, for example, the studies by Cervantes, F et al 2003a and 2003b, and Kantarjian, HM et al 2002c. etc. Other studies reported leukopenia with neutropenia, but no mention of granulocytopenia, e.g., Kantarjian, HM et al

2002a, Le Coutre, P et al 2003. This is misleading since these conditions overlap – the frequency of neutropenia could potentially be much higher, although this is unknown due to the terms applied by authors.

The definition of severity of adverse events was also another possible source of error although it was addressed to some extent by some authors. Most of the studies gave toxicity criteria which were used to define the severity of events. Unfortunately, only the most severe grades were usually described. Although perhaps more useful in the short-term, all grades should be reported to gain an idea of frequency for the long-term use of the drug, particularly in the case of new drugs.

The assessment undertaken in this thesis found that the studies upon which imatinib was licensed, were amongst the best in terms of reporting toxicity. There were more recorded toxicities in these studies compared with post-marketing studies, for example, abdominal pain was only described in phase 2 studies. This could either have been attributed to the observation of more toxicities in these particular studies, or better reporting of the adverse events observed. The latter suggestion seems more feasible since a phase one/two study of this nature would have had to be thorough to be granted a license (extra care taken to report all of the adverse events for the licensing process). However, the information provided by the published studies may still be only a selected proportion of the entire findings. The studies by Sawyers, CL et al 2002 and Talpaz, M et al 2002 only described serious (grades 3&4) toxicities as opposed to all of the adverse events findings.

An important point to consider is the presence of publication bias, particularly in the case of adverse event reporting. This occurs when the publication of research depends on the direction of the study results and whether they are statistically significant, and is one of the most difficult biases to overcome. Studies with positive findings can be as much as three times more likely to be published than negative studies (Egger, M et al 1998). Even if negative studies are chosen for publication they can face an increased delay or be published in a less visible source (Frank, E et al 1994). Negative publications produced by non-English authors may be submitted to a local non-English language journal that is less likely to be indexed by well-known databases such as Medline (Gregoire, G et al 1995). As a consequence, reviews may produce the same exaggerated

estimates of treatment effect. The review in this thesis is biased to an extent, since it has failed to incorporate studies that were not available in English. Another key limitation to this systematic review is that the inclusion and exclusion criteria were not assessed by an independent observer. Similarly, the validity criteria and data extraction were not checked by more than one author.

EXISTING LITERATURE

Systematic reviews of adverse events are rarely undertaken due to the vast information available, and the unreliability of the data. Accurate inferences are difficult to make due to the nature of adverse event findings, which prevents researchers conducting such reviews.

Published literature has shown various kinds of systematic reviews of adverse events. The most common type of review into toxicity involves the inclusion of RCT or other controlled data, and investigates the efficacy of agents, with the toxicity acting as a secondary objective (Dalziel, K et al 2004). Such reviews have been limited in the information that they have provided in terms of the risk profile of the drug, although a comparative assessment (to other drugs) can be made.

Other systematic reviews investigate a particular adverse event in a disease type, for example, the risk of myocardial infarction by angiotensin receptor blockers (McDonald, MA et al 2005). These types of systematic reviews have a clear research question, and therefore a smaller data subset to include in their review. Such reviews are clearly important when trying to determine whether there is a finite risk of developing certain toxicity from taking a particular therapeutic intervention.

In considering toxicity of other therapeutic agents, one systematic review was identified which included data from a variety of different sources in addition to clinical trials. A review of the safety of products derived from Echinacea species was undertaken by Huntley et al (2005). The group used data from spontaneous reporting programmes, such as WHO and other national bodies (such as the MHRA and Medwatch in the FDA). Manufacturers of the products were also approached for details of adverse events, presumably in post-marketing surveillance and unpublished trials. This appears to be the most comprehensive published assessment of adverse

events. Such a venture may however be impractical, in most cases particularly if the findings are not likely to influence drug prescribing.

A systematic review of anti-rheumatic drugs was conducted by Choy et al (2005), which described both the efficacy and toxicity of adverse events related to drug use. Toxicity was assessed by the numbers of patients who withdrew due to adverse events. This is a valid measure of toxicities, which was unfortunately lacking in the literature available in relation to imatinib at the time of conducting this review. Withdrawal information is key in determining the extent of patients ability to tolerate and therefore benefit from a new agent.

From the initial searches, it became evident that systematic reviews of adverse events were not commonly conducted using uncontrolled clinical data. Two reviews of this nature were identified in the preliminary stages of this project (Garside, R et al 2002 and Dalziel, K et al 2004). The reviews included uncontrolled data, alongside RCT data. They each took into consideration the varying quality of the different types of study when making inferences. The reviews, however, assessed the harm of taking the agents alongside the efficacy and cost-effectiveness. The reviews did not consider the factors which may have influenced the frequency of adverse events, as this review has, but merely reviewed the toxicities as described in section 1 of the results. The questions posed in section 2 of this thesis could be systematically reviewed individually, i.e., the effect of dose on the frequency of adverse events in CML is a legitimate question that may be addressed in further works.

The interaction of regulatory authorities and industry are crucial in determining the safety of a new therapeutic intervention. The recent public health scandal of the increased incidence of cardiac toxicity associated with the use of the Cox-2 inhibitor rofecoxib (Vioxx©) presented a major concern in the dissemination of adverse drug profiles by industry. The case involved the detection of an increase in cardiac toxicity in patients receiving Vioxx compared with the control group (Bombardier, C et al 2000). This was later confirmed by further studies, which showed a latent effect (cardiac toxicities generally emerged after 18 months of treatment with Vioxx). The case was highlighted when it was revealed through a meta-analysis that the problem was detectable seven years earlier (Juni, P et al 2004). The role of the FDA as the public health watchdog was scrutinised, as it had failed to detect this problem sooner. It emerged that the drug

manufacturer Merck were aware of the increased risk of cardiac toxicity and failed to provide the unpublished findings showing the increased risk (Horton, R 2004).

The resulting cardiac toxicity through continued use of Vioxx was observed in meta-analyses, which included RCT data alone (Juni, P et al 2004). RCTs have a larger sample size than phase 1 and 2 studies, and typically have a longer follow-up period. Since the observed events occurred after 18 months of use, RCT data may have been the most useful in determining the long-term effects of drug use. Similarly, a comparison allowed the effect to be determined against standard treatment, allowing a better assessment of risk/benefit. The case of Vioxx highlighted the issues concerning the safety of drugs, and proved that long-term testing in large patient populations were essential in determining the risk of new therapeutic agents. This thought was echoed in statements by major journal editorials which re-iterated the importance of post-marketing risk surveillance.

Another recent prominent case of drug safety is the incidence of suicide following the use of selective serotonin reuptake inhibitors (SSRIs). This has been highlighted by a number of studies, and three large systematic reviews have been undertaken to determine the association of this risk with the drugs (Fergusson, D et al 2005; Gunnell, D et al 2005; Martinez, C et al 2005). Fergusson et al (2005) conducted a systematic review of published RCTs, and found that there was a significant risk of suicide in patients taking SSRIs compared with the control agents. Gunnell et al (2005) included published and unpublished RCTs submitted by pharmaceutical companies to the safety review of the MHRA, and observed that there was no increased risk of complete suicide in patients taking SSRIs. A nested case-control study based on information extracted from the General Practice Research Database was conducted by Martinez et al (2005), and found that users of SSRIs were not at an increased risk of suicide or non-fatal harm. This case raises the importance of consideration of different types of evidence and the inferences that are made from them. Clearly, reviews have their limitations and these are to be taken into account when forming judgements.

ADVERSE EVENTS

This systematic review has given an insight into the adverse event profile of imatinib. There were differences in frequencies and severities of adverse events across the studies included in the assessment. Some of the findings related to the Gardembas et al (2003) study, which became somewhat of a control study for the uncontrolled clinical trials. The study investigated imatinib use in combination with cytarabine in patients with newly diagnosed (previously untreated or treated with hydroxyurea) CML patients. It was the only study in the review to use a combined treatment with imatinib. The study showed higher proportions of patients suffering from headaches, abdominal pain, nasopharyngitis, nausea and vomiting. The addition of cytarabine may have contributed to myelosuppression and in turn a greater susceptibility to infection. It was the only study in the review to report mucositis (13%) and asthenia (70%). Pruritus was observed in its highest proportions in the studies by Gardembas et al (2003) and Valeyrie et al (2003). Since the Valeyrie study focussed specifically on dermatological events, it appears to have described such toxicities with greater attention. The high frequency of pruritus was not observed in any other study which may indicate that cytarabine also influenced the prevalence of pruritus. These findings may suggest that the addition of cytarabine to imatinib treatment increased the frequencies of these events. It is unclear whether an assessment of the toxicity of imatinib should have included a study in which it was combined with a chemotherapeutic agent. Having conducted this review, it appears that including the Gardembas study highlighted the adverse events that were more likely to be attributable to imatinib rather than other agents (Gardembas, M et al 2003). Inclusion of studies assessing combination therapies provides a useful comparison in a largely uncontrolled data set.

Some of the adverse events may have overlapped or have been subjective. For instance, pain and ache were subjective terms. Some patients may not have made a distinction between the two terms. Similarly, the terms muscle pain and bone pain may have been confused. Some adverse events may have been associated with others, for example abdominal pain may have been associated nausea/vomiting and/or muscle cramps. Similarly, the presence of oedema may also have affected the weight of some patients - any observed weight gain in patients may have been attributed to oedema. A proportion of weight gain may be a direct result of the occurrence of fluid retention in many of the trial subjects. It is not clear whether such events that overlapped

were described separately as distinct events, or whether those recording toxicities described the more profound problem experienced by the patient.

An important consideration is the way in which adverse events were recorded. Patients may have neglected to mention certain adverse events, deeming them unrelated to the treatment. Other patients may have a tendency of over-reporting. It is at this stage that it is at the clinicians discretion to determine whether the patient is indeed experiencing an event related to the trial drug. Herein lies a potential bias. The style of the professional recording the adverse events may be important – if patients are prompted or rushed, this may lead to problems in reporting the true profile.

Renal failure, syndromes (e.g., Budd-Chiari syndrome), vascular problems, secondary malignancies and neurological symptoms were described by some of the studies. Most of the conditions are likely to be unrelated to imatinib, for instance, the presence of GVHD would have been a response to transplant rather than imatinib treatment (although, imatinib may have affected myelosuppression adversely and indirectly influenced this phenomena), and the presence of bronchogenic carcinoma was likely to have resulted from underlying problems in the patient. Neurological symptoms were present in a minority of patients. Some of the authors may have deemed these as unrelated to imatinib therapy – instead of describing them as individual events, the studies by Gardembas et al (2003) and Kantarjian et al (2004a) chose to classify them under the broad heading of neurological symptoms. Infections were likely to have been the result of the underlying disease; suppression of the immune system through general myelosuppression (either through imatinib treatment or the disease itself) would have led to an increased susceptibility to infections. Also, fatigue was described in the majority of studies. Fatigue was likely to have been the result of the disease as well as the use of imatinib.

The studies by Arora and Valeyrie focussed on dermatological events associated with imatinib (Arora, B et al 2004; Valeyrie, L et al 2003). This would also have affected the frequency of skin event reporting – dermatological events would have been specifically sought after in these studies, whereas other studies may have neglected to mention specific events that were unrelated to the primary objective of the study. Indeed these studies did report toxicities which were not observed in most of the other studies, for instance cheilitis, cutaneous dryness, hair darkening,

depigmentation, hyperpigmentation and photosensitivity. This highlights the problem of adverse event reporting – many of these patients were treated in other studies yet these events were not described in them. The aim of the study is important in the reliability of the results.

The study by Anderlini et al (2004) took place in patients treated with imatinib in the first 100 days of an allogeneic stem cell transplant. The level of thrombocytopenia was disproportionally high in this study. The transplant procedure would have resulted in some level of myelosuppression in itself, and treatment with imatinib may have increased the severity of the problem. Neutropenia was frequently observed across studies, in significant proportions. It was not reported in all of the studies however, which may be due to reporting –authors may have chosen to report severe grades only.

Bone pain was observed in nearly half of the patients in the study by Cortes et al (2003), disproportionally much higher than in the other studies. This may be due to the population of the patients treated or the manner in which bone pain and associated problems (such as limb pain, musculoskeletal pain etc) were reported.

INFLUENCING FACTORS

Published reviews explained that higher doses of imatinib may result in an increase in adverse events, and would require greater dose reductions (Deininger, MW et al 2003). This was not the case in the literature assessed in this review. Rash and pruritus were the only events that were significantly higher at increased doses. This occurrence may be due to the fewer studies assessing imatinib use at higher doses of imatinib. One of the two studies assessing imatinib at 800 mg was a study focussing on dermatological events alone (Valeyrie, L et al 2003). This may explain the occurrence of higher rates of dermatology related events (rash and pruritus) in this particular cohort. This study did not describe non-dermatological adverse events and so this reduced the evidence for adverse events in the 800 mg group further still. Similarly, the 600 mg imatinib dose was only assessed in two studies describing adverse event data, so it is difficult to assess imatinib use in this group of patients.

Anorexia, bone pain, GI symptoms, granulocytopenia, pruritus and weight gain were not described or observed in the blast crisis studies, which may be due to the lack of evidence (2 studies) in this end stage, or that these symptoms are not common in this patient group (Sawyers, CL et al 2002; Sureda, A et al 2003). Conversely, haemorrhage was not observed in patients in the chronic phase of CML, which may indicate that patients in later disease stages are more susceptible to this form of toxicity. The number of haemorrhages in advanced disease stages remains low, at below 5%, which indicates it is not frequent in this population either.
The frequency of granulocytopenia was 15% higher than in the interferon-failure group of patients, and about 20% higher than the newly diagnosed patients in the ASCT failed patients.
Patients in the ASCT group generally experienced fewer adverse events than the other two groups compared to it. This may be due to the reduced dose (in the study by Anderlini, P et al 2004).

Of the adverse events described in the newly diagnosed group, the frequency was variable; certain adverse events were significantly higher than the group that failed on standard drug regimens (e.g., abdominal toxicity), and lower for other toxicities (e.g., oedema). Again, this may be due to the larger proportion of evidence in patients who had failed on standard drug regimens compared to the newly diagnosed and ASCT failed groups

Other additional factors may have influenced toxicity which this review did not investigate; baseline characteristics (such as gender and ethnicity), concomitant therapies, genetic predispositions etc, may have affected the adverse event profile seen in patients.

PHARMACOGENETIC INFLUENCES

There were very few studies included in this review that examined imatinib use in different populations, as many were not published in English, and the review was limited to include literature in English only.

The study by Kim et al (2004) reported a higher proportion of arthralgia and myalgia than the other studies, and only the most serious grades of the events were described. This may have been

due to either under-reporting in other studies or the fact that imatinib may have a different reaction in the Korean patients followed in the study.

Similarly, the study by Morishima et al (2004) was a phase 2 study in Japanese patients; nearly half of all patients experienced dermatitis. This was a substantially higher proportion than in the other studies and again, the different population of patients may have contributed to this effect.

The study by Arora et al (2004) focussed specifically on dermatological events and reported the highest level of depigmentation than any of the other studies. The study took place in India. The problem of depigmentation may have been clearer in this subgroup rather than in other patients groups which were largely of Caucasian origin. Hyperpigmentation was also observed in this patient group. Changes in pigmentation were also seen in case-studies. It was proposed that the receptor c-Kit plays a role in the development of melanocytes and the interaction of imatinib with this receptor may interfere with pigmentation via this route.

IMPLICATIONS OF THE STUDY FINDINGS

The inconsistent reporting of adverse events suggests that any review or assessment of the adverse event profile of a drug could not be comprehensive.

When conducting a review of adverse events, problems of the inadequacies of toxicity reporting should be made clear to the reader, enabling them to consider the major factors likely to influence the outcomes. The FDA has published advice on addressing this point and requests that the following statement be cited when summarising toxicity data: -

'Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates'.

(FDA, . http://www.fda.gov/cder/guidance/1888dft.htm)

Where statistical methods can be applied, they should be used to show the significance of the outcomes. Studies with a degree of homogeneity may be looked at collectively to draw out emerging patterns, and subjected to statistical analyses.

It is hoped that reviews of adverse events may highlight the problems of harnessing toxicity data and may lead to a positive change in reporting this area of drug activity. A common ground should be developed by reviewers, showing how toxicity should be reported for them to be understood in context. Efficacy reporting in CML studies has been largely consistent; this should follow through to toxicity reporting. It seems that authors prefer to highlight the positive (benefit) aspects of drugs and play down the negative (risks) of drug taking, and may not report all of the side effects. To obtain a clear picture of drug activity, equal weight, should be applied to risks and benefits for external review purposes.

Future work may also focus on pharmacogenetic aspects of imatinib safety and efficacy. Other factors that are likely to influence adverse drug reactions, such as gender, age, ethnicity and drug interactions may also be investigated further.

Having conducted a systematic review of adverse events of imatinib in CML, an interesting development from this work would be to assess the adverse events of imatinib use in all indications. Imatinib is licensed for use in GIST as well as CML. This data may provide further reference points to determine the extent of the underlying diseases contributions to the frequency or severity of events.

6.0 Conclusion

This thesis has assessed all of the available toxicity data related to imatinib mesylate in CML patients. The study found that main adverse events associated with imatinib from randomised controlled studies are neutropenia, thrombocytopenia, superficial oedema and anaemia. The most common adverse events observed in uncontrolled studies are oedemas, nausea, thrombocytopenia, neutropenia, muscle cramps and vomiting respectively. Case reports showed that dermatological events (such as pigment changes and rashes of various kinds) were reported the most. Relapse and disease progression to other regions of the body (e.g., CNS involvement) were also frequent observations.

The most severe adverse events recorded were haematologic events (thrombocytopenia, neutropenia, granulocytopenia, anaemia, leukopenia). The most serious non-haematologic events were rash and oedema.

There is no conclusive evidence that the dose of imatinib, the disease stage, the previous history of patients, or the duration of drug therapy has any significant effect on the frequency of adverse events. There is a general trend that the frequency of toxicities increases as the disease stage progresses, though this cannot be confirmed due to the poor reliability of the data presented.
The inadequacies of toxicity reporting, and the highly biased data used in this review makes it difficult to be conclusive. However, it does provide an idea of the safety of imatinib use in CML patients, and suggests directions for further work to substantiate the findings reported here.

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8.0 Appendices

APPENDIX 1

Prognostic scores for CML

The Sokal score (Sokal, JE et al 1984).

Score = Exp [0.0116 (age-43.4)
+ 0.0345 (spleen size – 7.51)
+ 0.188 ([platelets/700]^2 – 0563)
+ 0.0887 (blasts – 2.1)]

Low risk	< 0.8
Intermediate risk	= 0.8 – 1.2
High risk	> 1.2

Hasford Score (Hasford, J et al 1998)

Score = 0.6666 x age (0 when age < 50, otherwise 1)
+ 0.042 x spleen size (cm below costal margin)
+ 0.0584 x blasts (%)
+ 0.0413 x eosinophils (%)
+ 0.2039 x basophils (0 when basophils < 3%; otherwise 1)
+ 1.0956 x platelet count (1 when platelets <1500, otherwise 1]) x 1000

Low risk	≤ 780
Intermediate risk	= 780 – 1480
High risk	>1480

APPENDIX 2

Description of quality assessments

Systematic reviews

The quality of systematic reviews was assessed using a checklist based on the following criteria of DARE (NHS Centre for Reviews and Dissemination, York 2000):

- Do the inclusion/exclusion criteria for the inclusion of studies in the review relate to study design, participants, intervention (s) and outcome (s) of interest?
- Is there evidence of a comprehensive and inclusive search of the literature, including attempts to identify unpublished studies?
- Is the validity of the studies included in the review adequately assessed?
- Are the individual studies presented in sufficient detail?
- Are the primary studies synthesized appropriately? If a meta-analysis has been performed, was heterogeneity tested for adequately?
- Have the inclusion/exclusion criteria been applied independently by more than one author?
- Have the data been extracted independently by more than one author?
- Have the validity criteria been applied independently by more than one author?
- Has the validity of the studies been taken into account in the synthesis of the studies?

RCTs

The RCT included in the review was assessed using the following criteria based on CRD report no. 4 (NHS Centre for Reviews and Dissemination, York 2001):

- Was the method used to assign participants to the treatment groups really random? (Computer-generated random numbers and random-number tables will be accepted as adequate, while inadequate approaches will include the use of alternation, case record numbers, birth dates or days of the week)
- Was the allocation of treatment concealed? (Concealment will be deemed adequate where randomization is centralized or pharmacy-controlled, or where the following are used: serially numbered containers, on-site computer-based systems where assignment is unreadable until after allocation, and other methods with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random-number lists and serially numbered envelopes even if opaque.)
- Was the number of participants who were randomized stated?
- Were the eligibility criteria for study entry specified?
- Were any co-interventions identified that may influence the outcomes for each group?
- Were the outcome assessors blinded to the treatment allocation?
- Were the individuals who administered the intervention blinded to the treatment allocation?
- Were the participants who received the intervention blinded to the treatment allocation?
- Was the success of the blinding procedure assessed?

- Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?
- Were the reasons for any withdrawals stated?
- Was an intention-to-treat analysis included?

Cohort studies and uncontrolled studies

Cohort studies and all uncontrolled studies were assessed according to the following criteria (Crombie, I et al 1996). This checklist was used for cohort studies and for uncontrolled studies, because the nature of the questions were deemed appropriate for both types of studies. Clearly, however, a properly conducted cohort study provides a better level of evidence than an uncontrolled study, irrespective of the results of the quality assessment.

- Is the group studied clearly stated?
- Was there any control group and, if not, was this appropriate?
- Was the follow-up adequate?
- Were the aims clearly stated?
- Was the study design appropriate?
- Was the sample size appropriate?
- Were the measurements valid and reliable?
- Were the outcome measures appropriate?
- Were all participants accounted for?
- Were the statistical methods appropriate and well described?

APPENDIX 3

NCI-CTC toxicity grades for reported adverse effects

An adverse event (AE) is any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may **not** be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. AEs are listed within Categories, which are broad classification of AEs based on anatomy and/or physiology. Within each category, AEs are listed accompanied by their descriptions of severity (Grade).

Grades

Grade refers to the severity of the adverse event. The CTC AE vers 3.0 displays grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1: Mild AE
Grade 2: Moderate AE
Grade 3: Severe AE
Grade 4: Life-threatening or disabling AE
Grade 5: Death related to AE

Definitions of quantifiable AEs

	Grade			
Adverse event	**1**	**2**	**3**	**4**
Hemoglobin	<LLN – 10.0 g/dL	<10.0 – 8.0 g/dL	<8.0 – 6.5 g/dL	<6.5 g/dL
Leukocytes	<LLN–3.0 x 10^9/L	<3.0-2.0 x 10^9/L	<2.0-1.0 x 10^9/L	<1.0 x 10^9/L
Neutrophils/granulocytes	<LLN-1.5 x 10^9/L	<1.5 -1.0 x 10^9/L	<1.0-0.5 x 10^9/L	<0.5 x 10^9/L
Platelets	<LLN-75.0 x10^9/L	<75.0-50.0 x 10^9/L	50.0-25.0 x 10^9/L	<25.0 x 10^9/L
Weight loss	5 - <10% from baseline	10 to < 20% from baseline	≥ 20% from baseline	-
Weight gain	5 - <10% of baseline	10 to < 20% of baseline	≥ 20% of baseline	-

APPENDIX 4

Included and exluded clinical trials assessing toxicity

Reference	Inclusion/Exclusion	Reason of inclusion/exclusion
Anderlini 2004	✓	Clinical trial describing adverse events
Arora 2004	✓	Clinical trial describing cutaneous reactions
Cervantes 2003a	✓	Clinical trial describing adverse events
Cervantes 2003b	✓	Clinical trial describing adverse events
Champagne 2004	✓	Phase 1 trial describing adverse events
Cortes 2003	✓	Clinical trial describing adverse events
Cortes 2004	×	Previous studies assessed, possible duplicates
Druker 2001a	✓	Phase 1 trial describing adverse events
Druker 2001b	✓	Phase 1 trial describing adverse events
Gardembas 2003	✓	Phase 2 trial describing adverse events
Kantarjian 2002a	✓	Phase 2 trial describing adverse events
Kantarjian 2002b	✓	Clinical trial describing adverse events
Kantarjian 2002c	✓	Clinical trial describing adverse events
Kantarjian 2002d	✓	Clinical trial describing adverse events
Kantarjian 2003a	✓	Clinical trial describing adverse events
Kantarjian 2003b	✓	Clinical trial describing adverse events
Kantarjian 2004a	✓	Clinical trial describing adverse events
Kantarjian 2004b	✓	Clinical trial describing adverse events
Kim 2004	✓	Clinical trial describing adverse events
Le Coutre 2003	✓	Clinical trial describing adverse events
Leis 2004	×	Patients had CLL, not CML
Medina 2003	×	Previous studies assessed, possible duplicates
Morishima 2004	✓	Phase 2 trial describing adverse events
O'Brien 2003a	✓	RCT describing adverse events
O'Brien 2003b	×	Toxicity relating to imatinib not given
Rosti 2004	✓	Clinical trial describing adverse events
Sawyers 2002	✓	Phase 2 trial describing adverse events
Sneed 2003	×	Previous studies assessed, possible duplicates
Sureda 2003	✓	Phase 2 trial describing adverse events
Talpaz 2002	✓	Phase 2 trial describing adverse events
Tsimberidou 2003	×	Previous studies assessed, possible duplicates

Valeyrie 2003	✓	Clinical trial describing cutaneous reactions
Van Deventer 2002	✓	Clinical trial describing haematologic adverse events
Zonder 2003	×	Previous studies assessed, possible duplicates

APPENDIX 5

Description of included and excluded case reports/series

Patient characteristics	Type of side-effect	Number of people	Reference
53-year old Japanese female	Follicular mucinosis	1	Yanagi T et al. 2004
Case report	*Acute cytolytic hepatitis*	*Excluded, French*	*Rocca P et al. 2004*
40-year old female	Severe hepatitis	1	Kikuchi S et al. 2004
Case report	*Retroperitoneal mass*	*Excluded, GIST*	*Demetri GD et al. 2004*
Case report		*Excluded, not toxicity*	*Cortes J et al. 2004*
Case reports	CNS relapse	2	Rytting ME et al. 2004
52-year old female	Lichenoid cutaneous reaction	1	Roux C et al. 2004
Case report	Contemporaneous pulmonary sarcoidosis	?	Pavithran K et al. 2004
49-year old male	Extramedullary relapse	1	Smaradottir A et al. 2004
78-year old Japanese female	Interstitial pneumonitis	1	Isshiki I et al. 2004
8-year old African-American male	Hypopigmentation	1	Grossman WJ et al. 2004
Case report	CNS relapse	2	Bujassoum S et al. 2004.
65-year old Caucasian male	Blast mantle cell lymphoma	1	Rodler E et al. 2004.
53-year old Caucasian female	Sweet's syndrome	1	Liu D et al. 2004
15-year old male	Anaemia & abdominal tumour	1	Lowe EJ et al. 2004
64-year old male	Interstitial pneumonia	1	Yokovama T et al. 2004
19-year old female	Fibrous dysplasia	1	Hon C et al. 2003
Case report	Pulmonary nocardiosis	?	Lin JT et al. 2004
Case report	Maculopapular rash	?	Dogra S et al. 2003
Case Report	CNS blast crisis	1	Bornhauser M et al. 2004
Case report	Interstitial pneumonitis	?	Ma CX et al. 2003
29-year old Caucasian female	Pulmonary alveolar proteinosis	1	Wagner U et al. 2003
2 males aged 32 and 58, 4 females aged 63, 77, 49, 52)	Hypopigmentation	6	Tsao AS et al. 2003
72-year old male and 55-year old male	CNS and cutaneous involvement	2	Abruzzese E et al. 2003
67-year old female	Porphyria cutanea tarda	1	Breccia M et al. 2004
Case report	Exfoliative dermatitis	?	Banka N et al. 2003
64-year old female	Panniculitis	1	Ugurel S et al. 2003
Case report		?	Antin JH. 2003
58-year old female	Acute renal failure	1	Pou M et al. 2003
63-year old male	Interstitial pneumonitis	1	Rosado MF et al. 2003
Case report	Erythema	?	Duncan E et al. 2003
58-year old female and 35-year old female	Acute hepatitis	2	James C et al. 2003
Case report	Cardiac morbidity	?	Sohn SK et al. 2003
Case report	Porphyria cutanea tarda	?	Ho AY et al. 2003
35-year old male	Intramuscular oedema	1	Shimazaki C et al. 2003
Case report	Carcinoma	?	Baskaynak G et al. 2003
42-year old male	Myelodysplastic syndrome	1	Chee YL et al. 2003
70-year old male	Periorbital oedema	1	Ramar K et al. 2003
8-year old male with CML, 14-year old female with Ewing sarcoma and 7-year old male with PNET	Pleural effusions	3	Goldsby R et al. 2002
50-year old Caucasian female, and 42-year old Caucasian female	AGEP	2	Schwarz M et al. 2002
18-year old male	Tumour lysis syndrome	1	Vora A et al. 2002
73-year old female	Pancytopenia	1	Sumi M et al. 2002
41-year old African-American female	Hypersensitivity pneumonitis	1	Bergeron A et al. 2002
Case series of 9 patients	Hair repigmentation	9	Etienne, G et al 2002
Case series of 8 patients	Skin rash	8	Drummond, A et al 2003
Case series of 11 patients	Dermatosis	11	Milojkovic, D et al 2002
Case report	Severe adverse cutaneous reaction (AGEP)		Brouard, M et al 2001
Case report	Stevens-Johnson syndrome	?	Vidal D et al. 2002
56-year old female	Hepato-toxicity	1	Ohyashiki K et al. 2002.
51-year old male	Cardiac tamponade	1	Barton JC et al. 2002
Case report	Pityriasis rosea	?	Konstantopoulos K et al. 2002

Case report	Oral lichenoid reaction	?	Lim DS et al. 2002
63-year old male	Periorbital oedema	1	Esmaeli B et al. 2002
61-year old female and 68-year old male	Cerebral oedema	2	Ebnoether M et al. 2002
Case report	Stevens-Johnson syndrome	?	Hsiao LT et al. 2002
67-year old male	Renal failure	1	Kitivakara C et al. 2002
Case reports		?	Burton C et al. 2002
52-year old male	Depigmentation	1	Raanani P et al. 2002
Case reports	*Lichenoid cutaneous reaction*	*?*	*Roux C et al. 2004*
Case reports	*Hypopigmentation*	*?*	*Tsao AS et al. 2003*
Case reports	Ocular side-effects	?	Fraunfelder FW et al. 2003

A total of 56 case reports were included. All of those in italics were excluded; 1 was excluded as its abstract was in French, 1 was excluded as it did not describe toxicity, 1 was excluded as it was in a GIST patient. Roux and Tsao were retrieved twice in the same search - the duplicates were excluded.

APPENDIX 6

Quality assessments of included studies

Quality assessment of systematic reviews

DARE criteria. Ref: NHS Centre for Reviews and Dissemination. Manual for selecting reviews and writing abstracts for the Database of Abstracts of Reviews of Effectiveness (DARE). York: NHS Centre for Reviews and Dissemination, University of York; 16 Oct 2000.

	STUDY	
	Garside 2002	**Dalziel 2004**
Inclusion/exclusion criteria relate to study design of interest	✓	✓
Inclusion/exclusion criteria relate to participants of interest	✓	✓
Inclusion/exclusion criteria relate to intervention of interest	✓	✓
Inclusion/exclusion criteria relate to outcomes of interest	✓	✓
Inclusion/exclusion criteria applied by more than one author	✓	✓
Valid inclusion/exclusion criteria	✓	✓
Validity systematically assessed	✓	✓
Validity criteria applied by more than one author	✓	✓
Validity taken into account in synthesis	✗	✓
Data extraction performed by more than one author	✓	✓
Primary studies are presented in sufficient detail	✓	✓
Primary studies have been synthesized appropriately	✓	✓
Meta-analysis has been performed	✗	✗
If 'Yes', has heterogeneity been formally assessed?	**N/A**	**N/A**

Quality assessment of RCT

(REF: NHS Centre for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness. CRD's guidance for carrying out or commissioning reviews. 2nd Ed. York: NHS Centre for Reviews and Dissemination; 2001)

	Study
Criteria	**O'Brien 2003a**
Random allocation	Yes
Method of allocation	Computer generated
Adequate concealment	Yes
No. of patients randomised	Yes
Comparable at baseline	Yes
Co-interventions	No
Inclusion/exclusion criteria	Yes
Patients blinded	No
Assessors blinded	No
Success of blinding checked	N/A
80% followed up	Yes
Reasons for withdrawals	Yes
ITT analysis	Yes

Quality assessment of uncontrolled studies

(Ref: Crombie, I. The pocket guide to critical appraisal: a handbook for healthcare professionals. 1st ed. London: BMJ Publishing Group; 1996.)

Study	Group clearly stated	Control group	If no control, OK?	Follow-up adequate	Aims	Study design appropriate	Sample size appropriate	Valid measures	Valid outcome measures	All patients accounted for	Are statistics well described?	Statistics appropriate
Anderlini 2004	Yes	No	Yes	Yes	No	Unclear	No	Unclear	Yes	Yes	N/A	N/A
Arora 2004	Yes	No	Yes	Yes	No	Unclear	Yes	Unclear	Yes	No	N/A	N/A
Cervantes 2003a	Yes	No	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	No	Yes
Cervantes 2003b	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Champagne 2004	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Cortes 2003b	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	N/A
Druker 2001a	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Druker 2001b	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gardembas 2003	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Kantarjian 2002a	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kantarjian 2002b	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kantarjian 2002c	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kantarjian 2002d	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Kantarjian 2003a	Yes	No	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	N/A	N/A
Kantarjian 2003b	Yes	Yes	No	Yes	No	Unclear	Yes	Yes	Unclear	Yes	N/A	N/A
Kantarjian 2004a	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kantarjian 2004b	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Kim 2004	Yes	No	Yes	Unclear	Yes	Yes	No	Yes	Yes	Yes	No	Unclear
Le Coutre 2003	Yes	No	Unclear	Yes	Unclear	Unclear	Yes	Yes	Yes	Unclear	No	Unclear
Morishima 2004	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	N/A
Rosti 2004	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sawyers 2002	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sureda 2003	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	N/A
Talpaz 2002	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Valeyrie 2003	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Van Deventer 2002	Yes	No	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Unclear