ORALLY ACTIVE ANTITUMOUR AGENTS, PATIENT COMPLIANCE AND CLINICAL TRIALS

by

PETER CLEMENT SECRETT

A thesis submitted for the degree of

Master of Philosophy

in

Aston University, Birmingham

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The first part of this project is concerned with non-compliance with drug therapy in breast cancer patients. It is assumed that cancer patients are highly motivated by fear of their disease and by the associated symptoms. This work attempted to evaluate the level of non-compliance in breast cancer patients taking tamoxifen and to determine the factors pre-disposing some patients to non-compliant behaviour. A structured questionnaire was developed and used to interview 151 patients in three different types of outpatient clinic. Nineteen (13%) patients were found to have stopped therapy at some stage. The reasons for non-compliance included side effects, having no faith in therapy, lack of comprehension and memory problems. These results suggest patients suffering from breast cancer are not fully compliant.

The second part of the project continued previous work on the pharmacokinetics of mitozolomide, an imidazo [5,1-d]-1,2,3,5,tetrazin-4 (3H)one undergoing a phase I/II clinical trial. Mitozolomide was administered orally to eighteen patients at a dose of 90 mg/m^2 to determine the activity of the drug at this dose, to extend the knowledge on the toxicity profile of the drug and to confirm the essential pharmacokinetic parameters, established in the phase I trial. A reversed phase high performance liquid chromatography method was used to assay drug levels in patients' plasma. Results indicated that the oral dose of the drug given bore no relation to the amount of drug absorbed nor to the peak plasma level attained. The bioavailability of the drug was found to vary between 25% and 100% and absorption could be delayed up to 1.8 hours. 22% of patients experienced a severe thrombocytopaenia; this toxicity could not be related to the pharmacokinetics of the drug. The lack of correlation between toxicity and the pharmacokinetics of the drug could limit the clinical usefulness of mitozolomide.

Key Words: Cancer, Patient Compliance, Tamoxifen, Pharmacokinetics, Mitozolomide.

DEDICATED TO MY FATHER

FOR HIS SUPPORT AND HELP TO ME

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ABBREVIATIONS

AIC	-	5-aminoimidazole-4-carboxamide
diazo-IC	-	5-diazoimidazole-4-carboxamide
DTIC	-	5-(3,3-dimethyl-1-triazenyl)imidazole-4-carboxamide
DNA	-	deoxyribose nucleic acid
MCTIC	-	5-[3-(2-chloroethyl)triazenyl]imidazole-4-carboxamide
BCNU	-	1,3-bis(2-chloroethyl)-1-nitrosourea
CCNU	-	1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea
NCI	-	US National Cancer Institute
CNU	-	1-(2-chloroethyl)-1-nitrosourea
LD_{10}	-	lethal dose for 10% of test population
HPLC	-	high performance liquid chromatography
MTD	-	maximum tolerated dose

PART 1 : COMPLIANCE STUDY

1.1 INTRODUCTION

1.1.1 Patient Compliance

'Patient compliance', 'patient dropout' and 'patient adherence', are all terms used to describe the extent to which a person's behaviour in taking medicines, keeping appointments etc. coincides with medical advice. Studies of the problem of non-compliance with therapy have dramatically increased over the last twenty years from only a handful of articles before 1960 to many thousands now.

A large review[1] of 537 articles found that less than 40 of these satisfied the author's strict criteria for study design, sample selection, description of illness and regimen, definition of compliance and adequacy of the methods used. Indeed estimates[2] of non-compliance have ranged from 15% to 93% depending not only on the population studied and the treatment regimen but also on the definition of compliance and the methods employed to measure it. Therefore attempts to compare studies are extremely difficult.

Non-compliance may be seen in a number of forms such as delay in seeking care, non-participation in health programmes and breaking of appointments as well as failure to follow physicians' instructions. Most of the literature on non-compliance with drug treatment has been confined to studying errors of omission.

1.1.2 Methods used in assessing non-compliance

The assessment of non-compliance can be achieved by direct or indirect methods.

Table 1.1.2 Comparison of methods for assessing non-compliance.

Direct	Indirect.
1. Blood levels	1. Patient Interviews.
2. Urinary excretion of: drug	2. Pill counts.
metabolite	3. Therapeutic outcome.
marker	
3. Other: Saliva, breath test etc.	

Direct methods for assessing non-compliance would appear to be the most accurate : however the reliability of these methods can be limited by the sensitivity and specificity of the test and individual differences in drug metabolism. These methods are also very intrusive and may give false indications of the level of non-compliance by temporarily decreasing it.

Patient interviews are simple to perform and may be the only feasible method in the clinical setting with respect to the time taken by the interviewer and convenience to the patient. The validity of interviews has received a lot of attention and whilst some reports[3] comparing interviews with pill counts and urine tests suggested patients under-reported non-compliant behaviour, a more recent study[4] with hypertensive agents indicated a good correlation between patient interviews and blood pressure control. Certainly the validity of interviews is dependent on the skill of the interviewer and the recall and the reliability of the patients.

Pill counts are based on the amount of medication that should have remained compared with the amount actually remaining, which can be calculated from the prescription and time elapsed since it was issued. This method relies on the assumption that the patient takes the medication and does not dispose of it in another way and also that the amount of medication that should be left is accurately known.

Therapeutic outcome for many treatments is not a valid method;

compliance does not necessarily ensure a satisfactory result and (with a multiple regimen) a response does not necessarily reflect compliance with every drug.

1.1.3 Factors affecting patient compliance

Many patient factors such as age, sex, education and socio-economic status have been considered in trying to distinguish between the compliant and the non-compliant patient. Whilst there are studies claiming to identify certain characteristics in patients, there are few significant differences between the compliant and non-compliant patient. Some non-compliance is associated with failure of memory, lack of understanding and complexity of the regimen, indicating that particular risk groups might include older people or people with a lower educational level.

Treatment factors seem to have a greater bearing on compliance as summarised in the following table 1.1.2.

Table 1.1.2 Important factors affecting compliance

	Effect on compliance
The disease	
Mental illness	Negative
Increasing numbers of symptoms	Negative
Disability	Positive
The referral process	
Long time from referral to appointment	Negative
The Clinic	
Long waiting time	Negative
Individual appointments	Positive
The treatment	
Parenteral drug administration	Positive
Long duration of treatment	Negative
Increasing number of drugs	Negative
Cost of drug to patient	Negative
Safety containers	Negative

Furthermore a more recent review[5] found that the attitude of patients to their treatment influences their compliance and that patients who perceive their illness as serious, believe in the efficacy of the treatment and have a good relationship with their doctor are more likely to be compliant.

Therefore with all these points in mind, let us consider the magnitude of the problem of non-compliance with cancer therapy.

1.1.4 Compliance in cancer patients

There have been few studies regarding the magnitude of the problem of non-compliance in cancer patients; a recent review[6] of the literature on the subject could find only three studies[7-9] specifically concerned with non-compliance in this group of patients.

It is assumed that cancer patients are highly motivated by fear of the disease and by the associated symptoms. Also a lot of the treatment, for example, parenteral chemotherapy and radiotherapy, is highly supervised by medical personnel and so non-compliance in this area is not a problem.

Many patients fail to show improvement to their therapy. Most of these failures will be due to ineffectiveness of the therapy, resistance of the tumour or extensive metastases but some patients[10] will cease therapy because of side effects, psychological stress and disruption of normal daily routines.

Hoagland et al [11] collected the views of 246 oncologists, by a postal questionnaire, on the subject of patient non-compliance, with reference to their views on appointment keeping, adherence to therapy at outpatient clinics or as inpatients and adherence to self-medication at home. The overall estimated non-compliance was 14% (Range 0-95%). Most of the oncologists felt that failure to complete therapy was the most significant problem and that non-compliance was less of a problem than with their other non-cancer patients. Below are the main reasons they gave for cancer patient non-compliance.

Table 1.1.3 Reasons given by oncologists for non-compliance

	Problem	Percentage
1	Psychological	29
2	Medical	19
3	Combination of 1 and 2	19
4	Don't know	13
5	Other reasons	20

Most of the oncologists did not consider that non-compliance was a major problem in their patients.

Another study[12] attempted to identify specific factors pertinent to non-compliance in cancer patients. This study claimed that a positive doctor-patient relationship can significantly increase patient compliance. The importance of this relationship has also been emphasised by other workers[13], and it has been shown[14] that lack of a strong affiliation with the health care system in general is associated with non-compliance in cancer patients. The therapeutic regimen in terms of duration of therapy, the extent to which the patients have to alter their normal habits and the side effects of treatment can affect compliance. The side effects experienced by many cancer patients are of a far greater magnitude than for other treatments, hair and weight loss adversely affect a patient's self-image and frequent visits to clinic for further courses of therapy are a constant reminder of the disease. Finally, decreased "psychological well-being" caused by feelings of dependence or helplessness and depression can adversely affect a patient's desire to continue, or, in some instances, initiate therapy.

On the psychological aspect of non-compliance in cancer patients, Barofsky[15] proposed several explanations, each reflecting a different

process and all of which could be relevant at sometime for any patient. In the "self-efficacy model", non-compliance occurs when a patient does not believe that by following the treatment a cure will result. The "health belief model" depends on two variables, the value placed on a particular goal and an estimation of the likelihood of accomplishing that goal. This relates more to how a person makes decisions and choices at any given time. "Non-comprehension" caused by poor communication between patient and doctor can lead to unintentional non-compliance and by enhancing cancer patient education, memory of the task and satisfaction with its outcome can be increased; thus enhancing compliance. Other authors have emphasised the necessity for clear, comprehensive education, proposing that compliant behaviour develops along with a patient's knowledge and beliefs about a treatment. Finally, when a patient takes a medicine which causes adverse effects a "conditioning process" occurs which can lead to non-compliance. This process has been used to account for the anticipatory nausea and vomiting experienced by some patients.

The studies discussed so far have dealt with beliefs about the reasons why cancer patients might not comply with their therapy; the following studies, summarized below, were concerned with the quantitiative examination of non-compliance.

The first[16] deals with referrals from a cancer screening project of 561 women sent for mammography. The data was analysed by signs, symptoms and cost. Compliance varied from 7.6% in asymptomatic women with normal examinations who had to pay for the tests (39.4% in those who did not pay) to 63.7% for symptomatic women with abnormal examinations who had to pay, (92.5% in those who did not pay). It is interesting to note that even for women with symptoms as well as abnormal examinations, cost caused a 30% decrease in compliance.

Non-compliance in screening follow-up was also studied[17] in a group of 177 family planning clinic patients with cervical dysplasia. Non-compliant women were defined as those who either did not make or did not keep an appointment at the clinic in a six month period after notification of an abnormal cervical smear. The study showed that three (1.7%) women failed to make an appointment and twenty-seven (15.2%) women made but did not keep their appointments. Women who failed to comply with the request for follow-up were more likely to have received less education and to have had fewer total health problems in the past than the women who returned for follow-up.

A further two studies[18-19] have investigated non-compliance in colorectal cancer screening programmes. In a study[18] of 581 patients invited to participate using a faecal occult blood test kit, 51% of patients who accepted the kit completed it. In men non-compliance seemed to be related to a lower educational status and was greater for smokers than in non-smokers. In women non-compliance decreased with increasing age and in those patients with either symptoms and/or a family history of the disease. A doctor-practice effect appeared to influence initial acceptance or refusal of the kit. The second study[19] randomised 17824 patients into three groups determined by the method of invitation to screening: a letter and a test kit were sent to the patient, or a letter with an appointment to attend the surgery was sent, or during a routine visit to the doctor patients were invited to participate. Compliance with respect to accepting and completing the kit was highest (57%) in the group offered the test during consultation, intermediate (49%) in the group offered an appointment and lowest (38%) in the group sent the kit by post. Some patients also received an educational booklet about bowel disorders and screening but this did not have a significant effect on compliance rates in any group. Individual general practices and doctors achieved higher

compliance rates, seven of the forty-one doctors involved in the study had a compliance rate of over 70%.

Non-compliance with cancer screening programmes would appear to be related to the financial cost to the patient in following medical advice, is associated with a lower educational level and occurs when there is a less direct input by medical personnel. The provision of written information about the condition does not ensure compliance which is more related to the motivation and enthusiasm of the individual doctor in gaining co-operation from the patient.

The following series of studies focuses on patients with leukaemia. Compliance was tested[7] in a group of fifty two patients, receiving oral prednisone therapy, using urinary levels of 17-ketogenic steroids, haemoglobin levels and weight change, as markers. Both haemoglobin levels and weight change were found to be useless as measures of compliance. Seventeen (33%) of the patients had assays indicating some degree of non-compliance and, furthermore, the non-compliance amongst adolescents in this group was 50%. Clearly this seemingly high level of non-compliance could adversely affect survival.

In a[20] further study of thirty one patients under fifteen years old compliance was tested by three urine assays between days 21 and 28 of the patients' prescribed course and by a personality test on the children and their parents. Thirteen (42%) of the children had assays indicating some degree of non-compliance. With respect to the personality test, it seemed that non-compliance was more closely related to the parents' personalities than to the child's and that this effect was greater in boys than in girls.

Further research to try to identify the factors which relate to an adolescents co-operation with cancer treatment has recently been published[21] Twenty seven leukaemia patients were studied by questionnaires on the following areas: co-operation with medical treatment, self-image, perception

of the disease, knowledge of cancer and health locus of control.

The health locus of control[22] is a measure of a person's expectancies regarding internal and external control over their physical health or well being and is used to try to predict health-related behaviour.

The study indicated that younger patients appeared to be more co-operative than the older ones. There was a good correlation between co-operation and a positive self-image and between co-operation and those who perceived their illness to be severe with a poor prognosis. When considering the health locus of control, those patients who believed that the doctor was in total control of their treatment and their disease were less likely to be as co-operative.

Finally interview techniques[23] were used to examine a group of ten adolescents (and their mothers) who totally refused treatment for their leukaemia, comparing them with a closely matched group of ten adolescents who had consented to therapy. The adolescents who refused treatment were able to perceive a given stressful situation as extremely threatening and aversive but were not anxious about their own medical condition, believing it to be out of their (or their doctor's) control and to be dependent on luck, fate or their religious convictions. The mothers of these adolescents displayed similar beliefs.

Research in adolescents has indicated that non-compliance is a problem in patients taking oral therapy and is related to both the patients' and their parents' beliefs concerning their ability to overcome the condition.

The following table 1.1.4[24] gives an indication of the degree of non-compliance observed in twenty seven patients taking oral therapy as part of a chemotherapy regime for haematological malignancies, when compliance was estimated by measuring levels of drug and metabolite in blood and by interview techniques.

Table 1.1.4 Comparison of non-compliance between blood levels and interview reports.

Drug	% Non-Compliers	% Full Compliers
Prednisone	50	42
Prednisolone	62	28
Allopurinol	71	20
Oxypurinol	45	42
Self-report	65	35

Not only is it interesting to note the high levels of non-compliance observed by direct measurement of body fluids but also the good correlation between the indirect measure, from patient self-reports, of non-compliance and the direct measurement.

Research[8] into the efficacy of a prophylactic oral antibiotic regimen (consisting of gentamicin, vancomycin and nystatin given every four hours) in a group of seventy hospitalised patients with acute leukaemia found that for the group as a whole 20% of the prescribed doses were not taken due to side effects such as bad after-taste, frequent nausea and diarrhoea. Six patients all of whom died during the first two weeks of therapy, never took the oral non-absorbable antibiotics for more than a few doses.

Even in an environment with constant supervision, many patients did not comply.

Finally, Itano[25] studied sixty-six patients retrospectively from clinical notes, defining compliance as a composite of:-

1 Number of laboratory tests, ordered and completed.

2 Appointments, scheduled and kept.

3 Intravenous chemotherapy, prescribed and administered.

Patients had to meet all of these criteria to be considered fully compliant. Independent variables of health locus of control, self-esteem anxiety, patient's understanding of his illness and patient's perception of nurse's care and concern were also determined by a series of questionnaires.

Fourteen patients (21.2%) were defined as non-compliant, although eight of these had an average compliance greater than 90%. The authors also concluded that being female, having high levels of anxiety, perceiving less severe side effects of chemotherapy and feeling treatment was under the control of other people all helped to promote compliant behaviour.

This last observation is quite different when compared with the study[21] on the adolescents who blatantly refused therapy, indicating once again that compliance is a very intricate subject.

Let us now consider specifically breast cancer and the problems of non-compliance in this group.

1.1.5 Breast Cancer and patient compliance

A study[26] of compliance with parenteral chemotherapy amongst seventy-eight breast cancer patients identified two patients who were non-compliant. A few days prior to therapy these patients who were chronic abusers of alcohol would use an excessive intake of alcohol, claimed to transiently lower their white cell count[27], and hence avoid the chemotherapy. Two patients rejected therapy without trying it, five patients were switched to alternative therapy due to side effects or tumour resistance and a further four who complied with the parenteral therapy admitted irregularly taking the oral portion of their treatment.

Research[28] into adjuvant chemotherapy (cyclophosphamide, methotrexate fluorouracil) for breast carcinoma indicated that out of forty-six patients, nine received less than the planned dose due to family problems, out-of-town trips or depression.

Therefore even in a highly supervised setting non-compliance is rife. The previous two studies[26,28] dealt with parenteral chemotherapy in the breast cancer patient. However there is a sizeable group of patients receiving long term oral hormone therapy for breast cancer, in whom there has been little investigation of the extent of non-compliance.

The agents used in these therapies include tamoxifen, aminoglutethimide and medroxyprogesterone.

The antioestrogen tamoxifen is widely used in breast cancer patients in the following three situations:

1 Primary treatment in elderly post-menopausal women

2 Adjuvant therapy to surgery and or radiotherapy

3 Treatment of recurrent disease

An interim analysis[29] of the results of a large trial of adjuvant tamoxifen after total mastectomy indicated a possible prolongation of disease free interval from twenty one to thirty months. The therapy was well tolerated and treatment discontinued in only fourteen (2.2%) of the patients. The response is comparable to adjuvant chemotherapy but with minimal toxicity. The effect was not dependent on menopausal, axillary lymph node or oestrogen receptor status. Compliance was monitored by serum analysis in thirty-five (5%) of the patients: only one patient having a low blood level indicative of recent non-compliance.

In a study[30] currently in process in Birmingham, patients who have failed to respond to tamoxifen or have responded and then relapsed are randomised to treatment with aminoglutethimide or medroxyprogesterone as second-line hormonal therapy, prior to cytotoxic chemotherapy.

Aminoglutethimide acts as a potent inhibitor of adrenal hormone production and by the blockade of the peripheral conversion of androstenedione to oestrogens.

High dose medroxyprogesterone suppresses adrenal function but also has intrinsic glucocorticoid activity which avoids the need for the hydrocortisone replacement required with aminoglutethimide.

The aim of the present work was to try to evaluate the level of non-compliance in breast cancer patients taking the various oral hormonal agents described above and to determine the factors which may predispose some patients to non-compliant behaviour.

1.2 METHODS

1.2.1 Recruitment of Patients for the compliance study

Patients were recruited into this study at three different outpatient clinics in the West Midlands Region. A copy of the study protocol, which was submitted to each consultant, is included in Appendix I.

Table 1.2.1 Recruitment of Patients

	Clinic	Drug	Number of patients
1	Mr Morrison, Breast Surgery Clinic Selly Oak Hospital.	Tamoxifen	76
2	Dr Priestman's Radiotherapy Clinic Dudley Road Hospital	Tamoxifen	26
		Aminoglutethimide	14
		Medroxyprogesterone	10
3	Dr Gopal, Radiotherapy Clinic Mr Williams, General Surgery Clinic Russell's Hall Hospital.	Tamoxifen	49

Pre-menopausal and post-menopausal women with recurrent or primary non-operable breast cancer receiving oral hormonal therapy and those receiving adjuvant oral hormonal therapy after surgery and/or radiotherapy were included. Patients commencing therapy and those already on therapy were included and informed consent obtained from each patient.

Data was collected by questionnaire.

A pill count was performed on a 10% random sample of patients.

It was not possible to analyse blood samples for levels of tamoxifen as the documented methods[31-32] employed a technique using high performance liquid chromatography with post-column fluorescence activation which was not available.

1.2.2. Questionnaire Design[33-35]

In developing the final questionnaire, there were three interview stages:-

(1) Unstructured Interviews.

(2) Partially structured Interviews.

(3) Totally structured Interviews.

1.2.2.1 Unstructured Interviews.

Having completed an initial literature search, unstructured interviews were performed on ten patients at clinic one as preliminary work to identify problem areas which were not initially considered. The unstructured interview allowed a great deal of freedom to probe specific areas and raise any queries which became apparent during the interview. The patients were encouraged to relate their own experiences and opinions as they wished and to talk about areas which were significant to them.

All ten patients had been on a twice daily dosage of tamoxifen for at least one year and were happy with the treatment that they were receiving. None of them reported any significant side effects apart from occasional hot flushes. None of the patients reported any non-compliance and all claimed to be taking their drugs as prescribed.

So no new areas for concern were uncovered in the unstructured interviews. This form of interview was difficult to conduct because most of the ten patients were either unwilling or unable to express themselves easily. As a design for a final interview this form would have been extremely difficult to analyse and information could be missed or lost.

1.2.2.2 Partially structured Interview - Pilot Study

A first questionnaire was constructed and a series of partially structured interviews carried out on twenty-one patients at clinic one as a pilot study. All twenty-one patients were asked to bring their tablets with them at the next clinic visit. This type of interview allowed the patients to express their own attitudes and experiences by leaving the answers to the questions open but using structured questions referring to areas of interest already identified and other specific topics relating to the study.

In this way the questions were tried out, then any ambiguities, bias and poor phrasing were corrected.

Results of the Pilot Study

Twenty-one patients were receiving tamoxifen 20mg twice daily for the following reasons:

Recurrence of cancer	13
Primary treatment	5
Adjuvant treatment to surgery	3

Six patients were non-compliant on the day of the clinic, that is, had not taken the drug that morning. Two of these patients had altered their normal lifestyle by going out earlier than usual to get to the clinic and they intended to take their tablets as soon as they arrived home, whilst a further patient had no set system for taking her drugs and could take them anytime during the day. The following table shows some of the variables concerning the other three patients.

TABLE 1.2.2 - Results of the Pilot Study

Patient Number	Age /years	Duration Breast Disease /months	Other Disease	Total Number Drugs	Duration Tamoxifen /months	Therapy used for:-	Number doses missed in previous week	Minor Side Effects
1	83	58	Yes	4	47	Recur-rence	2/3	2
2	73	282	No	2	40	Recur-rence	2	0
3	84	6	Yes	5	6	Primary Treat-ment	2	0

All three patients lived alone, the side effects experienced by patient 1 were hot flushes and exacerbated constipation but these effects were claimed to be minor.

Two patients, 1 and 3 had forgotten their tablets twice in the previous week, although patient 3 thought it could have been three times. Patient 2 had declared her intention to stop therapy as she no longer saw any reason for continuing therapy after three years, disease-free, following recurrence.

A further patient claimed that she had previously run out of tablets and had missed several doses because she had been unable to get to a pharmacy. One patient had received a fortnight's supply of tablets on discharge from the ward, had received no counselling and ceased therapy after the fourteen days.

The pilot study showed that one patient was totally non-compliant and a further two sometimes experienced difficulty in taking their tablets. Reasons for this non-compliance might have included age and memory, duration of therapy and problems of supply or counselling.

1.2.2.3 Totally structured Interview - the final questionnaire

After examining the results of the pilot study, with respect to the questionnaire itself, the following alterations were made.

Firstly the initial explanation was felt to be too brief, the patient often did not grasp the reason for the study or was not motivated enough to volunteer information. This section was totally re-written.

The following questions were abandoned:

1 What made you first think that there was something wrong?

2 How long ago did you realise that there was something wrong?

3 How long was it before you went to see the doctor?

4 Do you feel that the treatment is helping you?

5 Are there any reasons why you might not follow the doctor's advice?

Questions 1 - 3 referred to an often distant point in the patients' past and they were unable to answer them. Questions 4 - 5 were too emotive, disturbed the patient and did not yield useful results.

The order of the questions was altered so that more personal questions were placed towards the end of the questionnaire to try to draw the patients' interest without arousing a controversial response. The order of all the questions was re-arranged to ensure a better flow and questions regarding counselling and supply, potential problem areas discovered in the pilot study were included.

The questions specifically relating to the compliance of the patient were extended to include information about the system used to integrate the taking of tablets into the daily routine.

The final questionnaire (see appendix II) was now developed: the working and sequence of questions were fixed and identical for every patient. In this way any variation between responses should have reflected differences between patients rather than changes in the wording or interpretation of the questions by the interviewer. The questions were coded in accordance with procedures necessary for data transference to computer.

Information was now collected on the following aspects of the patients' life and therapy by interviewing the patients, with the interviewer asking the questions and filling in the answers, according to the questionnaire.

By Interview	From clinical case notes
Family support	Age
Working status	Delay in seeking treatment
Previous refusal of therapy	Duration of illness
Number of drugs	Other serious illness
Number of daily doses	Psychological problems $\pm$ drugs
Side effects - major or minor	Evidence of recurrence
Advice given	Previous non-compliance
Supply problems	Previous treatment
Compliance with last dose due	Current treatment
Cessation of therapy	Duration of hormone therapy
Missed doses	Reason for using hormone therapy
System for taking drugs	
General assessment	

All questionnaires were checked for completeness and transferred to the computer centre at Aston University for analysis of the data using the Statistical Package for Social Scientists, SPSS, system.

1.2.3 Computer Analysis of the Questionnaires

The statistical package for the social sciences[36], SPSS, is an integrated system of computer programs designed for the analysis of social science data. The raw data from the questionnaires was punched onto cards and entered into the computer along with the SPSS control cards and permanently retained as a SPSS system file. The control cards which instructed the system on the processing of the data were divided into two types: data-definition cards and task-definition cards. The SPSS package enabled descriptive statistics and cross-tabulations to be used in a simple convenient manner. The procedures which performed the calculations on the data were subprograms of the SPSS system and were selected using the task-definition cards. SPSS also provided a great flexibility in modifying the data file both temporarily and permanently and enabled new variables to be recoded, specified cases to be selected and further cases to be added to the system when required, such that the computer could be instructed to carry out the required tasks in any sequence.

1.3 RESULTS

1.3.1 Tamoxifen

In total 151 patients being treated with tamoxifen were interviewed. The following non-compliance was reported:

Table 1.3.1 - Non-compliance for the Tamoxifen patients

	Type of Non-compliance studied	Number of patients	
		N	%
1	Patients who had stopped therapy temporarily or permanently	19	13
2	Patients who had not taken the last dose	26	17
3	Patients who forgot or missed doses at the prescribed times	43	28

The questionnaire data concerning various aspects of the patients and their therapy has been divided into the following eight sections:-

1.3.1.1 Patient characteristics.

1.3.1.2 Appointment and clinic details.

1.3.1.3 Previous medical treatment.

1.3.1.4 Current medical treatment.

1.3.1.5 Supply of medicines.

1.3.1.6 Advice concerning medicines.

1.3.1.7 Patients' System to aid taking medicines.

1.3.1.8 Side effects.

The frequencies of the variables within each section have been included. The data has been analysed for the group as a whole. This assumes that there are no significant differences between the clinics with respect to the patients or the clinicians. The validity of the assumption is tested and discussed in the next chapter.

The "chi-squared" test of analysis has been used throughout the work to determine the association between the three types of non-compliance studied and the variable described in each of the eight sections. Full details of all the "chi-squared" analyses are included in appendix III.

The following table 1.3.2 shows the reasons why patients stopped their therapy.

TABLE 1.3.2 Patient's Reason for Stopping Tamoxifen Therapy temporarily or permanently

No	Reason for ceasing therapy	
1	Poor Memory:	Low motivation, forgets tamoxifen for several days rather than other drugs.
2	Side Effects:	Stopped therapy for three months due to dizziness.
3	Poor Memory:	Forgot completly whilst on holiday.
4	Unwell:	Stopped for three to four days.
5	No faith in drug:	Stopped permanently.
6	No faith in drug:	Stopped permanently.
7	Non-comprehension:	Thought the drug was to be taken when required for breathing.
8	Side Effects:	Stopped therapy but contacted doctor and dosage reduced.
9	No faith in drug:	Stopped permanently now and temporarily in the past, for several days when supply ran out.
10	Unwell:	Stopped therapy after a heart attack.
11	Side Effects:	Stopped permanently due to severe hot flushes.
12	Non-comprehension:	Patient halved dosage to decrease the total number of tablets taken per day.
13	Side Effects:	Stopped for three months due to severe cold sweats.
14	Lack of counselling:	Took for two weeks only on discharge from hospital.
15	No faith in drug:	Stopped permanently
16	Side Effects:	Stopped for four months due to shortness of breath.
17	No faith in drug:	Stopped permanently, ran out of tablets, did not bother to renew supply.
18	Side Effects:	Misses doses when going out due to dizziness.
19	No reason given:	

The following table 1.3.3 describes in more detail those patients who forgot or missed doses at the prescribed times.

TABLE 1.3.3 Patients who forgot or missed doses at the prescribed times.

Variable	Value	Number of Patients	% of those patients who forgot/missed doses
Number of doses missed in last week	1	12	27.9
	2	4	9.3
	7	1	2.3
	14	1	2.3
When most likely to miss a dose	Morning	7	16.3
	Afternoon	5	11.6
	Evening	13	30.2
	Do not know	18	41.9
Action taken when remember a dose is missed	Take as soon as remember.	25	58.1
	Miss out dose completely.	24	55.8
	Take twice next time.	3	7.0

Consider now various aspects of the patients and their therapy to examine whether a particular variable, eg age, is a significant factor in the three types of non-compliance studied. Associations found to be significant at the 5% level, using the chi-square test of association are detailed fully.

1.3.1.1 Patient Characteristics

TABLE 1.3.4 Patient characteristics for the group

Variable	Value	Number	% of Total
Age (years)	<50	14	9.3
	50-60	37	24.8
	61-70	40	26.8
	71-80	45	30.2
	>80	13	8.7
Family Support	Husband	87	57.6
	Family	48	38.1
	Other People	5	3.3
	Alone	42	27.8
Working	Full or Part Time	39	25.8
Interviewer's Assessment	Intellectual impairment	18	11.9
	Poor Vision	7	4.6
	Diminished Hearing	23	15.2
	Not able to answer questions	9	6.0
	Not in charge of medicines	9	6.0

Stopping therapy

There were no significant associations with age, family support, working or interviewer's assessment.

Not taking last dose

There were no significant associations with age, family support, working or interviewer's assessment.

Forgetting or missing doses

There were no significant associations with age, working or interviewer's assessment.

There was a strong association between those patients living with family and forgetting or missing doses, which was significant at 1.4%.

No such asociation was evident with patients living with their husband only or with patients living alone.

TABLE 1.3.5 Association between living with family and forgetting or missing doses

Variable :	Value	Number N	% of N who Forget or	Chi Square	Degrees of Freedom	Probability
Lives with:	Husband	87	26.4	0.419	1	0.517
	Family	48	41.7	6.011	1	0.014
	Alone	42	26.2	0.149	1	0.699
	Others	5	20.0	0.182	1	0.669

1.3.1.2 Clinic Number and Appointments

TABLE 1.3.6 Clinic number and appointment details for the group

Variable	Value	Number	% of Total
Clinic	1	76	50.3
	2	26	17.2
	3	49	32.5
Appointment Frequency	every 3 months	76	50.3
	every 6 months	39	25.8
	Other	26	17.2
	Now discharged	1	0.7
	Do not know	7	4.6
Missed Appointments	Once	10	6.6
	More than once	4	2.6
	Never	136	90.1
Reminded appointment is due by:	Husband	9	6.0
	Family	15	9.9
	Others	2	2.0

Stopping therapy

There were no significant associations with appointment frequency, missed appointments or patients not being reminded about their appointment There was a strong association between different clinics and stopping therapy which was significant at 0.8%.

TABLE 1.3.7 Association between clinic type and stopping therapy

Variable	Value	Number,N	% of N	Chi Square	Degrees of Freedom	Probability
Clinic	1	76	5.3			
	2	26	0.0	9.745	2	0.008
	3	37	8.8			

This indicated that it may not be appropriate to group the patients from the three different clinics together with analysing the results since there is a difference between clinics. This will be further investigated in section 1.3.1.9 of this chapter.

There were no significant associations with any of the variables in this section, and either not taking the last dose or forgetting or missing doses.

1.3.1.3 Previous Medical Treatment

TABLE 1.3.8 Previous medical treatment details of the group

Variable	Value	Number	% of total
Previous Therapy	Surgery	122	80.8
	Radiotherapy	66	43.7
	Chemotherapy	14	9.3
Previous Hormonal Therapy	Tamoxifen	3	2.0
	Medroxyprogesterone	1	0.7
	Norethisterone	1	0.7
	Megestrol	1	0.7
	Aminoglutethimide	0	0.0
Hormones were used as	Primary Therapy	1	0.7
	Adjuvant Therapy	0	0.0
	Recurrence Therapy	5	3.3
Previous Non-compliance	Refused Surgery	2	1.3
	Refused Radiotherapy	4	2.6
	Refused Chemotherapy	0	0.0
	With other medication	20	13.2
Duration of Symptoms before presentation (months)	0-1	53	35.1
	2-6	47	31.1
	> 6	20	13.2
Duration of Illness since presentation (months)	0-12	43	28.5
	13-24	30	19.9
	25-36	15	9.9
	37-48	11	7.3
	49-60	11	7.3
	> 60	34	22.5
Other Illness present	Yes	46	30.5
History of psychological problems	Yes	19	12.6

Stopping therapy

There were no significant associations with previous therapy, duration of symptoms before presentation, duration of illness since presentation, presence of other illness or history of psychological problems. There was a very strong association between previous non-compliance with other medication, and stopping therapy which was significant at less than 0.1%.

TABLE 1.3.9 Association between previous non-compliance and stopping therapy

Variable	Value	Number,N	% of N Stopping	Chi Square	Degrees of Freedom	Probability
Previous Non-compliance	Yes	19	36.8	20.818	1	0.00
	No	126	4.8			

Not taking last dose

There were no significant associations with previous non-compliance, duration of symptoms before presentation, duration of illness since presentation or history of psychological problems. There were associations between presence of other illness, previous tamoxifen and not taking the last dose, significant at 1.4% and 2.2% respectively.

TABLE 1.3.10 Association between presence of other illness and previous tamoxifen and not taking the last dose

Variable	Value	Number,N	% of N not taken last dose	Chi Square	Degrees of Freedom	Probability
Presence of other Illness	Yes	46	28.3	6.008	1	0.014
	No	101	11.9			
Previous dose	Yes	3	66.7	5.251	1	0.022
	No	148	16.2			

Forgetting or missing doses

There were no significant associations with previous therapy, previous non-compliance, duration of illness or history of psychological problems. There was an association between duration of symptoms before presentation to clinic and forgetting or missing doses, significant at 4.1%.

TABLE 1.3.11 Association between duration of symptoms before presentation to clinic and forgetting or missing doses.

Variable	Value	Number,N	% of N who forget/ miss	Chi Square	Degrees of Freedom	Probability
Duration symptoms before presentation /months	0-1	53	32.1			
	2-6	47	23.4			
	> 6	20	55.0	6.392	2	0.041

1.3.1.4. Current Medical Treatment

TABLE 1.3.12 Current medical treatment details of the group

Variable	Value	Number	% of Total
Present Therapy	Radiotherapy	2	1.3
	Chemotherapy	2	1.3
	Hormonal	150	99.3
Does the patient know the medicines she takes	Yes	129	85.4
Total number of medicines taken	1	59	39.1
	2	42	27.8
	3	28	18.5
	4	9	6.0
	> 4	13	8.6
Does the patient know when to take her medicines	Yes	143	94.7
Does the patient need to refer to the bottle label	Yes	9	6.0
Total number of doses taken in one day	1	23	15.2
	2	45	29.8
	3	17	11.3
	4	16	10.6
	> 4	48	31.8
Drugs taken which impair mental ability	Yes	8	5.3
Duration of Tamoxifen Therapy (months)	1-6	63	41.7
	7-24	47	31.1
	25-48	31	20.5
	> 48	8	5.3
Tamoxifen used as:	Primary Therapy	32	21.2
	Adjurant Therapy	41	27.2
	Recurrence Therapy	76	50.3

There were no significant associations with any of the variables in this section.

1.3.1.5 Supply of Medicines

TABLE 1.3.13 Supply of medicines details.

Variable	Value	Number	% of Total
Supply from	Hospital pharmacy	8	5.3
	GP-via local pharmacy	142	94.0
Supply a problem	Yes	7	4.6
Number of times run out of medicine	Never	145	96.0
	Once	5	3.3
	More than once	1	0.7

Stopping therapy

There were no significant associations with place of supply or supply causing a problem. There was a very strong association between the number of times the patient ran out of medicines and stopping therapy, significant at less than 0.1%.

TABLE 1.3.14 Association between running out of medicine and stopping therapy

Variable	Value	Number, N	% of N stopping	Chi Square	Degrees of Freedom	Probability
Number of times patient ran out of medicine	0	145	6.9	17.282	2	<0.001
	1	5	40.0			
	2	1	100.0			

There were no significant associations with any of the variables in this section, and either not taking the last dose or forgetting or missing doses.

Additionally there were no significant associations between age, living alone, place of supply, duration of tamoxifen therapy, duration of symptoms before presentation or number of medicines and the number of times the patient ran out of medicines.

1.3.1.6. Advice concerning medicines

TABLE 1.3.15. Advice concerning medicines for the group

Variable	Value	Number	% of Total
Person giving advice	Doctor	146	96.7
	Pharmacist	42	27.8
	Nurse	1	0.7
	Other Patients	13	8.6
	Nobody	2	1.3
Type of advice	When to take	73	48.3
	How often to take	148	98.0
	How long to take	53	35.1
	Important not to stop	112	74.2
	Other Information	32	21.2

Stopping therapy

There were no significant associations with either the person giving the advice or the type of advice given.

Not taking last dose

There was an association between not being told it was important not to stop taking the medicines and not taking the last dose due, significant at 3.5%.

TABLE 1.3.16. Association between advice given and not taking the last dose.

Variable	Value	Number, N	% of N not taken last dose	Chi Square	Degrees of Freedom	Probability
Told important not to stop medicines	Yes	112	13.4	4.453	1	0.035
	No	39	28.2			

No other associations were significant.

Forgetting or missing doses

There was an association between not being told when (that is, what time of day) to take the medicines and forgetting or missing doses, significant at 3.7%.

TABLE 1.3.17. Association between advice given and forgetting or missing doses

Variable	Value	Number, N	% of N who forget/miss	Chi Square	Degrees of Freedom	Probability
Told when to take medicines	Yes	73	20.5	4.362	1	0.037
	No	78	35.9			

No other associations were significant.

The following table 1.3.18 describes the type of advice given by the pharmacist compared with that given by the doctor.

TABLE 1.3.18. Type of advice given by the pharmacist compared with the doctor

Type of Advice	Doctors' Advice		Pharmacists' Advice	
	N	% of Doctors	N	% of Pharmacists
When to take	72	49.3	26	61.9
How often to take	143	97.9	41	97.6
How long to take	52	35.6	18	42.9
Important not to stop	110	75.3	29	69.0
Other Information	31	21.2	9	21.4

1.3.1.7. Patients' System to aid taking medicines.

TABLE 1.3.19. Patients' system to aid taking medicines

Variable	Value	Number	% of Total
System	At meal times - Before	13	8.6
	With	19	12.6
	After	47	31.1
	Put out daily doses	72	47.7
	Somebody reminds	49	32.5
	Use of a calendar or diary	5	3.3
	Other means	0	0.0
	At bedtime - on waking or retiring	32	21.2

Stopping therapy

There was an association between taking the medicine at meal times and stopping therapy significant at 1.8%.

TABLE 1.3.20. Association between taking medicine at meal times and stopping therapy

Variable	Value	Number, N	% of N stopping	Chi Square	Degrees of Freedom	Probability
Take medicine at meal times	No	72	8.3			
	Before	13	30.8			
	With	19	0.0			
	After	46	6.5	10.104	3	0.018

Not taking last dose

There was an association between taking the medicine on waking or going to bed and taking the last dose due, significant at 1.7%.

TABLE 1.3.21 Association between taking the medicine on waking or going to bed and taking the last dose

Variable	Value	Number, N	% of N not taken last dose	Chi Square	Degrees of Freedom	Probability
Take medicine on waking/ going to bed	Yes No	32 119	3.1 21.0	5.658	1	0.017

This association implied that the patients who took their medicine at this time were more likely to have taken the last dose due on the day of the clinic.

Forgetting or missing doses

There were no significant associations with any of the patients' systems for taking their medicines.

1.3.1.8. Side Effects experienced

TABLE 1.3.22. Side effects of Tamoxifen

Variable	Value	Number	% of Total
Side Effect	Unable to sleep	1	0.7
	Lack energy	6	4.0
	Feel unusually tired	10	6.6
	Feel irritable	6	4.0
	Feel depressed	6	4.0
	Feel dizzy	9	6.0
	Hot flush	31	20.5
	Rash	1	0.7
	Headaches	1	0.7
	Bone pain	7	4.6
	Altered vision	2	1.3
	Feel sick	13	8.6
	Be sick	2	1.3
	Diarrhoea	4	2.6
	Constipation	11	7.3
	Appetite change	17	11.3
	Weight change	33	21.9
Side Effects causing therapy to stop	Yes - Temporarily	5	3.3
	Yes - Permanently	1	0.7
	No - Never	145	96.0

The most common side effects, encountered by 20% of the population, were hot flushes and weight change.

Stopping therapy

There was an association between the following side effects and stopping therapy.

TABLE 1.3.23 Associations between side effects and stopping therapy

Variable	Value	Number, N	% of N Stopping	Chi Square	Degree of Freedom	Probability
Lack Energy	Yes	6	50.0			
	No	120	6.7	13.467	1	< 0.001
Feel Dizzy	Yes	9	33.6			
	No	132	6.8	7.608	1	0.006
Feel Depressed	Yes	6	33.3			
	No	114	7.9	4.430	1	0.035
Hot Flush	Yes	31	19.4			
	No	102	5.9	5.257	1	0.022
Altered Vision	Yes	2	50.0			
	No	130	8.5	4.112	1	0.043

Not taking last dose

No significant associations with any of the side effects.

Forgetting or missing doses

There was an association between the following side effects and forgetting or missing doses.

TABLE 1.3.24 Associations between side effects and forgetting or missing doses.

Variable	Value	Number, N	% of N who forget or miss	Chi Square	Degree of Freedom	Probability
Hot Flush	Yes	31	48.4			
	No	103	22.3	7.963	1	0.005
Appetite Change	Yes	14	52.9			
	No	131	26.0	5.317	1	0.021

1.3.1.9 Clinic Number

It was seen in section 1.3.1.2. for those patients who stopped therapy there was a significant difference between clinics. Therefore, the data was analysed by comparing the clinic attended with all of the variables. The following variables in Table 1.3.25 were found to be significant. Full details of all the "chi-squared" analyses are included in Appendix III.

TABLE 1.3.25 Significant association between the clinics attended and variables studied.

Variables	Value	Clinic Number 1	2	3	Chi Square	Degrees of Freedom	Probability
Appointment Frequency	every 3 months	54	2	20			
	every 6 months	14	11	14			
	Not known	1	3	3			
	Discharged	1	0	0			
	Other	6	9	11	36.441	8	< 0.001
Number of doses	1	13	8	2			
	2	20	3	22			
	3	11	4	2			
	4	7	5	4			
	> 4	24	6	18	22.884	10	0.011
Advised when to take drugs	Yes	32	19	22			
	No	44	7	27	7.786	2	0.020
Duration of illness since treatment commenced /months	0-12	27	2	14			
	13-24	11	4	15			
	25-36	4	0	11			
	37-48	4	5	2			
	49-60	8	2	1			
	> 60	20	9	5	36.854	10	< 0.001
Absence of other illness	Yes	30	2	14			
	No	44	24	33	9.729	2	0.008
Previous Radiotherapy	Yes	20	13	33			
	No	56	13	16	20.891	2	< 0.001
Previous Chemotherapy	Yes	12	0	2			
	No	64	26	47	8.064	2	0.018
Duration Tamoxifen therapy /months	1-6	42	5	16			
	7-24	15	11	21			
	25-48	15	5	11			
	>48	3	5	0	26.206	6	< 0.001
Hormone used as treatment:	Primary	17	4	11			
	Adjuvant	9	6	26			
	Recurrence	49	16	11	30.692	4	<0.001

1.3.2 Aminoglutethimide and Medroxyprogesterone

In total fourteen patients being treated with aminoglutethimide and eleven patients being treated with medroxyprogesterone were interviewed. The following non-compliance was reported:

TABLE 1.3.26 Non-compliance for the aminoglutethimide and medroxyprogesterone patients

Type of Non-compliance studied	Aminoglutethimide	Medroxyprogesterone
Patients who had stopped therapy temporarily or permanently	1	5
Patients who had not taken the last dose	3	3
Patients who forgot or missed doses at the prescribed times	2	1

1.3.2.1 Aminoglutethimide

The patient who permanently stopped therapy did so after only three doses and claimed to have experienced severe headaches and dizziness. This patient did not contact the doctor and had also discontinued both tamoxifen and medroxyprogesterone, in the past, for the same reasons. This patient, aged 76, had a multitude of medical problems including glaucoma, mitral valve disease, peptic ulcer and hypertension, necessitating seven different drugs. The patient was not anxious about her breast disease, had waited six years before presenting to clinic and was not motivated towards therapy.

Two patients claimed to miss out or forget doses sometimes but neither had done so in the previous week.

1.3.2.2 Medroxyprogesterone

Out of eleven patients, five patients had stopped therapy for the following reasons:

TABLE 1.3.27 Patients' reasons for stopping medroxyprogesterone temporarily or permanently.

No	Reason for ceasing therapy	
1	Side Effects:	Stopped therapy due to headaches, depression, dizziness and constipation.
2	Side Effects:	Stopped due to swollen hands.
3	Side Effects:	Stopped due to dizziness, malaise, shakiness but contacted doctor and dosage reduced.
4	No faith in drug:	Stopped permanently
5	No faith in drug:	Stopped permanently

The important factors in this group of patients are the side effects experienced, which can be a problem with the high dose medroxyprogesterone[30] regimen, and the fact that two of these patients had no faith in their therapy. One had received four previous treatments (surgery, radiotherapy, tamoxifen and aminoglutethimide) which had all failed to control the disease whilst the other had received three previous treatments (surgery, tamoxifen and aminoglutethimide) but had been non-compliant with both previous hormonal treatments.

Two patients claimed to miss out or forget doses sometimes; one had missed one dose in the previous week and the other had missed two doses. It should be noted that the regimen required the patient to take four tablets each day.

For both the aminoglutethimide and medoxyprogesterone patients, the numbers interviewed were too small to enable a "chi-squared" test of analysis to be employed.

1.4 DISCUSSION

1.4.1 Stopping Therapy

The following is a summary table of the reasons why the interviewed patients who admitted non-compliance with tamoxifen stopped their therapy.

TABLE 1.4.1 Summary of reasons for stopping tamoxifen therapy.

Reason	Number
Side Effects	6
No faith in drug	5
Non-comprehension	3
Unwell	2
Memory	2
Unknown	1

Side effects, having no faith in the drug and non-comprehension appear to be important factors in accounting for these patients' intentional non-compliance.

1.4.1.1 Side Effects

For tamoxifen the general incidence of side effects is low and usually not severe[29]. Six patients in this study reported stopping therapy for the following reasons.

Dizziness	2
Shortness of breath	1
Hot flushes	2
General malaise	1

The patient experiencing general malaise had been prescribed a high loading dose of tamoxifen and when the dosage was reduced, the symptoms resolved.

Hot flushes, light-headedness and fluid retention are reported in the data sheet for the drug. The patient who experienced shortness of breath also had increased weight as well, possibly indicating that fluid retention could have been the cause. For the group as a whole, hot flushes and weight change were experienced by 20% of patients. Appetite change was also seen in 11% of patients, feeling sick in 9% of patients and constipation in 7% of patients.

When the "chi-squared" test of analysis was performed between the side effects reported and stopping therapy, lacking energy and feeling dizzy were found to be highly significant at the 1% level in those patients who stopped therapy. Feeling depressed, experiencing hot flushes and altered vision were also significant at the 5% level. Although the number of patients experiencing these side effects (apart from hot flushes) is small a probability as low as 1% suggests that there is a strong association, despite the limitations, of analysing such small numbers.

It is interesting to note that those patients who experienced decreased energy were most likely to stop their therapy.

There were associations between experiencing either hot flushes or appetitie change and forgetting or missing doses, the former significant at the 1% level. This could indicate that patients will sometimes omit doses in order to avoid uncomfortable side effects such as hot flushes.

Thus, for tamoxifen side effects accounted for six of the nineteen

failures to comply with therapy. Dizziness and hot flushes each resulted in two patients stopping therapy.

1.4.1.2 Having no faith in the drug and non-comprehension

Five patients stopped tamoxifen through having no faith in the drug. Two of these were receiving the drug for recurrence of the disease and they had been on this regime for three and five years. A further two patients had been on therapy for only eight and nine months but were receiving the drug as adjuvant therapy. These patients considered themselves cured by previous surgery and radiotherapy and saw no reason to take the tamoxifen. Data is unfortunately incomplete for the fifth patient. Clearly there are two types of patient: the former group who had complied with therapy had been symptom-free for a long period of time, now decided there was no necessity for treatment; and the other group of patients had recently commenced tamoxifen but placed little importance on adhering to therapy. A further three patients failed to comply with therapy because of lack of comprehension. One had received a fortnight's supply on discharge from hospital and had not renewed the supply, one thought tamoxifen was for her breathing and she only took the drug when required and the third, not knowing why tamoxifen was being taken, halved the dosage because she wanted to take fewer tablets during the day.

For these three patients and the two on adjuvant therapy who had no faith in the drug, counselling had failed. Consider the advice given to these patients. This study showed no associations with either the person giving the advice or the type of advice given and stopping therapy at the 5% level of significance. Most patients (97%) received some advice from the doctor with 75% of the patients remembering being told that it was important not to stop therapy. Pharmacists gave advice to 28% of patients and 69% of these patients were told not to stop therapy. When advice was given by the pharmacist the quality of this advice did not appear to

differ greatly from that given by the doctor. However counselling failed in some patients.

Consider aspects of the patients and their medical treatment.

Most patients (82%) were aged between 50 and 80, with 28% living alone, no association was observed between age, family support or whether working or not and stopping therapy at the 5% level of significance.

Interestingly, those patients who lived with their family were more likely to forget or miss doses, this was significant at the 2% level. Again, age was not significant.

With regards to previous medical treatment, no associations were observed between previous therapy, duration of symptoms before presentation, duration of illness since presentation, presence of other illness or history of psychological problems and stopping therapy, significant at the 5% level. There was a very strong association between previous non-compliance with other medication, as reported in the notes and stopping therapy which was significant at less than 0.1%.

With regards to current medical treatment, no associations were observed between the patient knowing which medicines she took and when to take them, total number of medicines taken, number of doses taken each day, duration of tamoxifen therapy, whether tamoxifen was used as primary, adjuvant or recurrence therapy and stopping therapy, significant at the 5% level.

With regards to the supply of medicine, whether the patient obtained tamoxifen from the hospital (5%) or through the GP (94%) there was no association with stopping therapy significant at the 5% level. However, patients whose supply had run out (4%) were more likely to stop therapy, significant at 0.1% reflecting either difficulties in reaching the GP/ pharmacy or a low motivation to continue therapy.

For the eight patients who stopped tamoxifen (five through no faith in the drug and three who failed to comprehend the reason for taking the drug) this study has shown only two significant differences with respect to patient characteristics, medical treatment, supply and counselling when comparing non-complies with complies: previous non-compliance with therapy and a supply problem. These results would suggest that there are other reasons for the non-compliance of these patients, not tested in this study. Hoagland[11] suggested that psychological reasons for non-compliance could account for 29% of non-compliance and in combination with medical reasons a further 19%. Certainly the patients in this study who had lost faith in their therapy could be explained in terms of both the "self-efficacy model" and the modified "health belief model" proposed by Barofsky[15]. The former model applied to those patients who had been on therapy and had been symptom-free for a long period of time, and who no longer believed that continuing treatment was necessary for a cure. The latter model applied to the patients who placed a low value on the tamoxifen as adjuvant therapy with a low estimation of the usefulness of this aspect of therapy.

1.4.1.3 Memory problems and feeling unwell

There are five other patients to consider who discontinued their tamoxifen at some stage during treatment. For one patient data is unavailable, two patients stopped therapy when unwell (one had suffered a heart attack), and the other two stopped because of memory problems. Considering more closely the two patients with memory difficulties. One patient with low motivation in taking any of her four drugs claimed

to forget and stop tamoxifen for several days at a time, whilst the second patient had forgotten to take tamoxifen on holiday with her, missing out all the doses due during that period, and now never takes tamoxifen when staying away from home. In total forty-three (28%) of patients admitted forgetting or missing out doses at the prescribed times. Whilst twenty-five (58%) of these claimed taking the dose as soon as it was remembered, twenty-four (56%) claimed missing out doses completely and three (7.0%) claimed at some time to have taken double the dose the next time. With regards to the most frequent timing of the missed dose, 42% did not think there was any particular time when doses are more likely to be missed and of the remainder of patients, twice as many were more likely to miss an evening dose than a morning or afternoon dose. For tamoxifen the plasma half-life is fourteen days, so an error of timing by itself is not important. Infrequent errors of omission or extra doses taken will probably not alter steady state plasma levels to produce any significant clinical effect. However, two patients missed a majority of the previous week's doses giving more reason for concern.

1.4.2 Forgetting or Missing Doses

Consider the various aspects of the patients and their medical treatment and the association with forgetting or missing doses. As already noted, associations were seen between experiencing either hot flushes or appetite change and forgetting or missing doses, the former being significant at the 1% level. There were no associations between age or working and forgetting doses significant at the 1% level. However, those patients who lived with their family were more likely to forget or miss out doses; this was significant at the 2% level. With respect to previous therapy, there was an association between duration of symptoms before presentation to clinic and forgetting doses, significant at the 4% level. The association indicated that patients who waited more than six

months before presenting to clinic were more likely to forget or miss doses than those patients who presented sooner than six months.

There were no associations between current medical treatment, the supply of medicines and forgetting doses significant at the 5% level.

Considering the advice given to the patient there was an association between not being told when to take the medicines and forgetting doses significant at the 4% level, i.e. those patients who were not told at what time of day to take their medicines were more likely to forget doses. However, none of the other questions relating to advice proved significant and when the patients' system for taking their medicines was investigated no associations were evident at the 5% level. A patient who had no system for taking her medicine was no more or less likely to forget a dose than a patient who had a definite system.

To summarise the results for the patients who forget or miss out doses, 28% of patients admitted forgetting or missing out doses at the prescribed times, 1.4% (2) stopped therapy for limited periods due to memory problems. Side effects such as hot flushes or appetite change were also a significant factor to forgetting doses. Patients living with a family, patients who had avoided presenting to clinic for over six months after first symptoms and patients who had not been told when to take their medicines were more likely to forget doses. However, the last two associations had a much weaker significance (at the 4% level). These results might also indicate either that there are other reasons for patients missing or forgetting does not tested in this study or that there are no specific reasons why a group of patients forget doses.

1.4.3 Not Taking Last Dose

The final measure of compliance, considered those patients who had not taken the last dose, either on the morning of the clinic or the night before. Twenty-six (17%) of patients admitted this form of non-compliance

Four variables in total were found to be significant. Patients who were told not to stop the drug, patients who usually took their medicine on waking or going to bed, patients who had no other illness and patients who had not had previous tamoxifen treatment were all less likely to have missed the last dose due. When a reason was given by the patient for not taking the last dose it was always explained by disruption of normal daily routines because of having to come to clinic and that the dose would be taken when the patient returned home. It is interesting that patients who took the drug immediately on waking or retiring to bed were more likely to have taken the last dose than those who used other systems to remember taking the drug. Disruption of normal routine could also be a factor in the group of patients who routinely forget or miss doses. Unfortunately this was not tested in the study.

1.4.4 Clinic differences

In performing the "chi-squared" test of analysis throughout this work all non-compliers were grouped together and all compliers grouped together. It was assumed that there were no significant differences between the clinic with respect to the patients or the clinicians. However, there was a strong association between stopping therapy and the clinic attended which was significant at 0.8%. Whilst 5% of clinic 1 patients stopped therapy, none in clinic 2 stopped therapy and 19% of clinic 3 patients stopped therapy. This indicates that it may not have been appropriate to group the patients from the three different clinics together when analysing the results. Consider the variables which indicated significant differences between the clinics (see table 1.3.25). Appointment frequency, duration of illness since presentation, presence of other illness, previous radiotherapy, duration of tamoxifen treatment and the reason for using tamoxifen were all significant at the 1% level. Clinic 1

was a large breast surgery clinic, clinic 2 an oncology radiotherapy clinic and clinic 3 a mixed surgery and radiotherapy clinic. Therefore it might be expected that a variable such as previous radiotherapy would be significant. In clinic 3 over 50% of patients were receiving the drug as adjuvant therapy following surgery and/or radiotherapy whilst in clinics 1 and 2, 5% and 20% of patients respectively received the drug as adjuvant therapy. It might be expected that the reason for using tamoxifen as well as the duration of tamoxifen (since it is only more recently that tamoxifen has been used as adjuvant therapy) would be significantly different between clinics. Patients who had received tamoxifen for treatment of recurrence and had been symptom-free for two years would be more likely to have less frequent appointments than those recently commenced on adjuvant therapy, explaining this difference between the clinics. Although there are differences between the clinics with respect to treatment rationale for tamoxifen - recurrence vs adjuvant, - none of these differences could be associated with stopping therapy when considering the group as a whole. Patient differences such as presence of other illness, duration of illness and total number of doses of all drugs taken each day differed significantly between clinics, again none of these could be associated with stopping therapy. Clearly there is a difference between clinics and stopping therapy, however this difference has not been explained in this study. It should be noted that the number of patients interviewed in clinic 1 accounted for 50% of patients, clinic 2, 14% of patients and clinic 3, 33% of patients, and that a total of 151 patients were interviewed. The differences between the clinics may in part be due to the small numbers of patients involved in the study. For example, only twenty-six patients were interviewed in clinic 2.

Although patients from all three clinics were analysed together, since the numbers in the individual clinics were too small to analyse

separately, it should be noted with caution that the clinic attended might have made a contribution to the non-compliance of the patients. However, this study did not give any indication of the reasons for the difference between clinics in non-compliant behaviour.

1.4.5 Aminoglutethimide and Medroxyprogesterone

For both aminoglutethimide and medroxyprogesterone, the numbers of patients interviewed were too small for an in-depth analysis of the results using "chi-squared" tests. However, five out of eleven medroxyprogesterone patients stopped therapy, three because of side effects and two because of lack of faith in therapy whilst one out of fourteen aminoglutethimide patients stopped therapy because of the side effects and also because she lacked faith in therapy. This would indicate that groups of patients on these drugs could be of great interest in the area of non-compliance in breast cancer patients, on hormonal therapy, if only sufficient numbers of patients could be recruited into a study.

1.5 CONCLUSION

The aim of this work was to try to evaluate the level of non-compliance in breast cancer patients taking tamoxifen and to determine the factors which may predispose some patients to non-compliant behaviour.

151 patients from three clinics were interviewed and nineteen (13%) were found to have stopped therapy at some stage. Six patients discontinued therapy because of side effects including dizziness, hot flushes, shortness of breath and malaise. When a "chi-squared" test of analysis was used, lacking energy was also shown to be significant in patients stopping therapy. Five patients stopped through having no faith in therapy. Two patients had been on therapy and had been symptom-free for a long period of time and no longer believed continuing treatment was necessary whilst a further two patients had recently commenced tamoxifen as adjuvant therapy after surgery and/or radiotherapy and placed little importance on taking the tamoxifen. A further three patients failed to comply because of lack of comprehension. When a "chi-squared" test of analysis was used, only two associations were seen with respect to patient characteristics, medical treatment, supply of medicine and counselling when comparing non-compliers with compliers. Previous non-compliance and difficulty in obtaining further supplies of the drug are indications that a patient may be non-compliant with current treatment. Two patients stopped therapy when unwell through other medical conditions, for one patient data is unavailable and two stopped because of memory problems. Memory problems accounted for forty-three (28%) of patients forgetting or missing out doses at prescribed times. Side effects such as hot flushes or appetite change, living with a family, presenting to clinic greater than six months after first symptoms and not being told when to take their medicine were factors more likely to predispose a patient to forget or miss out doses.

Finally, the clinic attended has a significant effect on the likelihood of compliance although this study could not identify the reasons for this. Psychological tests were not employed in this study but could be useful in future work to examine more closely the reasons why certain patients develop an attitude of having no faith in therapy.

This work has shown that non-compliance was a problem in 13% of the patients interviewed who were taking tamoxifen as hormonal therapy for breast cancer. For aminoglutethimide and medroxyprogesterone non-compliance may also be a problem, whereby patients may adopt an attitude of having no faith in therapy because they have already failed several other courses of therapy. Therefore it should never be assumed that cancer patients are fully compliant just because of the seriousness of the condition.

Whether a patient's failure to improve is because of resistance of the cancer to therapy, treatment ineffectiveness, disease progression or non-compliance with treatment, there is an urgent need for new agents to be developed which are non-toxic and have improved antitumour activity. The next section of this work investigated the oral pharmacokinetics of a new drug, mitozolomide.

PART 2: PHARMACOKINETIC STUDY

2.1 INTRODUCTION

2.1.1 The Chemistry of Mitozolomide

Mitozolomide, 8-carbamoyl-3-(2-chloroethyl)-imidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one was the first of a series of compounds to be synthesised by Robert Stone[37] in 1980 whilst working on cyclic and acyclic modifications of 5-amino-imidazole-4-carboxamide (AIC).

The rationale behind the synthesis of mitozolomide can be seen by considering two groups in particular: the NNN group and the 2-chlorethyl side chain.

Properties of the NNN group had been previously studied in a range of acyclic triazenes[38] and cyclic 1,2,3-triazines[39]. It was known that diazonium ions had antitumour activity, Shealey[40] had produced 5-diazoimidazole-4-carboxamide, (diazo-IC) by the diazotisation of AIC but this had limited use because of its tendency to cyclise to 2-azahypoxanthine. Diazo-IC had been coupled with secondary amines, one product being 5-(3,3-dimethyl-1-trizenyl)imidazole-4-carboxamide, (DTIC) which was designed to act as a pro-drug of Diazo-IC.

Work on the chloroethylnitrosoureas[41] had indicated that the ability of these compounds to alkylate and crosslink DNA was due either to the formation of a chloroethyldiazohydroxide group or the carbamoylating activity of the isocyanate group itself.

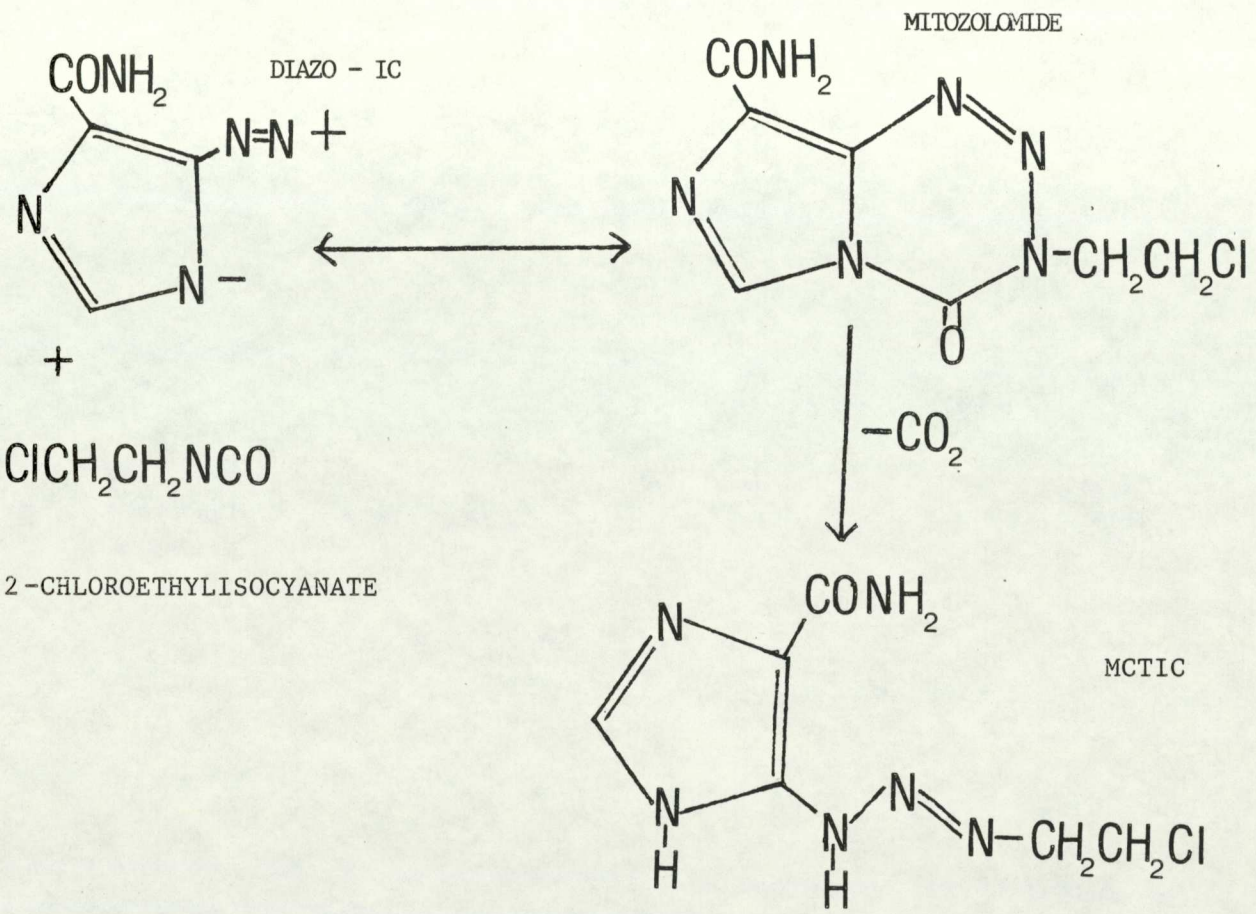
It was proposed to incorporate features of diazo-IC and the isocyanates via a NNN link into the same molecule which should decompose and generate products with potent antitumour activity. Mitozolomide is a novel compound by virtue of the 1,2,3,5-tetrazinone ring fused to an imidazole ring.

Previous synthetic work on the interaction of diazoazoles and isocyanates had been carried out by Ege and Gilbert[42] and it was thought

that by using diazo-IC with different alkyl or aryl isocyanates under the same conditions, a series of imidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)ones would be produced.

When diazo-IC and 2-chloroethylisocyanate were stored in dichloromethane at 25 °C in the dark for twenty days, mitozolomide was produced in a yield of 90%[43]. The structure of mitozolomide was confirmed from the IR and HNMR spectra and by X-ray crystallography[43]. Previous work on the 1,2,3-benzotriazin-4(3H)-ones[39] and the imidazo[5,1-c]-1,2,4-triazin-4(3H)-ones[44] indicated two possible decomposition pathways for mitozolomide. One route in cold methanol or ethanol involved reversion to the diazo-IC and 2-chlorethylisocyanate with further decomposition to 2-azahypoxanthine and N-(2-chloroethyl)carbamate. The second route involved hydrolytic attack and then ring opening to produce 5-[3-(2-chloroethyl)-triazen-1-yl]imidazole-4-carboxamide, MCTIC, with further decomposition to AIC and 2-chloroethanol, this occurred under aqueous conditions in phosphate buffer. The decomposition of mitozolomide under aqueous conditions was seen to be pH-dependent. Whilst mitozolomide was stable in concentrated sulphuric acid, even when hot, under basic conditions, decomposition was rapid and in phosphate buffer at pH 7.4, the half-life at 28 °C was 98 minutes.

Figure 2.1.1 Synthesis of mitozolomide from (and possible decomposition to) diazo-IC and 2-chlorethylisocyanate and possible decomposition of mitozolomide to MCTIC.



2.1.2 Experimental Activity of Mitozolomide

Mitozolomide was shown to possess potent inhibitory activity against a number of murine tumours. Screening for antitumour activity was performed at three centres, the "Cancer Research Campaign Experimental Chemotherapy Group" at Aston University, Rhône Poulenc Santé in France and the Institut Jules Bordet in Belgium in a collaborative programme[45]. Two types of assay were used, according to National Cancer Institute procedures, a murine tumour survival-time model and a murine solid tumour inhibition assay. For the survival time models, at single doses of 20-40 mg kg^{-1}, the compound elicited cures against the L1210 and P388 leukaemias regardless of either route of tumour introduction or drug administration and exhibited some activity against the TLX5 lymphoma, Lewis lung carcinoma and colon 26 tumours. Significant increase in survival time was seen against the B16 melanoma but few cures. For the tumour inhibition models mitozolomide exhibited pronounced activity against the Lewis lung carcinoma (and it also eliminated pulmonary metastases in this model), colon 38, M5076 reticulum cell carcinoma and the ADJ/PC6A plasmacytoma but weak activity against the CD8F, mammary tumour.

Cross-resistance studies[45,46] using resistant L1210 leukaemia and KHT sarcoma tumours suggested similarities in the spectrum of antitumour activity between mitozolomide and the nitrosoureas: 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) but no such similarity with DTIC or cyclophosphamide. A comparison of mitozolomide with other agents in the NCI murine tumour panel[45] showed it to be as active as BCNU, cisplatinum, adriamycin, cyclophosphamide and more active than DTIC.

Screening for antitumour activity was also performed at the Norsk Hydro Institute in Norway[47], using xenografts (transplantation of human

tumours into athymic, nude mice) from human melanomas, sarcomas and lung and colon carcinomas. Three types of assay were used, inhibition of the colony forming ability of cell suspensions of various tumours in soft agar, sensitivity to the drug in vitro of a panel of tumours and a six day subrenal capsule xenograft assay in athymic mice. Results showed cures in melanoma, small cell lung carcinoma and sarcoma with good agreement between assay systems. Other work on human xenografts[46] showed the activity of mitozolomide to be similar to CCNU, both being inactive against the colon carcinoma HT29 and the large cell lung tumour L23 but very effective against the small cell lung carcinoma H69.

Having defined the antitumour activity of mitozolomide against a range of murine tumour systems, the mode of action was then investigated.

2.1.3 Mode of Action Studies on Mitozolomide

The mechanism of the antitumour activity of mitozolomide was investigated[48] by comparing the effects of the drug with BCNU and MCTIC on the incorporation of radiolabelled thymidine and uridine into nucleic acids in TLX5 cells and on the enzymes glutathione reductase, chymotrypsin and transglutamase (known to be inhibited by nitrosoureas). The aim being to determine whether mitozolomide decomposes via the isocyanate or the MCTIC pathway. The study showed that whereas the enzymes tested were completely inhibited by BCNU and 2-chloroethylisocyanate, mitozolomide did not inhibit the enzymes. This suggested that the drug does not decompose via the isocyanate. With regards to the effect on precursor incorporation into nucleic acids, BCNU showed a marked effect within one hour, while both mitozolomide and MCTIC produced little change within 24 hours. All these drugs showed similar *in vitro* toxicity.

Further work[49] was carried out to investigate the effects of mitozolomide, compared with MCTIC and 1-(2-chloro-ethyl)-1-nitrosourea (CNU), on the cross-link formation of DNA with proteins and between DNA strands in L1210 murine leukaemia cells. All three drugs showed similar *in vitro* cytotoxicity and DNA interstrand cross-link formation. However these cross-links formed more rapidly with CNU (peak at six hours) than with mitozolomide and MCTIC (peak at nine hours). The results indicated that CNU, MCTIC and mitozolomide acted through a common pathway in forming DNA interstrand and DNA-protein cross-links. Further study[50] on the mechanism of this interaction with DNA, using normal IMR-90 and transformed VA13 (O6-methylguanine repair deficient) human embryo cells showed that, like the nitrosoureas, concentration-dependent interstrand cross-linking occurred with the VA13 cells but there was little or no such effect seen in the IMR-90 cells. DNA-protein cross-link formation was found to be similar for both cell types indicating that drug uptake

and intracellular toxicity were essentially unaltered. This work pointed to the fact that part of the mechanism of action of MCTIC and mitozolomide was through an O6-guanine interstrand cross-link, necessary for the cytotoxicity of the drug and similar to a process described for nitrosoureas[51].

A flow cytometric analysis[52] of DNA distribution in Lewis lung carcinoma cells after treatment with mitozolomide and MCTIC showed that both drugs produced a block in the same regions of the cell cycle.

In summary the nitrosoureas, MCTIC and mitozolomide probably all affect DNA interstrand cross-linking via an O6-guanine adduct, however the time course is much slower for MCTIC and mitozolomide. Also mitozolomide and MCTIC do not affect certain enzymes known to be inhibited by nitrosoureas, and do not block precursor uptake into nucleic acids within a time span of twenty-four hours, unlike the nitrosoureas. Both mitozolomide and MCTIC act at the same stage in the cell cycle. The above evidence seems to substantiate the theory that *in vivo*, mitozolomide decomposes *via* the MCTIC pathway.

2.1.4 Pharmacokinetics of Mitozolomide in Mice

The essential pharmacokinetic parameters of mitozolomide were determined in a study[53] using BALB/c mice as a prelude to a full pharmacokinetic study in the phase I clinical trial[62]. Antitumour screening work[45] had shown that 20 mg kg^{-1}, as a single dose, produced cures in L1210 and P388 leukaemias whilst prolonged survival was seen at 5 and 10mg kg^{-1}. Mice were dosed by the intra-peritoneal route at five dose levels between 0.25 and 20 mg kg^{-1} and by the oral and transdermal routes at 20 mg kg^{-1}. Blood samples were taken at time intervals up to six hours post-dosing with between four and seven mice sampled each time. At all doses mitozolomide was rapidly absorbed with some evidence of an absorption phase being seen between five and ten minutes after dosing at 20 mg kg^{-1}. The data was fitted to a one compartment model and a near linear relationship seen between area under the curve, (AUC) and peak plasma concentration with ascending dose. The study also showed mitozolomide to be well absorbed orally with significant amounts absorbed transdermally.

The pharmacokinetics of mitozolomide were seen to be quite different from those observed with the nitrosoureas[54,55] which display two-compartment model kinetics with plasma levels rapidly falling from an initial peak within one hour. It was proposed that the relatively sustained levels of mitozolomide compared with the nitrosoureas could promote therapeutic activity.

The plasma and tissue disposition of mitozolomide was studied[56] in female AKR mice, some of which had been implanted with the ROS osteosarcoma, to investigate the effect of tumour presence on the pharmacokinetics of the drug. Some mice had been pretreated with phenobarbitone to investigate the effects of enhanced liver metabolism on the drug. Plasma and tissue disposition of mitozolomide appeared again

to follow a simple one compartment model with an elimination half-life of under one hour. The drug was seen to be rapidly distributed to all tissues studied with significant concentrations present in the brain and tumour tissue. The presence of ROS tumour significantly decreased the elimination half-life of the drug indicating that possibly the tumour had induced hepatic enzymes. This idea that hepatic metabolism may be involved in the breakdown of mitozolomide was further substantiated by the discovery that phenobarbitone pretreatment decreased plasma and tissue levels of mitozolomide with an increase in liver weight being observed. Similar results were obtained by Workman and Lee[46].

2.1.5 Clinical Trials in cancer patients

The reason for initiating a clinical trial research programme for mitozolomide was to confirm in man the useful properties of the drug predicted by the preclinical work described above.

The regulations of the American Food and Drug Administration define early human clinical trials with any new drug as follows[57].

"Phase I starts when a new drug is first introduced into man (only animal and in vitro data are available) with the purpose of determining human toxicity, metabolism, absorption, elimination and other pharmacological actions, preferred route of administration, and safe dosage range; phase II covers the initial trials on a limited number of patients for specific disease control or prophylaxis purpose ..."

For cancer patients the phase I trial[58] utilises those patients with advanced malignancies who have either failed standard treatment or for whom such a treatment does not exist. The main aim is to determine both the qualitative and quantitative toxicity profile of the new drug and so find a "biologically active" dose which all patients can tolerate. This aim is achieved using a dose escalation study and relies on the assumption that a biologically active dose will occur at or near the drug's maximum tolerated dose, MTD; this being the highest dose to be safely given. So even if a therapeutic response does not occur, it is hoped that an active dose has been given. The phase I trial should also indicate the pharmacokinetic behaviour and metabolism of the drug, its effect on a whole range of physiological functions and a preferred route of administration for further studies. Efficacy[59] is not a defined goal of the phase I trial, since a lack of activity may reflect the patients themselves who may be debilitated by both unevaluable, rapidly progressive, disease and heavy pretreatment, as well as the fact[60] that many will have received subtherapeutic doses.

The specific purposes of the phase II trial[57-61] are to determine the activity or response rates of the drug in a limited series of malignancies (at the optimum dosage and using the route previously defined in the phase I trial) and to further extend the knowledge of the toxicology and general pharmacology of the drug with the overall aim of benefitting the patients. Ideally patients in phase II trials should have maximum performance status, minimum disease and prior therapy. It has been shown[61] that heavy pretreatment with chemotherapy has a negative effect on the chances of a response. Patients should have tumours that can be assessed accurately and treatment generally continues until either the cancer progresses or unacceptable chronic toxic effects become evident as a result of cumulative doses. Clearly ethical limitations to patient selection occur when a potentially curative therapy already exists, however it has been proposed[61] that a phase II trial drug could be used as initial therapy in disease groups such as slowly progressive metastatic breast, extensive small cell lung and Stage IV ovarian cancer, crossing over to a standard treatment immediately the disease progresses or if there is no response.

2.1.6 Phase I Clinical Trials on Mitozolomide

The phase I clinical trial[62,63] on mitozolomide was a collaborative study carried out at two centres: Charing Cross Hospital, London and St Chad's Hospital, Birmingham. The following were the stated objectives of the trial:-

(1) To determine the maximum tolerated dose of a single intravenous dose.

(2) To identify and investigate the toxicity profile.

(3) To define a safe mode of administration for subsequent studies.

(4) To determine the pharmacokinetics of the drug at different doses and the bioavailability of the drug.

Thirty-seven patients (fifteen male and twenty-two female) were entered into the trial, all patients had microscopically confirmed cancer with progressive disease which had not responded to any established therapies for that disease. The minimum haematological requirements were a white blood cell count greater than 4000 mm^{-3} and a platelet count greater than 100,000 mm^{-3}.

The starting dose used in the study (based on 1/20 LD_{10} studies in mice) was 8.0 mgm^{-2} with dose increments up to a maximum of 153 mgm^{-2}, according to a modified Fibonacci sequence. Where no toxicity occurred, a second dose was given after three weeks at doses below 82 mgm^{-2} and after six weeks at doses above that level. The patients received the drug as a slow intravenous infusion in normal saline over one hour.

The human pharmacokinetics of mitozolomide could be described using a one compartment model but with some evidence to indicate that at the two highest doses, a small distribution phase was present. Lack of absorption data time-points prevented attempts to fit data to a more complex model. The elimination half-life was found to vary between

1.0 and 1.4 hours which could be compared[62] with a half-life of 0.9 hours in phosphate buffers at pH 7.4(37 ^{o}C). This also supported the hypothesis that chemical degradation is the main route of elimination in man. The mean value for the volume of distribution was 36.4L which approximated to that of total body water (about 40L for an average man) lending support to the one compartment model theory. There was a near linear relationship between total area under the curve, and peak plasma concentration with ascending dose with correlation coefficients of 0.993 and 0.985 respectively.

The oral bioavailability was investigated in seven patients at three dose levels whereby each patient received identical oral and intravenous doses of the same drug. The oral formulation was shown to be 95% available, based on the average results of six patients. However two patients exhibited rapid absorption with maximum plasma concentrations at 0.5 hours, three showed a much slower absorption with peak plasma levels 2-3 hours after administration.

The clinical toxicity of the drug was also examined at doses up to 82 mgm^{-2}, nausea and vomiting was either mild or absent; at higher doses seventeen out of twenty-eight (61%) experienced moderate vomiting. The dose limiting toxic effect was a late, severe and prolonged dose related myelosuppression which first became evident, though acceptable at a dose of 115 mgm^{-2}. This presented as a thrombocytopenia occurring about twenty-five days after drug administration with the count remaining low for two weeks or more. The thrombocytopenia was followed by a less intense leucopenia which occurred about thirty-two days after drug administration but which recovered more quickly than the thrombocytopenia. Severe thrombocytopenia at 153 mgm^{-2} necessitated dosage reduction to 140 mgm^{-2} and then 125 mgm^{-2}. Thus, in common with nitrosoureas[54], mitozolomide exhibited a dose-limiting myelosuppression.

There were several transient responses in the study and two of ten adenocarcinoma of the ovary patients attained the WHO criteria for a partial response.

The results provided sufficient evidence to warrant further studies, to evaluate the oral formulation of the drug at a dose of 90 mgm^{-2} and at intervals of six to eight weeks. The aims being to determine the activity of the drug in lung, breast and ovarian carcinomas and to determine whether or not the myelosuppression is dose-dependent. It was the aim of this work to determine whether the myelosuppression caused by the drug could be related to its pharmacokinetics.

2.2 METHOD

2.2.1 Materials and Equipment

2.2.1.1 Chemicals

Mitozolomide

This had been supplied for previous work[63] by Dr E Lunt of May and Baker Ltd., Dagenham, Essex.

Internal Standard (Batch Number GB 5.119)

3-(2-hydroxyethyl)-1,2,3-benzotriazin-4(3H)-one

This was synthesised by Mrs G U Baig within the Department of Pharmaceutical Sciences at Aston University.

2.2.1.2 Solvents

Chloroform, ethyl acetate, methanol, dimethylsulphoxide, acetic acid. These solvents were obtained as Analar/HPLC grade from Fisons Ltd., Loughborough and were used as obtained.

Water was obtained from a Fisons, Fi-Stream water still.

2.2.1.3 Glassware

All glassware had undergone a thorough washing procedure which included an acid rinse (due to the inherent instability of mitozolomide under basic conditions[63]) prior to use.

2.2.1.4 Weighings

All weighings were carried out using pre-weighed glass bottles using a Sartorius 1207 MP2 four figure balance, reserved specifically for high hazard compounds.

All pipettings were were carried out using the most appropriate Gilson-Pipetman pipette (0.2,1 or 5 ml) or for volumes of 0.025 ml or less a Gilson-Microman positive displacement pipette was used. The ethyl acetate was measured using an Oxford Laboratory pipettor set at 2.5 ml.

2.2.2 Extraction of mitozolomide from plasma

A previously described extraction technique[63,64] was used to extract the mitozolomide from the plasma samples, as follows:

1 a 0.025 ml aliquot of internal standard solution (400 mg l^{-1}) in methanol was added to a 10 ml centrifuge tube followed by 0.075 ml 1M hydrochloric acid and 0.5 ml freshly thawed patient's plasma. Each sample was prepared in duplicate.

2 Ethyl acetate (2.5 ml) was added, the contents were well mixed by vortexing twice and the layers were separated by centrifuging for ten minutes at 2000 rpm, using a Heraeus "Christ" Labofuge 6000 centrifuge.

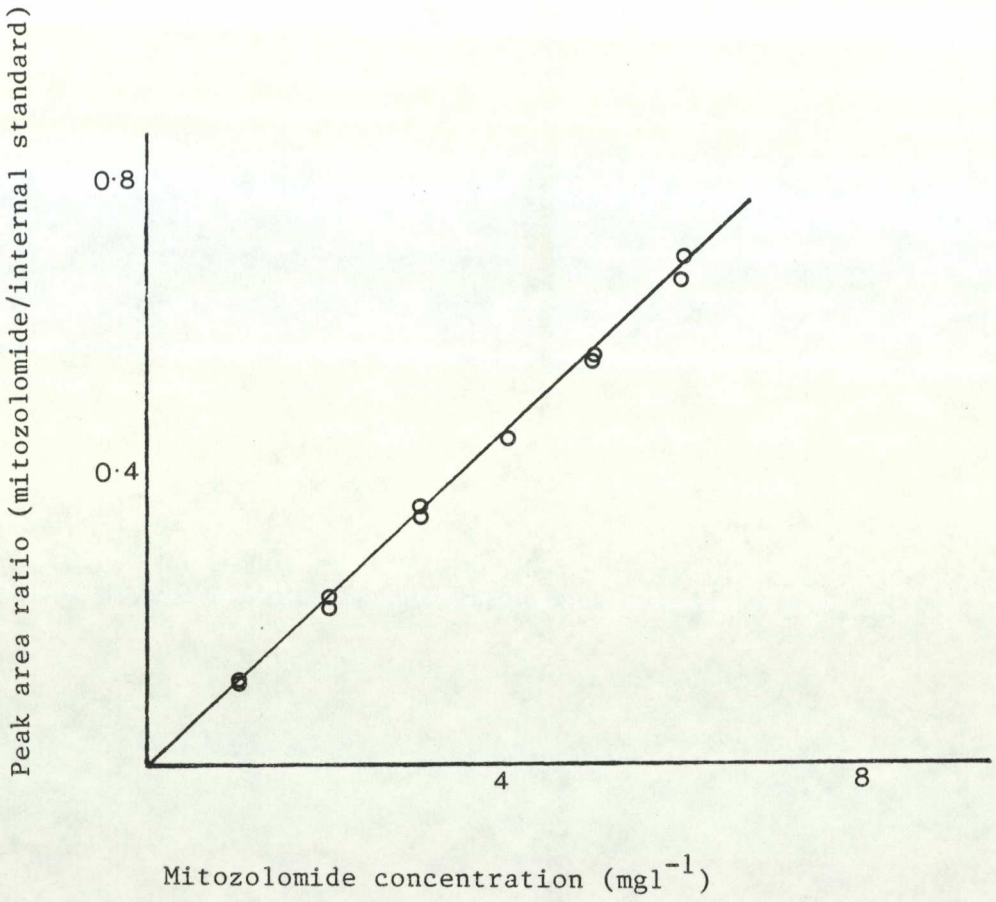
3 A 2 ml aliquot of the organic layer was removed and evaporated to dryness using a Savant Speed-Vac solvent concentrator.

4 The residue was dissolved in 0.150 ml methanol, mixed by vortexing and 0.150 ml of 5% acetic acid in water immediately added. The final solution was mixed again by vortexing and transferred to a low volume insert and then stored at 4 ^{o}C until analysed.

A calibration curve was constructed for each run, over the appropriate concentration ranges by adding 0.100-0.600 ml aliquots of a mitozolomide solution in chloroform in duplicate to centrifuge tubes, evaporating to dryness in a stream of air, using a Techne Dri-block DB-3 sample concentrator and adopting the method described above, (for the test samples) using a control sample of 0.5 ml plasma in this case. A typical calibration curve is shown in figure 2.2.2. It was plotted using least square regression analysis.

Using radiolabelled mitozolomide, previous workers had shown that extraction of the drug from ethyl acetate over the concentration range 1-20 mgl^{-1} was constant at 76%. (Range: 75% - 78%)

Figure 2.2.2- Typical calibration curve obtained using standard mitozolomide solutions.



2.2.3 High performance liquid chromatography, of mitozolomide

The HPLC analytical method for mitozolomide in biological fluids used for this work had been developed[63,64] and successfully used for analysing all of the patient samples from the phase I clinical trial.

The isocratic mobile phase consisted of:

Methanol	15-40%
5% Acetic acid solution in water	85-60%

depending on the condition of the column. This was pumped at a constant flow-rate within the range 1.0-2.0 ml min^{-1} using a Waters 10 HPLC pump.

Waters., (100 x 5 mm, 5 or 10 mcm particle size C-18) reversed phase Radial-Pak compression columns with C-18 Guard-Pak, pre-columns were used in conjunction with a Waters RCM 100 compression unit.

The samples were analysed using a system manufactered by Waters Associates, Northwich which included a Waters 840 data and chromatography control station linked through a system interface module to either a Waters 490 programmable multiwavelength detector or a Lambda-max 480 LC spectrophotometer and an automatic 710B Waters intelligence sample processor. The injection volume was 0.020 ml and detection was at 325 nm. The internal standard used was 3-(2-hydroxyethyl)-1,2,3-benzotriazin-4(3H)-one. The analysis time for each sample was about five minutes and up to forty-eight samples could be processed automatically overnight.

2.2.4. Recruitment of patients into the phase I/II oral clinical trial on mitozolomide.

The phase I/II clinical trial on mitozolomide was a collaborative study carried out at two centres:- St Chads Hospital, Birmingham and Gartnavel General Hospital, Glasgow. The aims of the trial were:-

1) To determine the activity of the drug at a dose of 90 mgm^{-2} using the oral route.

2) To extend the knowledge of the toxicity profile of the drug at this dose.

3) To confirm the pharmacokinetic parameters established in the phase I trial[62] and to determine whether the myelosuppression caused by the drug could be related to its pharmacokinetics.

Eighteen patients (six male and twelve female) received twenty-four doses of mitozolomide in the course of the pharmacokinetic study, eight patients and fourteen doses of which were entered in the Birmingham half of the trial.

The oral formulation of mitozolomide used was supplied by May and Baker Limited, Dagenham Essex as hard gelatin capsules in 50,60 and 70 mg strength. All patients received an oral dose of the drug as near to 90 mgm^{-2} as feasible using an appropriate combination of capsules.

Five of the Birmingham patients received a second equivalent dose of mitozolomide six weeks after the first dose, administered as a slow intravenous infusion over about one hour in 500 ml normal saline. Mitozolomide had previously been formulated[63] as a 10% solution in dimethylsulphoxide and the required volume was injected into 500 ml normal saline immediately before administration. Previous studies[63] had shown the drug to be stable for a two hour period at room temperature under these conditions.

Blood samples were taken, using a three way tap attached to a venous venflon positioned in the patient's arm, at the following times after drug administration: 0.25, 0.50, 0.75, 1.00, 1.33, 1.67, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00 and 12.00 hours. The addition of 0.5 ml of 1000 unit ml^{-1} heparin solution through the tap, after taking each sample, prevented blood clotting in the venflon. Consequently 2 ml of blood was drawn off and discarded before sampling, then about 6 ml blood was taken transferred to a cooled Sterilin,heparin blood sample tube, mixed and the blood immediately spun down using a Heraeus centrifuge (set at $4^{o}C$) at 2000 r.p.m for about seven minutes. The plasma was removed, transferred to a 5 ml Sterilin sample tube labelled and stored at $-20^{o}C$ until analysed by high performance liquid chromatography. Patient plasma samples from the Glasgow half of the trial were received frozen and analysed in the same way as those obtained in Birmingham.

2.2.5 Pharmacokinetic analysis of plasma data

The results were described by a simple[63] one compartment model. This model may be employed for the pharmacokinetic analysis of a drug in body fluids provided that the drug rapidly distributes between body fluids and tissues on entering the systemic circulation. The model assumes that for a change in the plasma drug level, there are corresponding relative changes in tissue levels and that, on oral administration, the drug enters the body by an (apparently) first-order process and is eliminated also by a first-order process. The following equation has been derived[65,66]:

$$C_t = \frac{k_{ab}\, F\, D}{V\,(k_{ab} - k_{el})}\,(e^{-k_{el}(t-t_o)} - e^{-k_{ab}(t-t_o)})$$

where C_t is the plasma drug concentration at time, t

k_{el} is the elimination rate constant

k_{ab} is the absorption rate constant

V is the apparent volume of distribution

F is the fraction of the administered dose, D, absorbed

t_o is the lag time

Other pharmacokinetic parameters can be derived:

Peak plasma concentration, $C_{p\,max} = \frac{F\,D}{V}\, e^{-k_{el}\, t_p}$

where t_p is the time at which peak plasma concentration occurs

Volume distribution, $V = \frac{F\,D}{AUC.k_{el}}$

Plasma clearance, $CL = \frac{F\,D}{AUC}$

where AUC is the total area under the plasma concentration-time. This AUC was obtained using the trapezoidal rule.

The raw data was further manipulated using PCNONLIN. This is a computer program for estimating the parameters in a nonlinear model. By modifying initial estimates of certain parameters, using a nonlinear least squares regression analysis, better estimates are obtained which result in a small sum of squared deviations between the observed values and the values predicted by the model. This process continues until the minimum sum of squares is reached.

2.3 RESULTS

2.3.1 Clinical Pharmacokinetics of mitozolomide

The pharmacokinetics of mitozolomide at a dose of 90 mg m^{-2}, using the oral route were investigated in all patients entering the phase I/II clinical trial. Table 2.3.1 summarises the patient characteristics of the group studied with a more detailed list in appendix IV.

Table 2.3.1 Patient characteristics

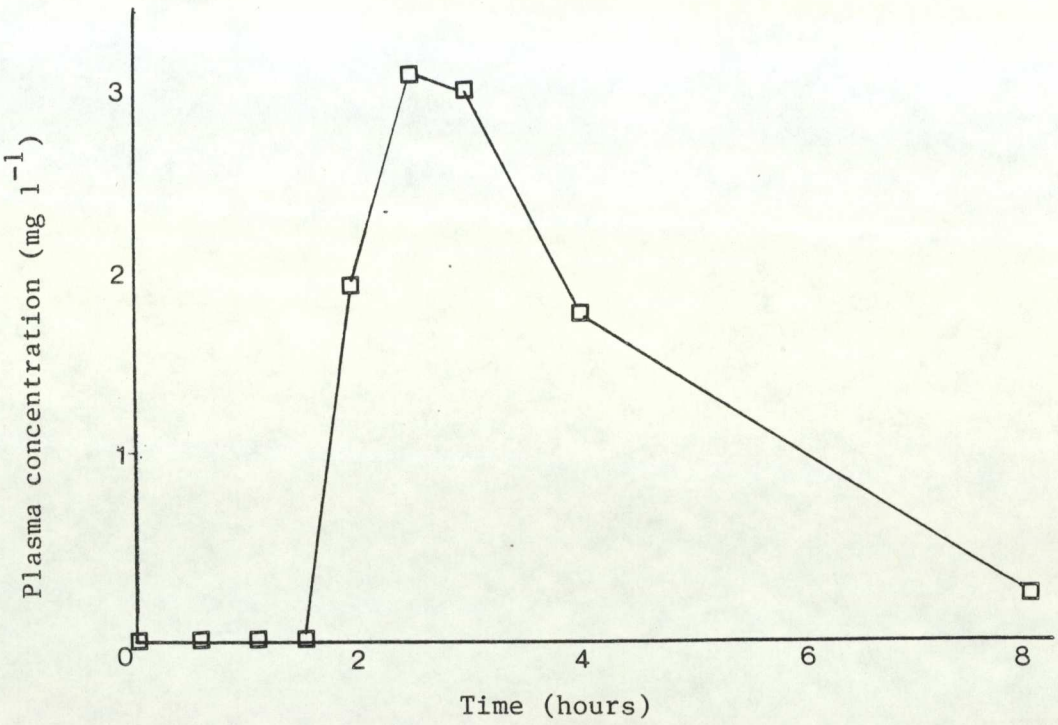
Variable		Number
Total number of patients treated		18
Total number of doses administered		24
Male:Female ratio		6 : 12
Age	Mean	57.2
	Range	23-77
Prior Therapy	1. Surgery	0
	2. Radiotherapy	2
	3. Chemotherapy	0
	4. Combination of 1,2 or 3	5
	5. No prior therapy	1
	6. Data not complete	10
Tumour Type	Lung	4
	Ovary	4
	Melanoma	3
	Breast	2
	Bladder	1
	Pancreas	1
	Parotid	1
	Astrocytoma	1
	Unknown	1

The plasma concentrations of mitozolomide for the twenty-four courses of treatment are reported fully in appendix V, together with the fitted plasma values obtained using the PCNONLIN computer program.

There were considerable variations between patients as illustrated in figures 2.3.1 and 2.3.2.

Figure 2.3.1 shows a rather slow absorption phase but a one compartment model and figure 2.3.2 indicates a two compartment model.

Figure 2.3.1 Plasma concentration against time and ln(plasma concentration) against time plots, as shown by patient 7.



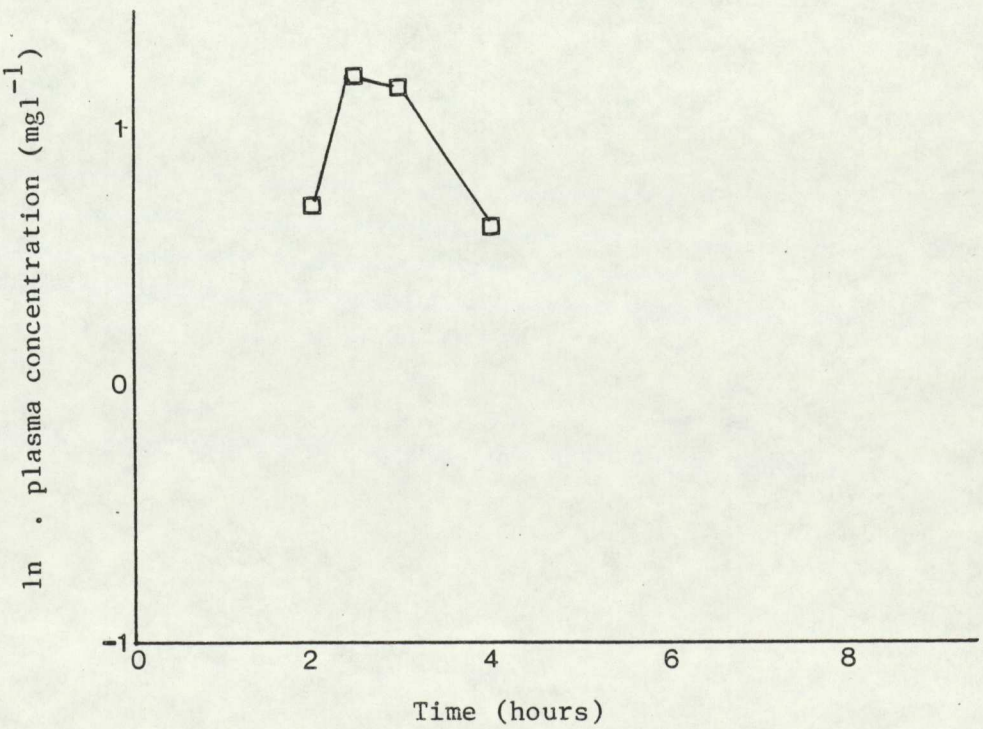
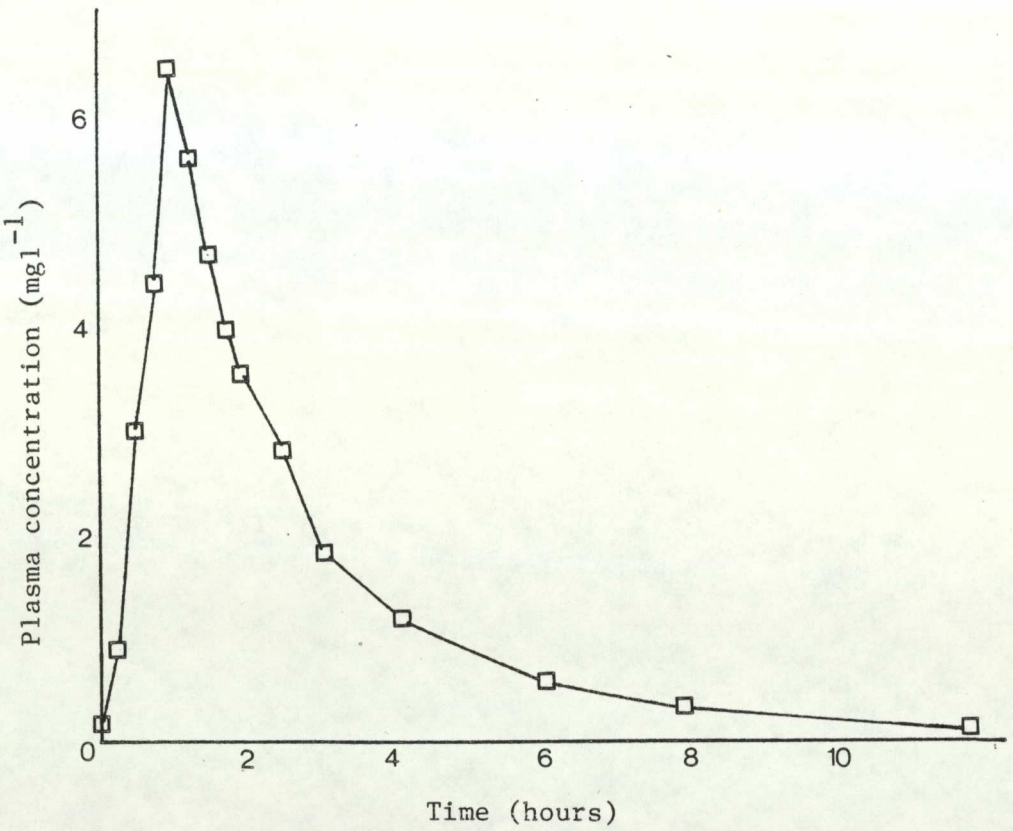
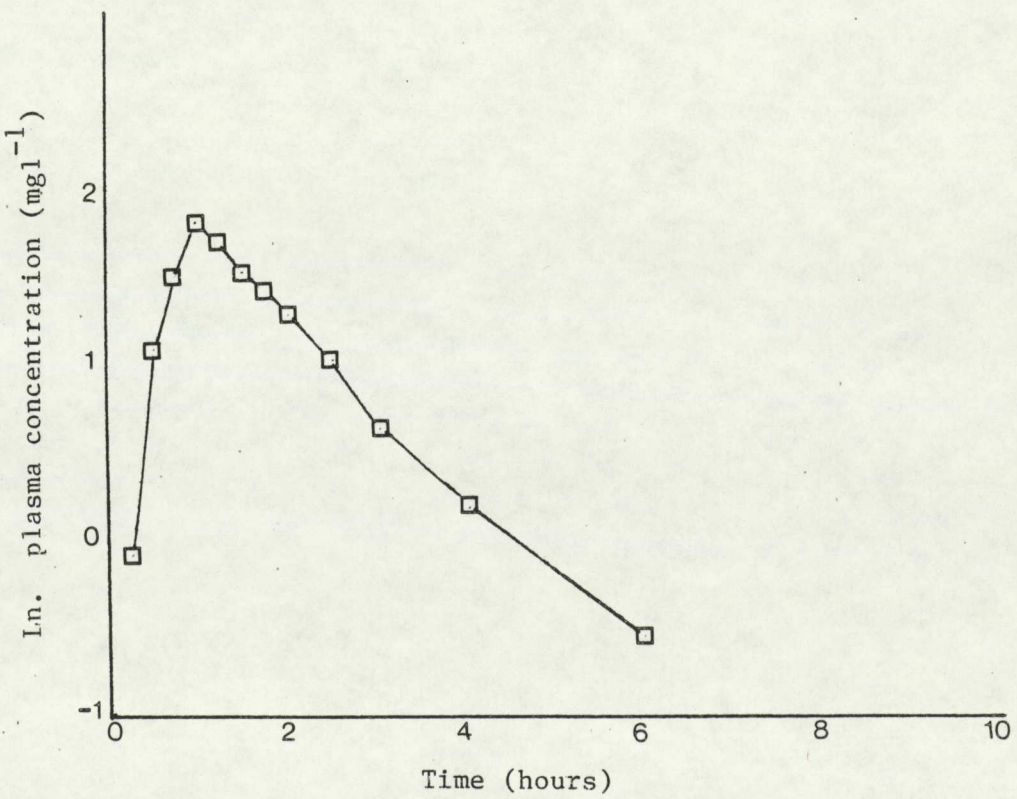


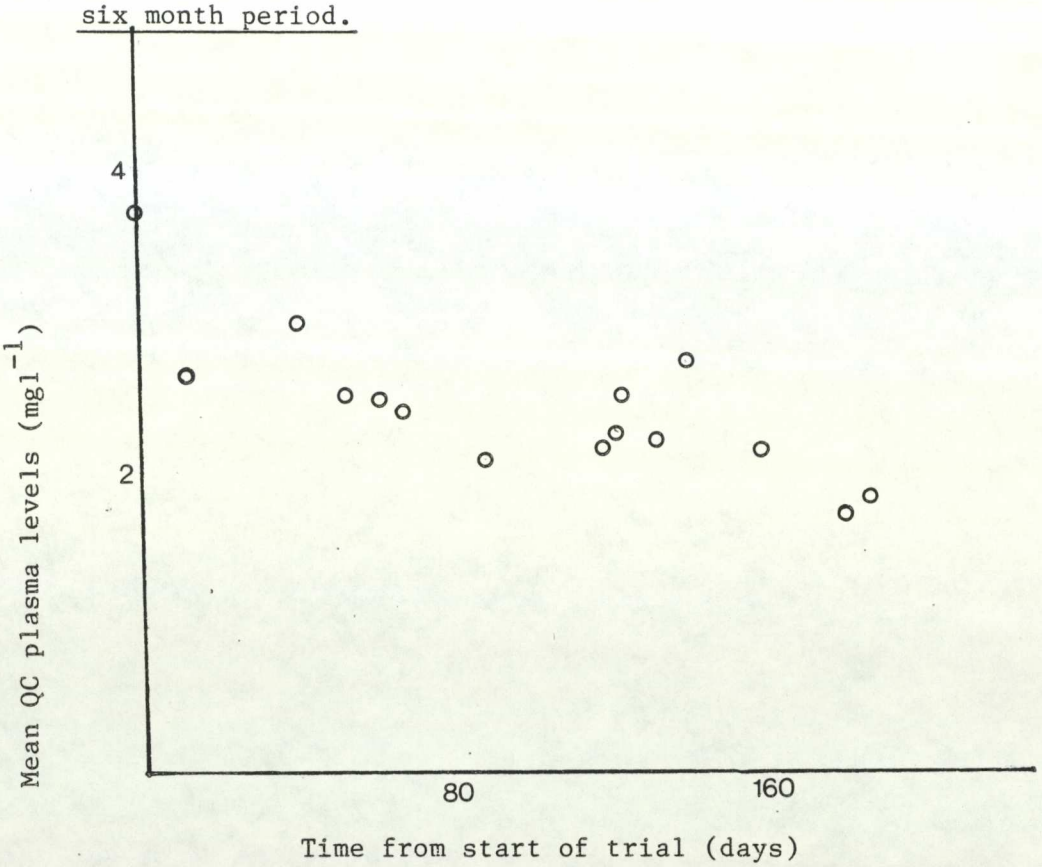
Figure 2.3.2 Plasma concentration against time and In (plasma concentration) against time plots, as shown by patient 15.





Plasma quality control samples were assayed with each batch of samples and as shown in Figure 2.3.3, there is evidence that mitozolomide levels declined whilst stored at -20° over a six month period. After collection from patients, the mean time to analysis was eighteen days (Range: 5-40 days). At this time the amount of mitozolomide lost could have been about 15% (Range: 5% -33%).

Figure 2.3.3 Plot of mitozolomide concentration in plasma samples stored at -20° C against time, showing decline in levels over a six month period.



The results for the mitozolomide plasma levels were fitted to a one compartment model[62,63] and the essential pharmacokinetic parameters of the drug were calculated. Full details of the pharmacokinetic parameters for each patient are set out in appendix VI. The mean and standard deviation of the pharmacokinetic parameters are set out in table 2.3.2.

Table 2.3.2 Pharmacokinetic parameters of Mitozolomide.

Pharmacokinetic Parameter	Trapezoidal Values		Fitted Values	
	Mean	Standard Deviation	Mean	Standard Deviation
Dose ($mg.m^{-2}$)	89.4	6.38	-	-
Total Area under the curve, AUC ($mg\ h\ l^{-1}$)	9.611	3.79	9.299	3.69
Threshold AUC > 1 $mg.h.\ l^{-1}$	4.28	2.87	-	-
Threshold AUC > 2 $mg.h.\ l^{-1}$	2.01	2.15	-	-
Threshold AUC > 4 $mg.h.\ l^{-1}$	0.46	0.95	-	-
Peak Plasma level (mg)	4.13	2.01	3.76	1.90
Volume Distribution (l)	36.86	12.73	27.00	11.08
Clearance ($l.h^{-1}$)	17.46	5.34	-	-
Elimination Half-life (h)	1.57	0.50	1.17	0.42
Elimination Rate Constant (h^{-1})	0.49	0.15	0.69	0.26
Absorption Half-life (h)	0.37	0.31	0.51	0.44
Absorption Rate Constant (h^{-1})	4.82	5.66	4.27	6.02
Lag Time (h)	0.40	0.42	0.46	0.40

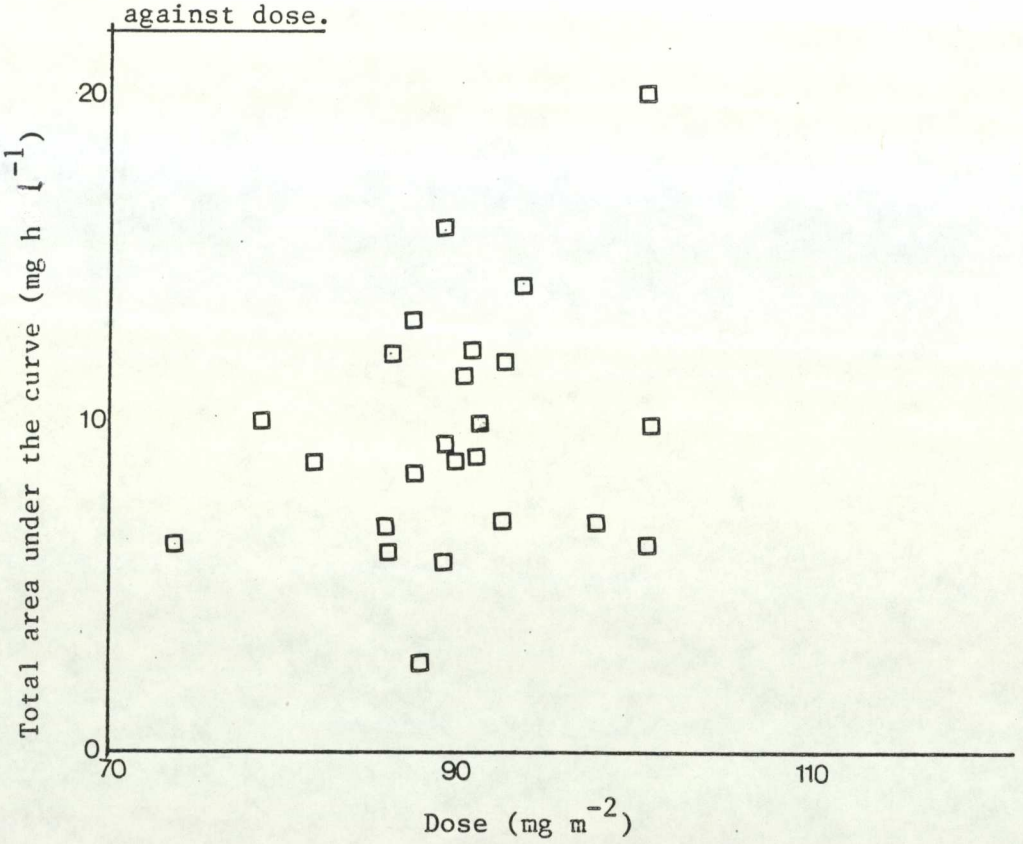
Scatter plots of the area under the curve, peak plasma level, volume of distribution and elimination half-life against dose and against age were constructed. Correlation coefficients for these plots, obtained using the least squares method of analysis, are shown in table 2.3.3.

Table 2.3.3 - Correlation coefficients for plots of selected pharmacokinetic parameters against dose and against age

Pharmacokinetic Parameters		Dose (mgm^{-2})	Age (years)
Area under the curve, AUC ($mg\ h\ l^{-1}$)	Trapezoidal Fitted	0.28 0.31	0.14 0.17
Threshold AUC > 1 $mg.hr\ l^{-1}$ ($mg\ h\ l^{-1}$)	Trapezoidal Fitted	0.25 -	0.12 -
Peak Plasma level ($mg\ l^{-1}$)	Trapezoidal Fitted	0.02 0.05	0.05 0.02
Volume distribution (l)	Trapezoidal Fitted	-0.03 -0.07	0.08 -0.14
Elimination Half-life (h)	Trapezoidal Fitted	0.03 0.03	- -

Examples of the scatter plots for AUC against dose and peak plasma level against dose are shown in figure 2.3.4. Scatter plots were also constructed for elimination half-life and peak plasma level against area under the curve, with correlation coefficients of -0.06 and 0.78 respectively. These plots are shown in figure 2.3.5.

Figure 2.3.4 Scatter plots of total trapezoidal area under the curve against dose and trapezoidal peak plasma level against dose.



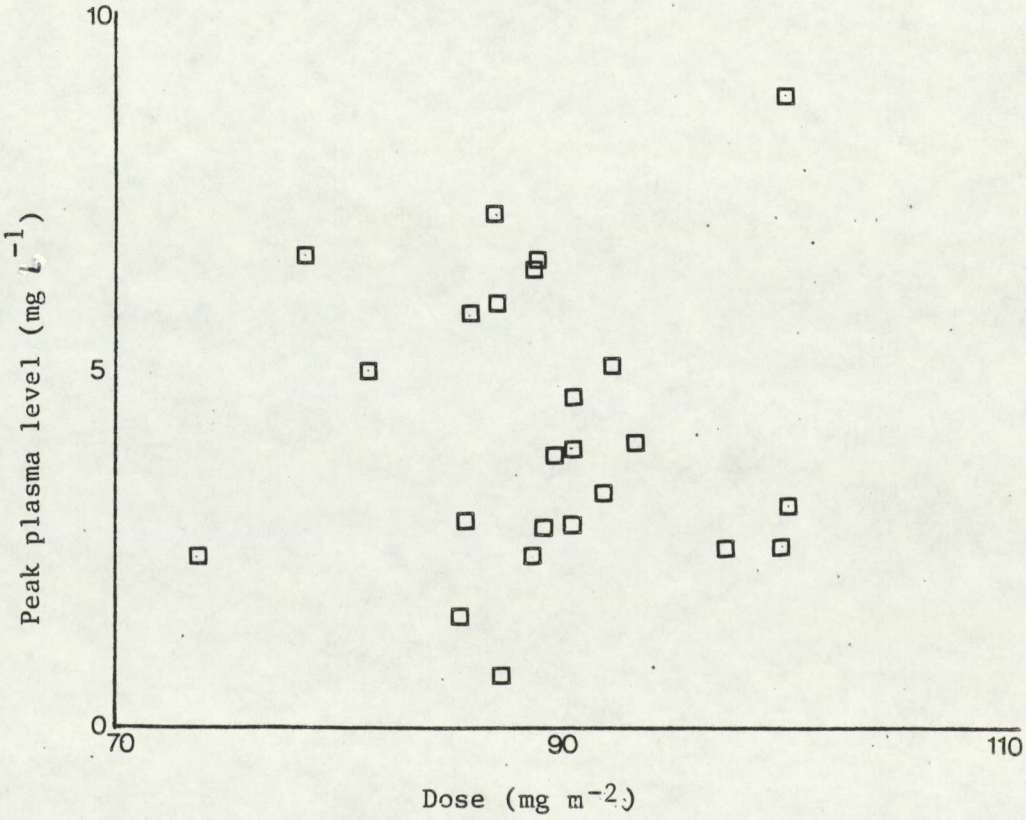
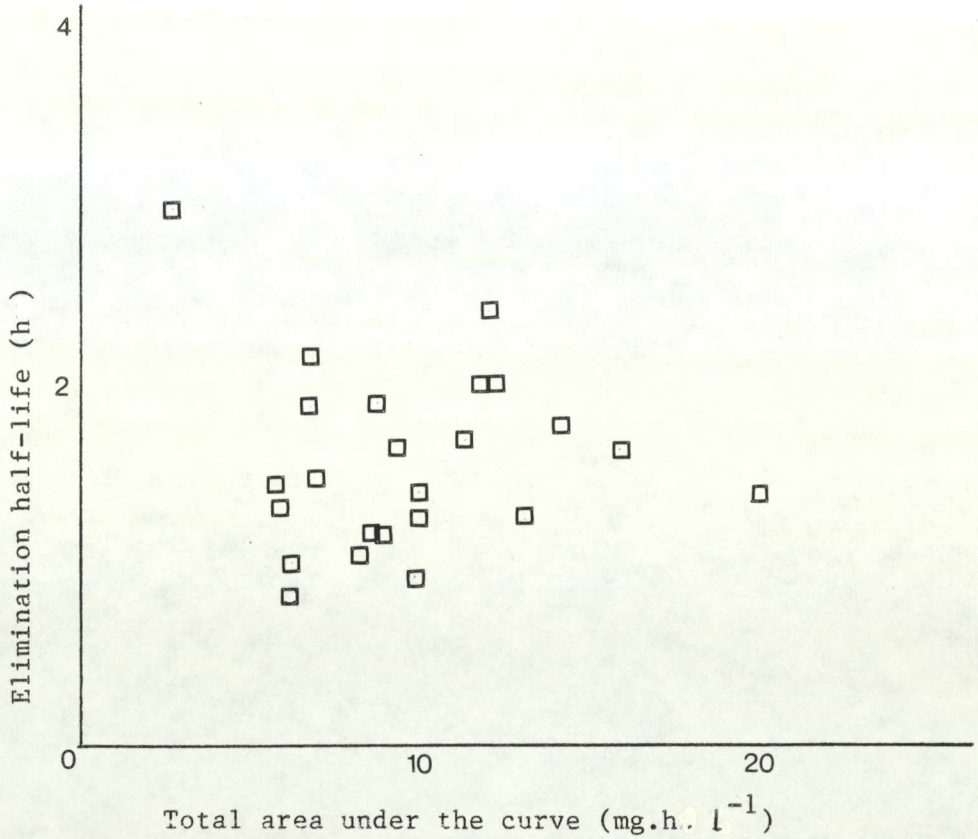
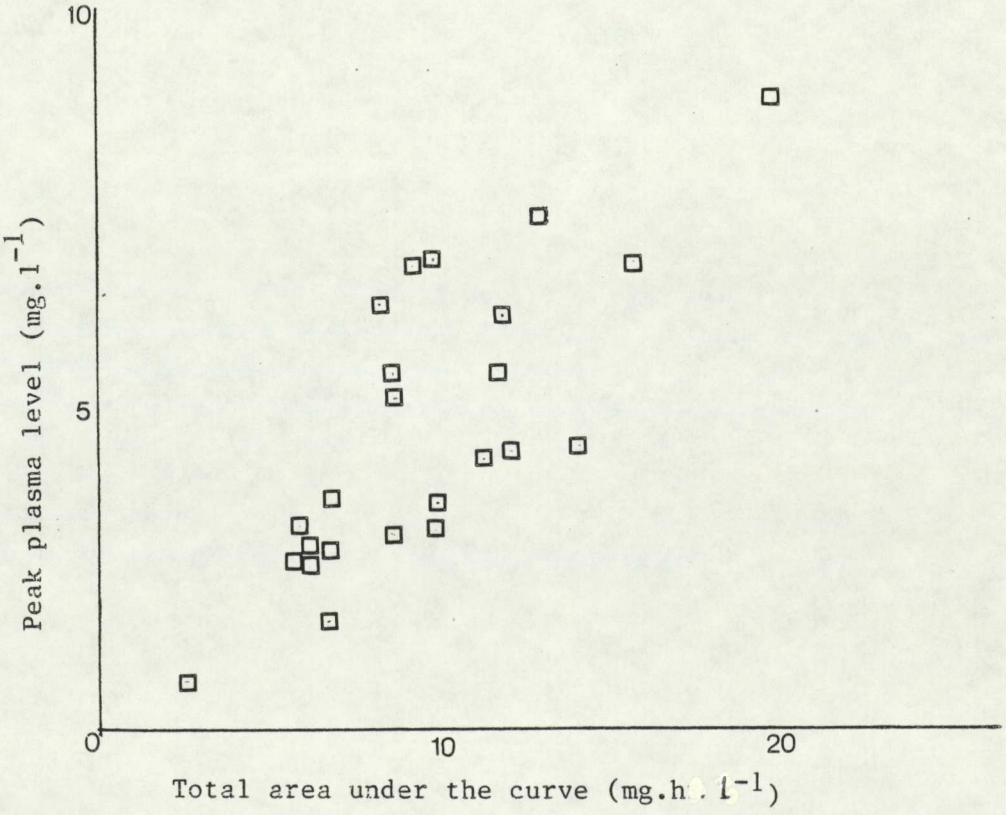


Figure 2.3.5 Scatter plots of trapezoidal elimination half-life against trapezoidal area under the curve and trapezoidal peak plasma level against trapezoidal area under the curve.





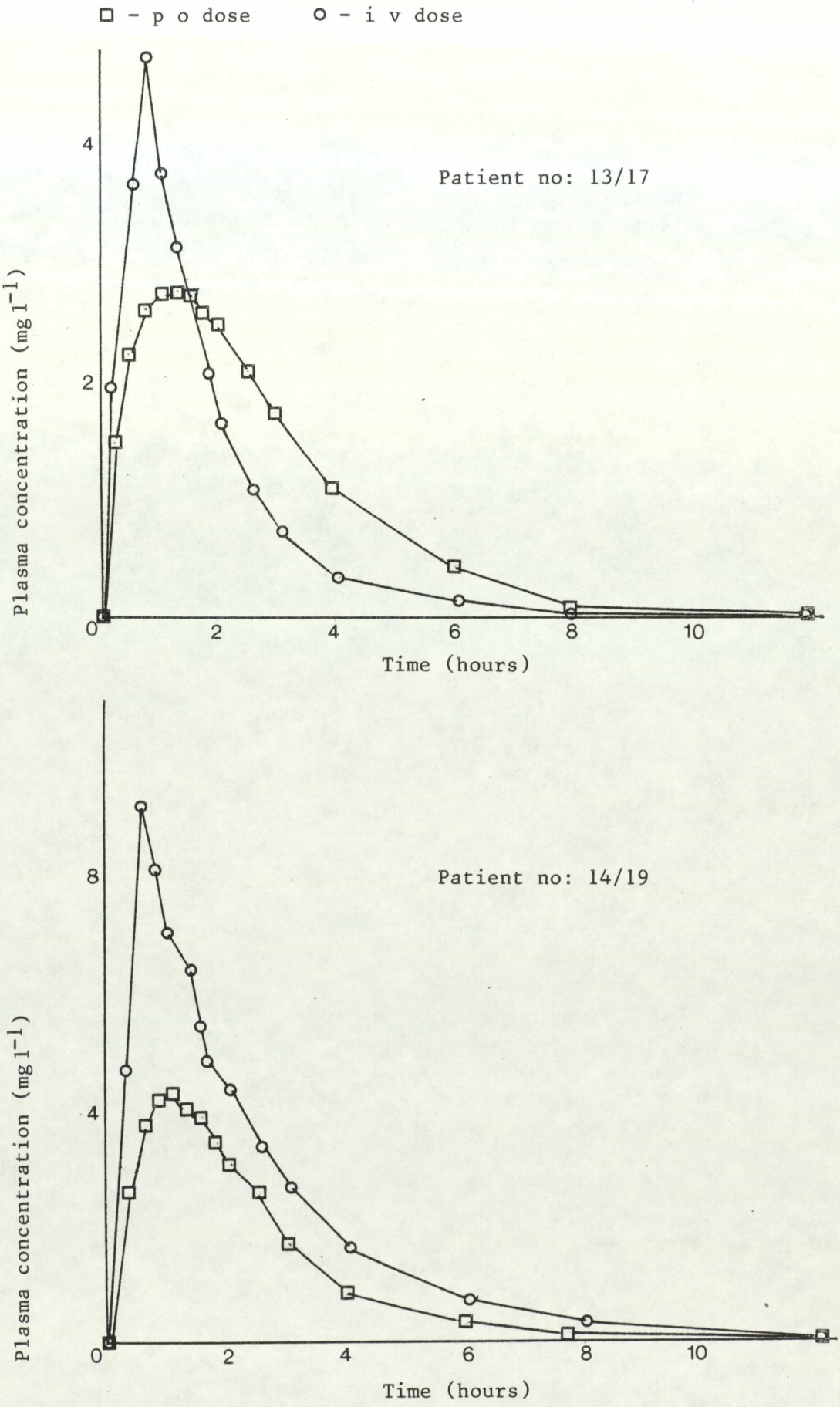
2.3.2 Oral Bioavilability of mitozolomide

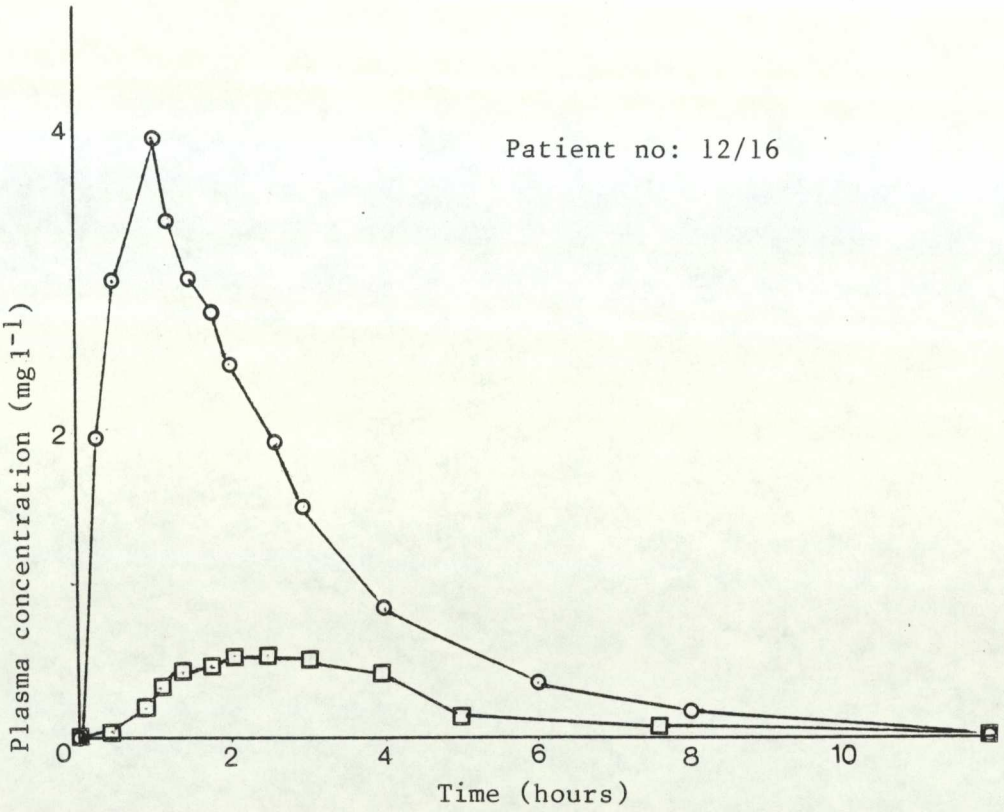
The bioavailability of mitozolomide was investigated in five of the Birmingham patients who received a second dose of mitozolomide, six weeks after the first dose administered as a slow intravenous infusion. One patient received a second oral dose, six weeks after the intravenous dose. The plasma concentration of mitozolomide against time plots for these five patients are shown in figure 2.3.6 and the essential pharmacokinetic parameters are described in table 2.3.4.

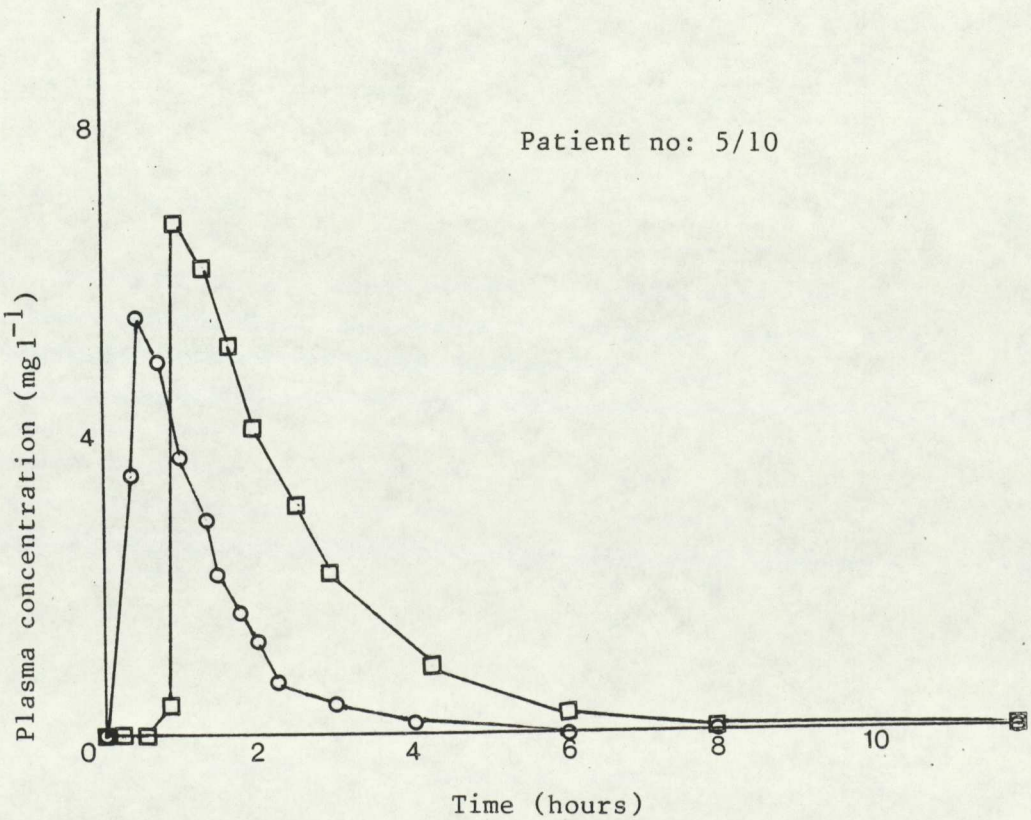
Table 2.3.4 Oral Bioavailability of Mitozolomide

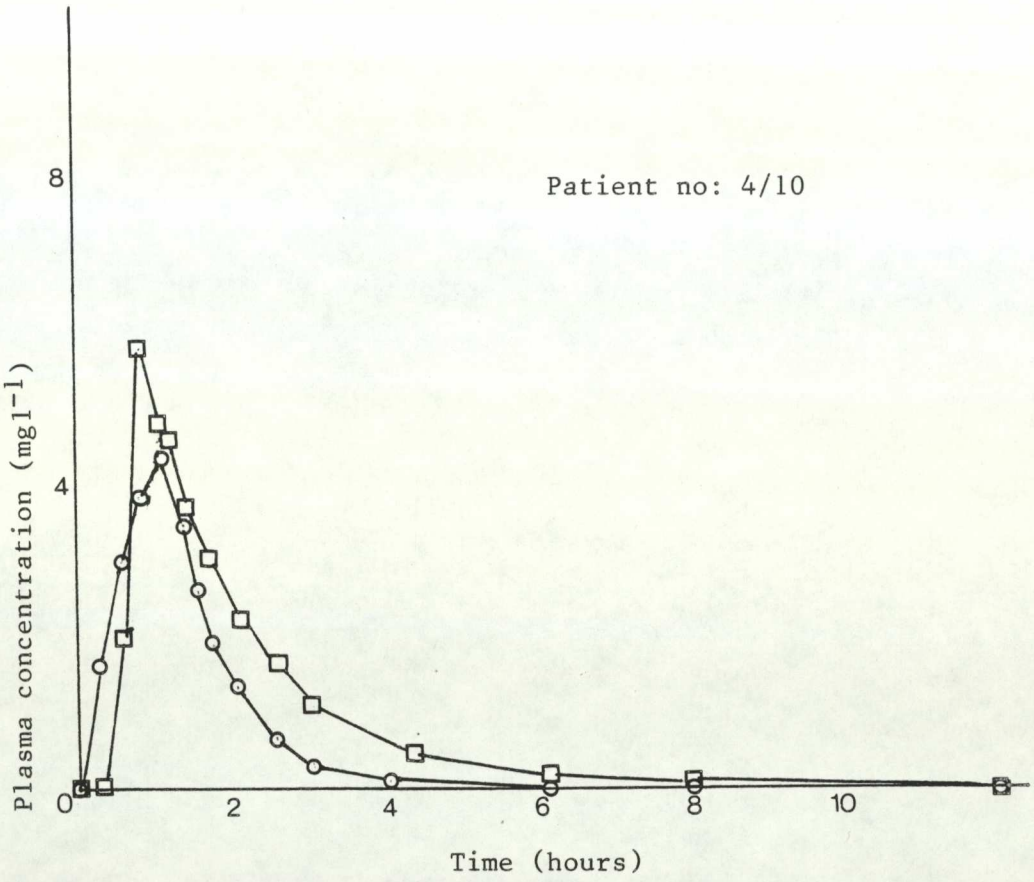
		1		2		3		4		5		
Route		oral	IV	oral	IV	oral	IV	oral	IV	oral	IV	oral
Trial Number		4	11	5	10	12	16	14	19	13	17	21
Dose ($mg.m^{-2}$)		78.5	81.3	87.1	87.1	87.5	85.9	92.3	100.1	90.6	90.6	89.8
Volume Distribution (l)	Trap.	25.61	22.45	23.82	32.81	207.39	40.18	35.36	13.96	27.53	35.42	43.25
	Fitted	17.69	12.73	21.27	22.97	156.46	27.01	12.54	13.58	27.98	27.69	24.45
Clearance ($l\ h^{-1}$)	Trap.	14.32	13.64	13.30	21.74	48.58	11.63	12.32	7.01	20.47	21.25	17.73
Elimination Half-life (h)	Trap.	1.24	1.14	1.24	1.05	2.96	2.39	1.99	1.38	0.93	1.16	1.69
	Fitted	0.94	0.46	1.07	0.64	2.22	1.46	0.67	1.36	1.11	0.83	0.97
Peak Plasma Level (mg)	Trap.	6.50	4.93	7.10	5.88	0.67	5.71	4.95	8.78	2.77	4.54	3.74
	Fitted	6.12	4.57	6.86	5.90	0.53	4.41	4.10	9.07	2.79	4.87	3.34
Area under the Curve ($mg.h.l^{-1}$)	Trap.	9.93	8.62	13.09	8.28	2.60	12.04	11.78	19.98	9.90	8.82	11.33
	Fitted	9.23	6.29	13.05	7.23	2.86	10.92	10.77	20.28	10.32	7.82	10.33
Bioavilability	Trap.	1.15		1.58		0.22		0.59		1.12	1.28	
	Fitted	1.47		1.81		0.26		0.53		1.32	1.32	

Figure 2.3.6. - Plasma concentration against time profiles for the five patients entered into the bioavailability study.




Patient no: 12/16
Plasma concentration (mg l^{-1})
4
2
0
2
4
6
8
10
Time (hours)


Patient no: 5/10
Plasma concentration (mg l^{-1})
8
4
0
2
4
6
8
10
Time (hours)


Patient no: 4/10
Plasma concentration (mg l-1)
8
4
0
2
4
6
8
10
Time (hours)

2.3.3. Haematological Toxicity of Mitozolomide

Haematological data (see appendix VII) were available for eighteen of the twenty-four courses of mitozolomide administered. Table 2.3.5 summarises the extent of the thrombocytopenia and figure 2.3.7 shows a typical percentage fall in platelets (from initial value) against time profile.

Table 2.3.5. Thombocytopenia data

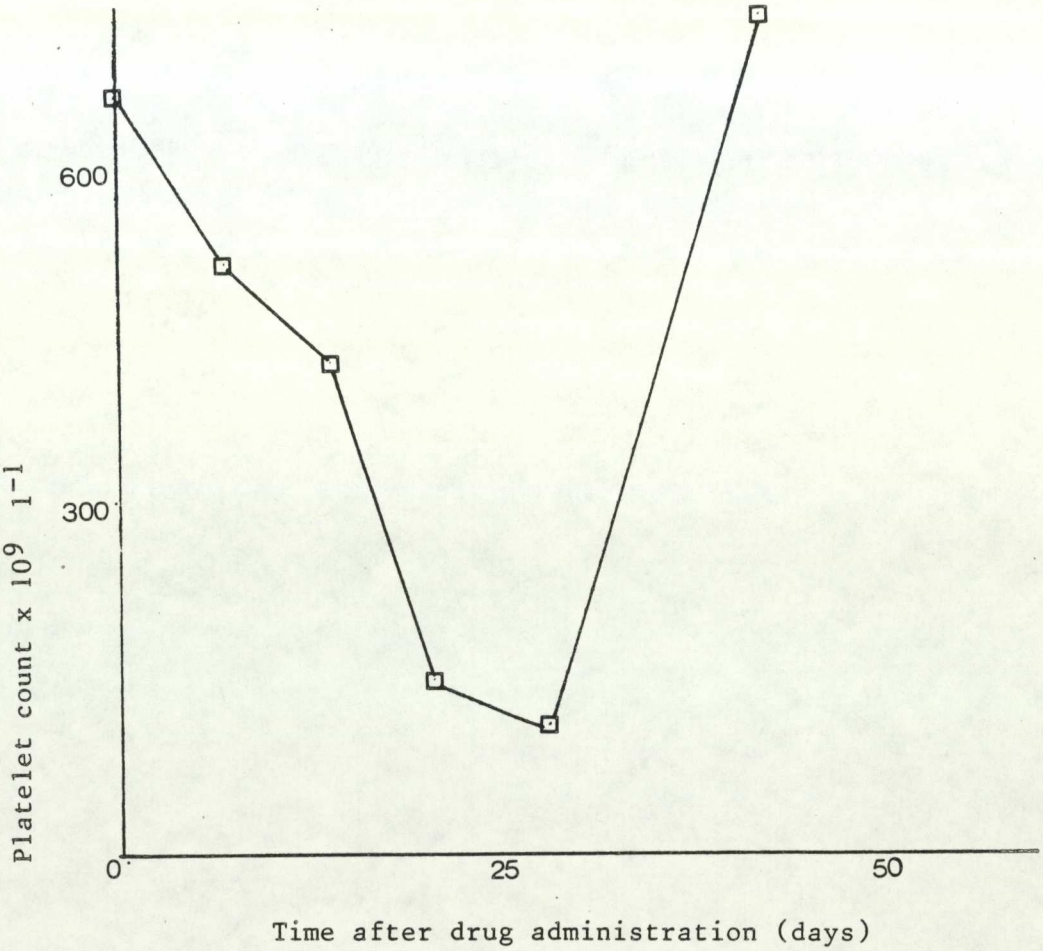
Number of Patients	Mitozolomide	Platelet count x 10^9 L^{-1} (WHO grade)			
		90-75 (1)	74-50 (2)	49-25 (3)	24-0 (4)
18	0	2	2	3	3
	3	0	1	0	1
	Total	2	3	3	4

Table 2.3.6 summarises the extent of the leucopenia.

Table 2.3.6 Leucopenia data

Number of Patients	Prior Mitozolomide	White Blood Cell count x $10^9 L^{-1}$ (WHO grade)			
		3.9-3.0 (1)	2.9-2.0(2)	1.9-1.0(3)	1.0-0(4)
17	0	3	4	3	0
	3	0	0	0	1
	Total	3	4	3	1

Figure 2.3.7. - Typical platelet count against time profile for a patient after mitozolomide therapy.



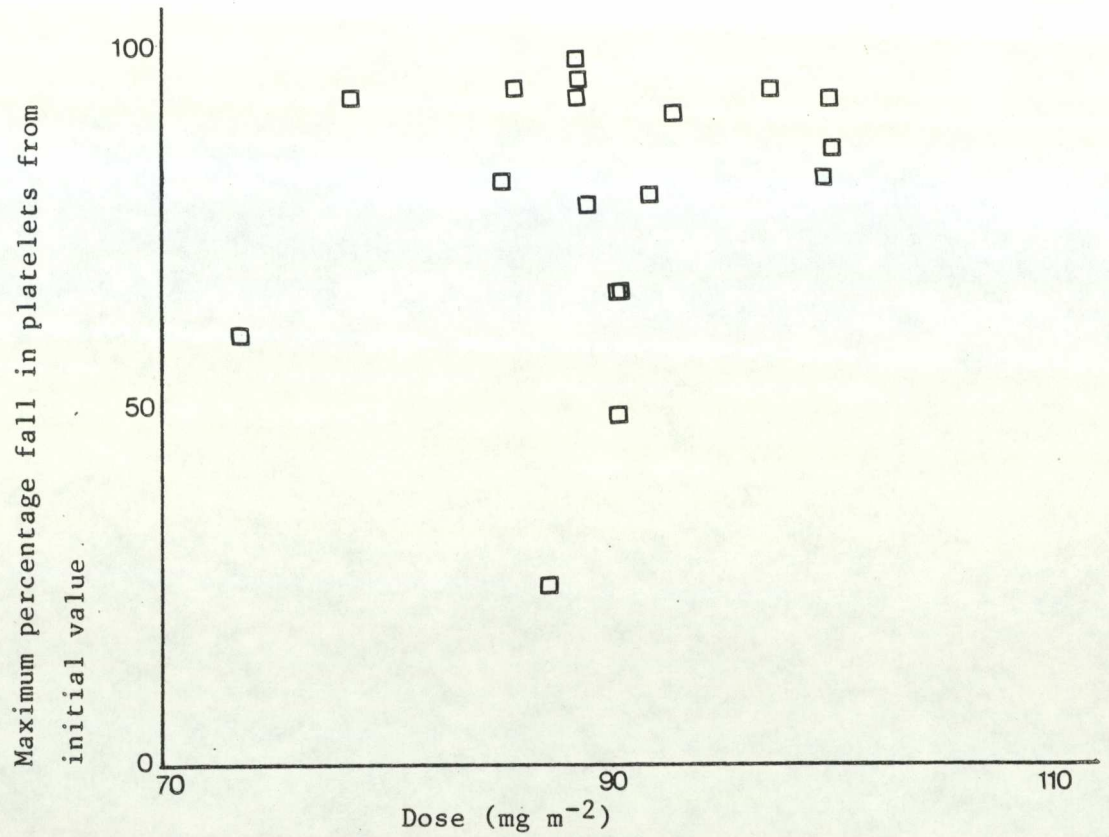
Scatter plots of dose, age, area under the curve, peak plasma level, volume of distribution and elimination half-life against maximum percentage fall in platelets and against maximum percentage fall in white blood cell count were constructed. Correlation coefficients for these plots, obtained using the least squares method of analysis, are shown in table 2.3.7.

Table 2.3.7 Correlation coefficients for plots of selected pharmacokinetic parameters against maximum % fall in platelets and white blood cells

Pharmacokinetic Parameters		Maximum Percentage fall in:	
		Platelet count	White blood cells
Dose (mg m^{-2})		0.23	0.36
Age (years)		0.26	0.11
Area under the curve, AUC (mg h l^{-1})	Trapezoidal Fitted	0.46 0.44	0.22 0.15
Threshold AUC > 1 mg h l^{-1} (mg h l^{-1})	Trapezoidal Fitted	0.41 -	0.18 -
Threshold AUC > 2 mg h l^{-1} (mg h l^{-1})	Trapezoidal Fitted	0.36 -	0.17 -
Peak plasma level (mg l^{-1})	Trapezoidal Fitted	0.49 0.41	0.21 0.06
Volume Distribution (L)	Trapezoidal Fitted	-0.64 -0.66	-0.04 -0.16
Elimination Half-life (h)	Trapezoidal Fitted	0.27 -0.33	0.49 -0.03

Examples of the scatter plots for percentage fall in platelets and percentage fall in white blood cells against dose, area under the curve and peak plasma level are shown in figures 2.3.8 - 2.3.10.

Figure 2.3.8 Scatter plots of maximum percentage fall in platelets against dose and maximum percentage fall in white blood cells against dose.



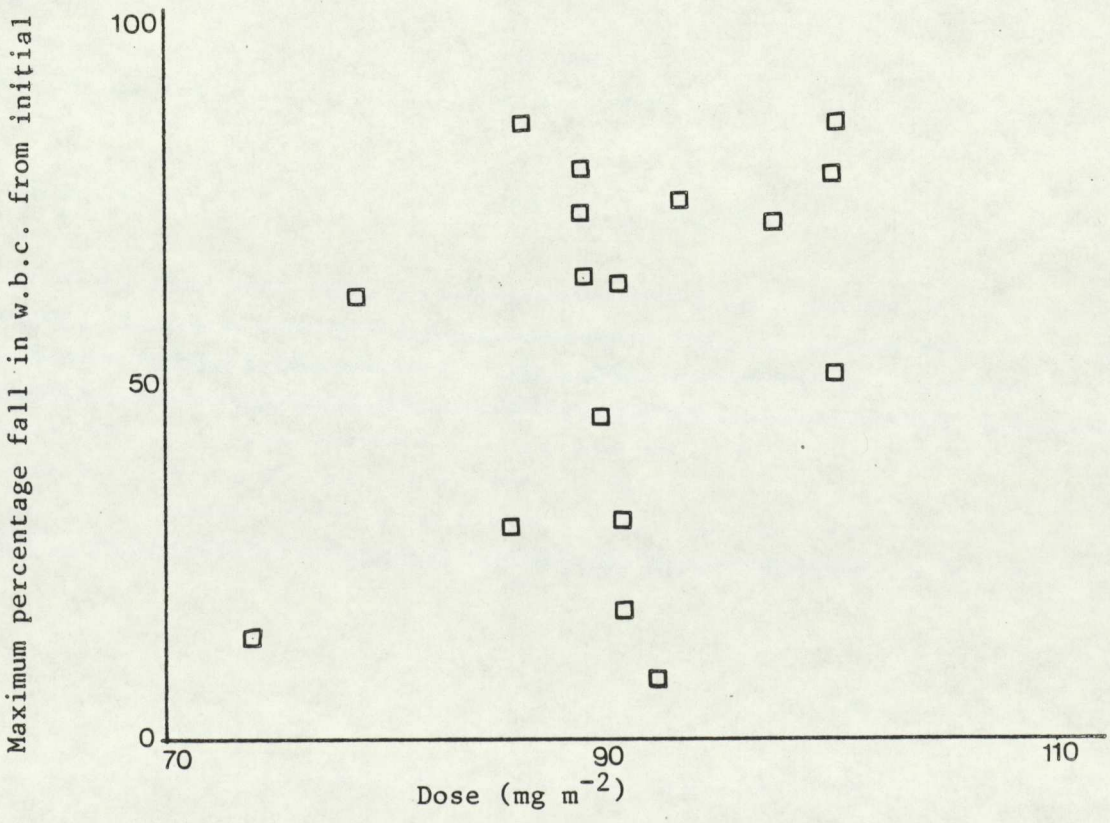
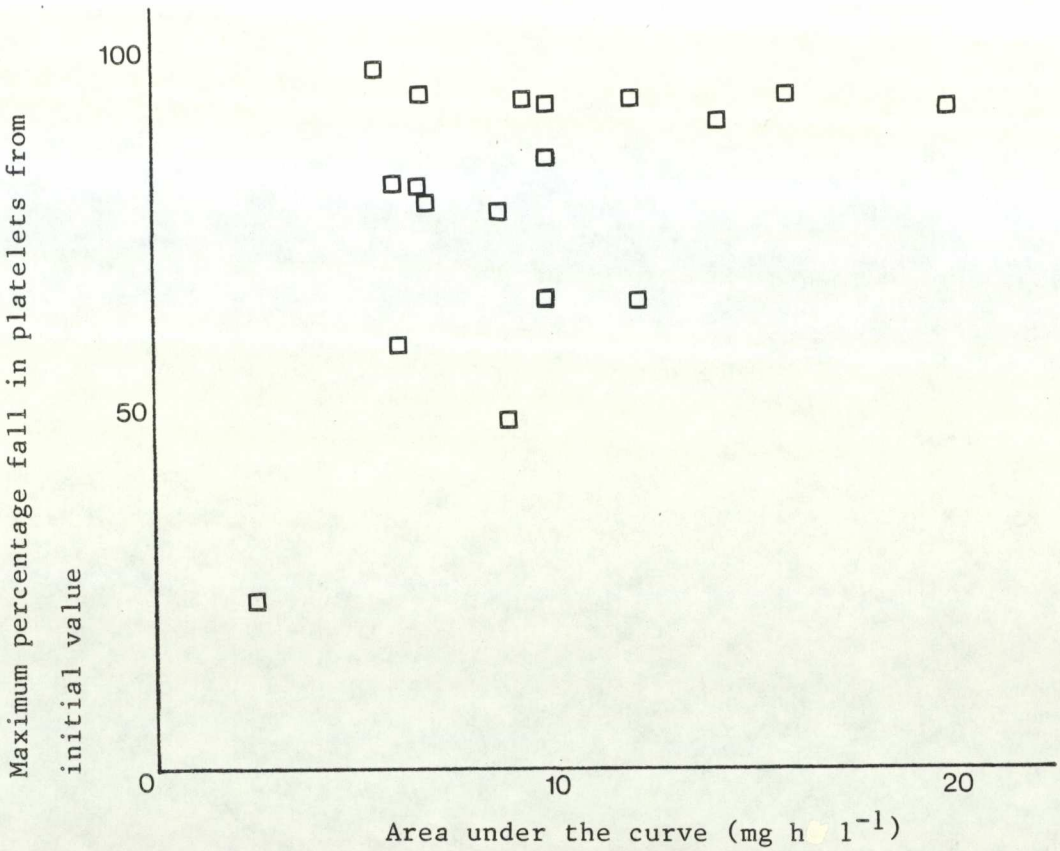


Figure 2.3.9. - Scatter plots of maximum percentage fall in platelets against area under the curve and maximum percentage fall in white blood cells against area under the curve.



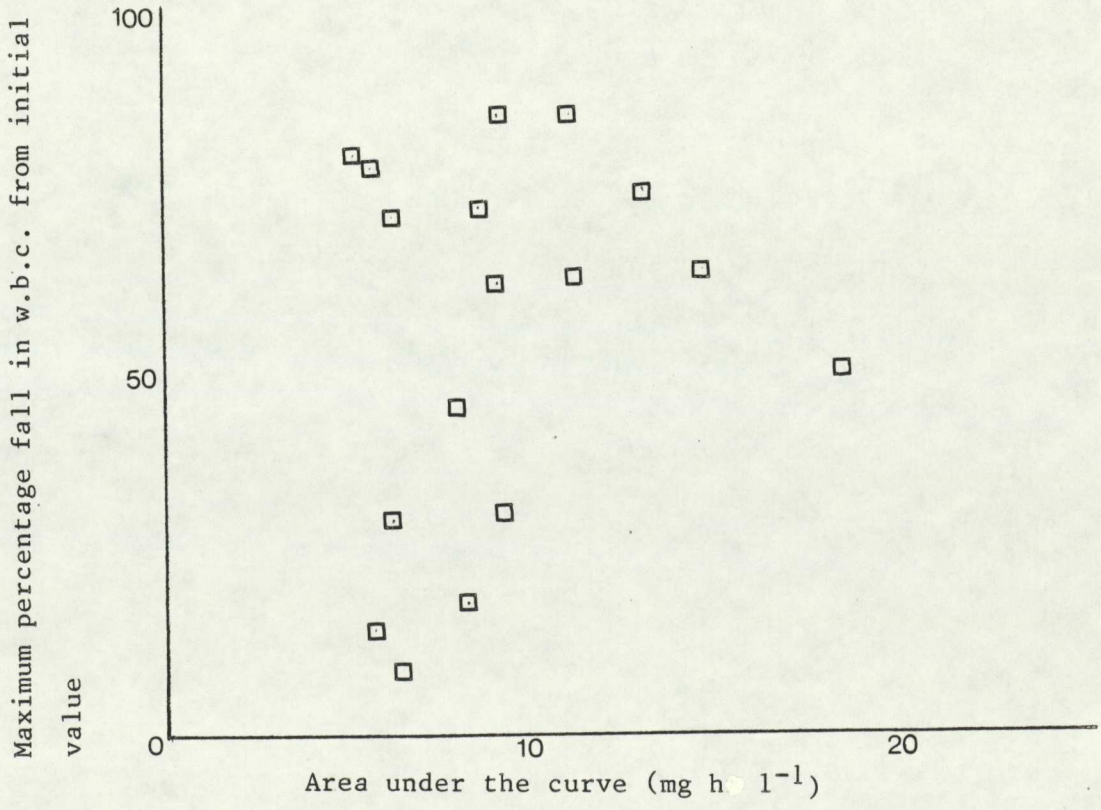
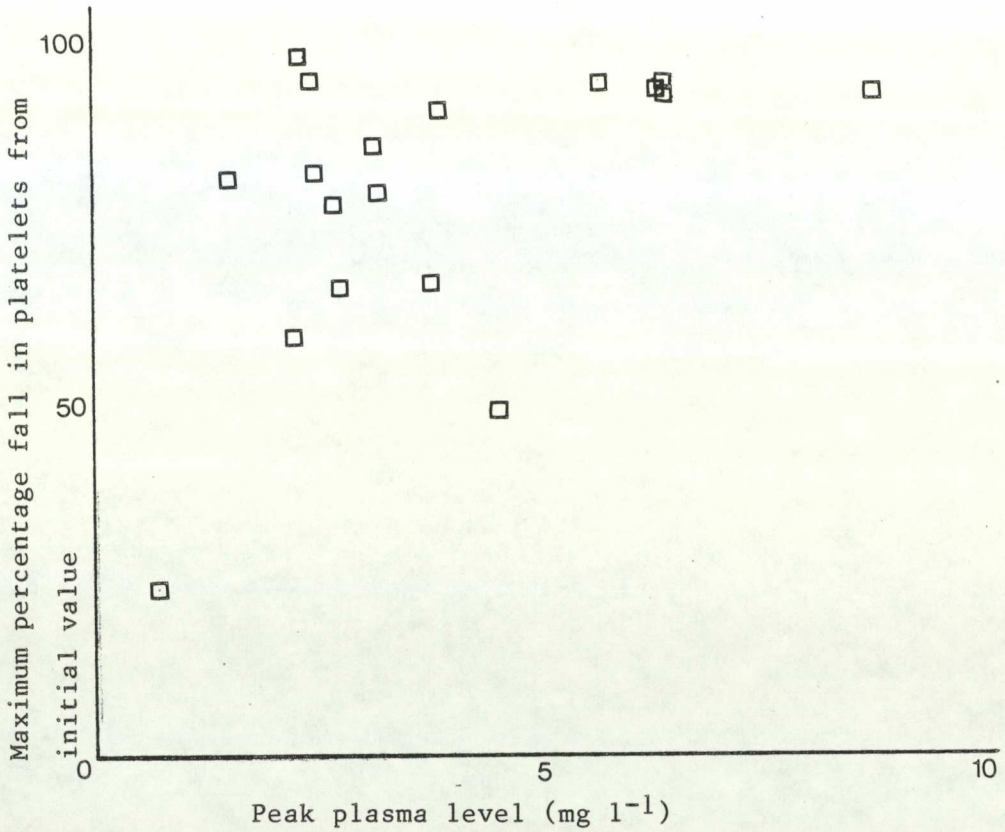
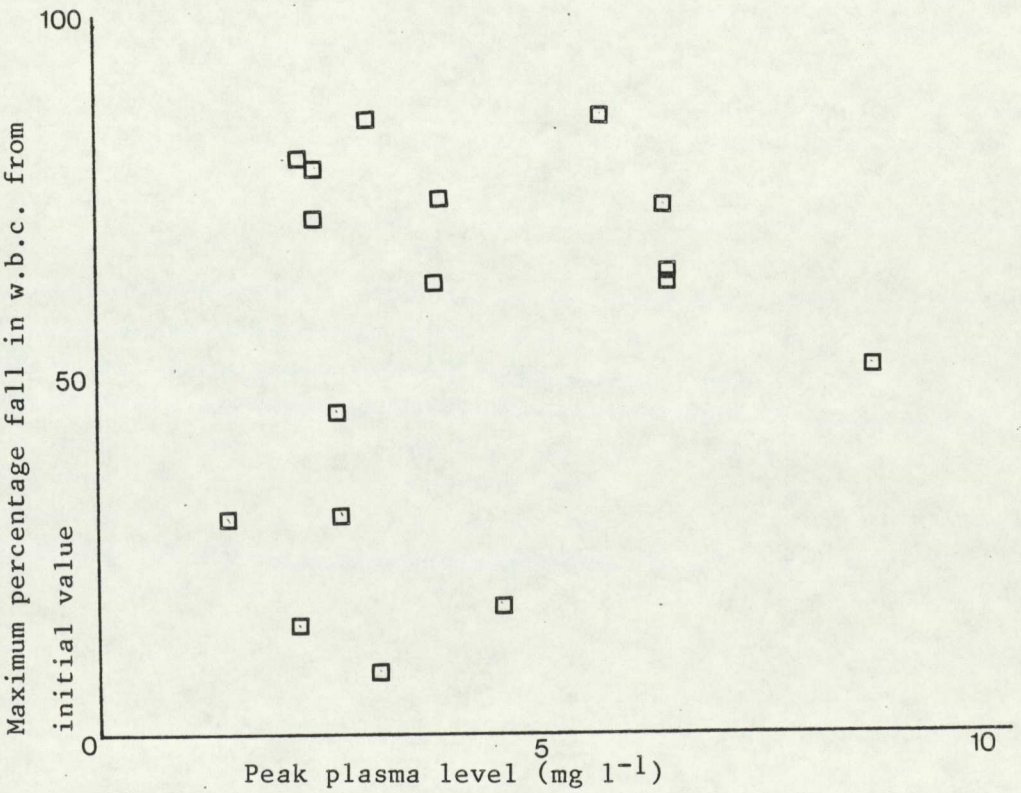


Figure 2.3.10 - Scatter plots of maximum percentage fall in platelets against peak plasma level and maximum percentage fall in white blood cells against peak plasma level.





2.4 DISCUSSION

It was the general aim of this phase I/II trial to confirm the pharmacokinetic parameters established in the phase I trial, to extend the knowledge on the toxicity profile of mitozolomide at a dose of 90 mgm^{-2}, using the oral route, and to determine whether the myelosuppression caused by the drug could be related to its pharmacokinetic parameters. Work on methotrexate[67,68], has shown a definite relationship between plasma methotrexate concentrations and clinical toxicity.

From the phase I clinical trial[62,63] it was determined that the human pharmacokinetics of mitozolomide could be described using a one compartment model but with some evidence that at the two highest doses of 140 mg m^{-2} and 153 mg m^{-2} a small distribution phase was present. In the present work, all patient plasma data was fitted to a one compartment model. However in the case of patient 15, as shown in figure 2.3.2, some indication of a biphasic elimination phase seemed to be present.

The elimination half-life was found to vary between 0.5 and 2.2 hours (mean 1.2 hours) compared to a range of 1.0 to 1.4 hours in the phase I trial. The mean value for the volume of distribution was 36.9L which approximated to that of total body water (about 40L for an average man). This is in agreement with the value of 36.4L obtained in the phase I trial.

All patients had received no food on the day of mitozolomide treatment. The mean lag-time for absorption of the oral formulation of the drug was 0.4 hours. However, in the case of patient 7, as shown in figure 2.3.1, the lag-time was 1.8 hours. This patient absorbed the drug much more slowly although the total area under the curve was 9.9 mg h L^{-1}, close to the average value of 9.6 mg h L^{-1} for the whole group. Whilst patient 12 was not a slow absorber of the drug, figure 2.3.6 shows that this patient absorbed the drug poorly with a total area under the curve of 2.6 mg h L^{-1}, compared with the mean value of 9.6 mg h L^{-1}.

Results from the construction of various scatter plots between pharmacokinetic parameters, as described in table 2.3.3 showed that there were no relationships between area under the curve, peak plasma level, volume of distribution, and elimination half-life with the dose of drug given, significant at the 5% level. Neither were there any relationships between area under the curve, peak plasma level, volume of distribution and elimination half-life with the age of the patient, significant at the 5% level.

It would appear that the oral dose of the drug given bears no relation to the amount of drug absorbed (area under the curve) nor to the peak plasma level attained and this would certainly limit the usefulness of the drug by this route.

The oral bioavailability of mitozolomide was studied in five patients, as described in table 2.3.4. The values obtained varied considerably. As already noted, patient 12/16 absorbed the drug poorly when given orally, absorbing only 25% of the oral dose compared with an equivalent intravenous dose. Patient 14/19 also displayed problems with only 50% of the oral dose given being absorbed compared with an equivalent intravenous dose. Patients 4/11 and 13/17/21 absorbed the drug fully. However for patient 5/10 the oral bioavailability was calculated to be 158% that of an equivalent intravenous dose. It can only be surmised that progressive disease may have contributed to this unusual result. A similar "higher than expected" bioavailability result was observed for one patient in the phase I trial at a dose of 140 mg m^{-2}, with no satisfactory explanation.

By the oral route, some patients will absorb 100% of a dose of mitozolomide, other patients will absorb far less of that dose (into the systemic circulation).

An abbreviated phase I[69] clinical trial of intravenous mitozolomide has been carried out, at the same time as the present work described in this thesis, by the European Organisation for Research on Treatment of

Cancer Early Clinical Trials Group. Eleven patients (nine male and two female) were entered into the trial at an initial dose level of 100 mg m^{-2} (six patients, eight courses) and then 90 mg m^{-2} (seven patients, nine courses). A dose-limiting myelosuppression was again evident, presenting as a thrombocytopenia [median nadir count: 54 x 10^9 L^{-1} (Range: 27-113 x 10^9 L^{-1}) at 100 mg m^{-2} and 80 x 10^9 L^{-1} (Range: 30-156 x 10^9 L^{-1}) at 90 mg m^{-2}] at about thirty days after drug administration with the count remaining low for about six weeks. This was followed by a leucopenia [median nadir count: 2.2 x 10^9 L^{-1} (Range: 1.3-3.9 x 10^9 L^{-1}) at 100 mg m^{-2} and 3.5 x 10^9 L^{-1} (Range: 2.6-8.3 x 10^9 L^{-1}) at 90 mg m^{-2}] about forty days after drug administration recovering after about seven weeks. The other toxic effects reported were mild. No antitumour activity was observed.

In the present work, haematological data were collected from eighteen of the twenty-four courses of mitozolomide administered, as described in tables 2.3.5- 2.3.6. Thombocytopenia was experienced by twelve patients. The platelet count fell below 49 x 10^9 L^{-1} (WHO grade 3) in seven patients and below 24 x 10^9 L^{-1} (WHO grade 4) in four of these patients.

Leucopenia was experienced by eleven patients. The white blood cell count fell below 1.9 x 10^9 L^{-1} (WHO grade 3) in four patients and below 1.0 x 10^9 L^{-1} (WHO grade 4) in one of these patients.

Results from the construction of various scatter plots between maximum percentage fall in platelets or white blood cells and pharmacokinetic parameters, as described in table 2.3.7 showed that there were no relationships between either maximum percentage fall in platelets or maximum percentage fall in white blood cells with dose, age of patient, area under the curve, volume of distribution or elimination half-life, significant at the 5% level. There appeared to be a weak relationship between trapezoidal peak plasma level and maximum percentage fall in platelets, significant

at the 5% level. Such a relationship was not confirmed when analysing fitted peak plasma level and maximum percentage fall in platelets.

These results show that the severe and life-threatening thrombocytopenia produced in 22% of the patients in this study could not be related to the essential pharmacokinetic parameters of the drug or the oral dose of the drug given.

In summary, this work indicated that following oral administration of mitozolomide at a dose of 90 mg m^{-2}, the bioavailability may vary between 25% and 100%, and absorption may be delayed up to 1.8 hours. No relationships were found to be significant at the 5% level between the dose given and the essential pharmacokinetic parameters of the drug. Whilst 22% of patients experienced a severe thrombocytopenia, this toxicity could not be related to pharmacokinetics of the drug. Because of the unpredictability of this toxicity, the clinical usefulness of this drug is questionable.

PART 3 : FINAL CONCLUSION

3. FINAL CONCLUSION

This project considered two quite distinct areas of cancer therapy. The first section considered the compliance of patients taking an established and well tolerated oral hormonal agent, tamoxifen. Thirteen per cent of patients admitted stopping therapy at some stage of treatment for various reasons. Therefore it should not be assumed that cancer patients are fully compliant just because of the seriousness of their condition. Some patients will fail to show improvement to their therapy and whilst most of these failures will be due to ineffectiveness of the therapy, resistance of the tumour or extensive metastases, some may be due to non-compliant patients ceasing therapy.

Whatever the reason for the therapy failures and for many solid tumours, eg lung and breast, the prognosis is still poor, there is a great need to develop new, effective and non-toxic antitumour agents. The second section of this work further investigated the pharmacokinetics of a new agent, mitozolomide, undergoing a phase I/II trial in solid tumours. Eighteen patients received the drug by oral administration and the pharmacokinetics of the drug in these patients was monitored from analysis of plasma samples using a HPLC technique. One of the main objectives of the work was to determine whether there was a relationship between the pharmacokinetics of mitozolomide and the delayed onset of severe thrombocytopenia. No significant relationships were found.

APPENDIX 1 - Protocol for compliance study

A study of non-compliant behaviour in a group of patients with breast carcinoma receiving oral therapy

Introduction

Non-compliance with therapy is a well documented problem in many areas of medicine. When patients receive medication, many do not take the drug at all or do not take the drug as prescribed and may stop the treatment as soon as they are feeling better. However, there are very few studies on the extent on non-compliance by cancer patients.

Smith et al (1) studied prednisone compliance in children with acute leukaemia and lymphoma by urine assay and showed that about 33% of the group were non-compliant. Hahn et al (2) studied prophylactic antibiotic therapy in patients with acute leukaemia and found that 69% discontinued therapy at some point with a subsequent increase in the incidence of infection. Finally, Baum et al (3), in a study of tamoxifen, monitored compliance in a 5% sample of patients by serum assays and found that 1/35 indicated a recent failure to comply.

1. Smith S D et al. A reliable method for evaluating drug compliance in children with cancer. Cancer 1979, 43: 169-173.

2. Hahn D et al. Infection in acute leukaemia patients receiving oral nonabsorbable antibiotics. Antimicrob. Agents Chemother. 1978, 13: 958-964.

3. Baum et al. Controlled trial of tamoxifen as adjuvant agent in management of early breast cancer. Lancet 1983, 5 Feb: 257-261.

Study Objectives

The aim of this study is to investigate the side effects and non-compliance (missed doses) in patients taking oral therapy for the treatment of breast carcinoma.

The main interest is to assess the level of non-compliance and to determine the factors which may predispose some patients to non-compliant behaviour.

Study Design

This will be an open study conducted on an outpatient basis with the patients being assessed at three monthly intervals.

Patient Selection

Pre-menopausal and post-menopausal women with recurrent or primary non-operable breast carcinoma receiving oral hormonal therapy. Both patients commencing therapy and those already on therapy will be included. Informed consent will be obtained from each patient.

Study Evaluation

Data will be collected by a questionnaire on entry into the study and again after 3, 6, ~~9 and 12~~ months. If practical, pill counts and serum drug analysis will also be performed at these times as an indicator of compliance.

Data Analysis

Data, recorded initially on questionnaires, will be transferred to a computer at Aston University and associations between reported non-compliance, side effects, family support, stage of disease and duration of therapy investigated.

Appendix II - Questionnaire for Compliance study

QUESTIONNAIRE PCS/85a

I am Peter Secrett. I am a hospital pharmacist and I am working with the Pharmacy Department at Aston University and .. .. to try and find out any problems or difficulties you are experiencing in taking your medicines.

Each patient is an individual and whilst some people might have unwanted effects of a medicine, others might find difficulty in actually taking the medicine or remembering to take it. It is part of our job to try to avoid all of these problems and to help you with your medicines.

Therefore it would be very useful if you would agree to answer the following questions to find out if there are areas which can be improved. Some questions may appear to be unrelated to your medicines and treatment but are necessary to analyse the results as they describe you as a person.

It might be possible to improve the effectiveness of the medicines you are taking by checking a small blood sample. Would you be willing to help us in this way another time?

No names will be used in the final report so all information will be treated in complete confidence and you are free to refuse to answer a particular question.

Thank you very much for your help.

STATEMENT OF VOLUNTEER IF A BLOOD SAMPLE IS TAKEN

I understand the above explanation, I agree to take part in this project and if necessary give a small blood sample another time. I understand that I am free to withdraw at any time.

Signed.....

Date.....

FOR OFFICE USE ONLY

QUESTIONNAIRE NUMBER | | | | 1 | Code | 1-4

1.	How often are your clinic appointments at the moment?	every 3 months		1	
		every 6 months		2	
		don't know		3	5
		now discharged		4	
		other*		5	
	*Other - please specify				
2.	Have you missed any clinic appointments? eg:because of illness, holiday or transport problems	Once		1	
		more than once		2	6
		Never		3	
3(a)	Does anyone remind you when your clinic appointment is due?	Yes*		1	7
		No		2	
	*IF YES:				
(b)	Who reminds you?	husband		1	8
		other family members		1	9
		others		1	10
		clinic		1	11
			Yes	No	
4.	Does your present treatment include?	Radiotherapy	1	2	12
		Chemotherapy	1	2	13
		Oral therapy	1	2	14
			Yes	No	
5.	Have you ever refused any of the following the doctor offered you?	Surgery	1	2	15
		Radiotherapy	1	2	16
		Chemotherapy	1	2	17

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6. Can you tell me or describe all the medicines you take?

A
B
C
D
E
F
G

Yes 1
No 2

18

Total number of medicines ☐☐

19-20

7(a) Can you tell me when you take your medicines?

A
B
C
D
E
F
G

Yes 1
No 2

21

OR

(b) Do you need to refer to the bottle label each time?

Yes 1
No 2

22

Total number of doses of all medicines taken each day ☐☐

23-24

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THE FOLLOWING QUESTIONS REFER TO THE UNWANTED EFFECTS CALLED SIDE EFFECTS WHICH MANY MEDICINES AND NOT NECESSARILY YOUR MEDICINES CAN CAUSE

8. Has your present treatment ever caused any of the following?

	Yes Major	Yes Minor	No	Don't Know	
unable to sleep	1	2	3	4	25
lack energy	1	2	3	4	26
feel tired	1	2	3	4	27
feel irritable	1	2	3	4	28
feel depressed	1	2	3	4	29
feel dizzy	1	2	3	4	30
hot flush	1	2	3	4	31
rash	1	2	3	4	32
headaches	1	2	3	4	33
bone pain	1	2	3	4	34
altered vision	1	2	3	4	35
feel sick	1	2	3	4	36
be sick	1	2	3	4	37
diarrhoea	1	2	3	4	38
constipation	1	2	3	4	39
appetite change	1	2	3	4	40
weight change	1	2	3	4	41
others*					

*Others - please specify

..... 42

				FOR OFFICE USE ONLY
9(a)	Has any side effect ever made you stop treatment?	Yes-temporarily*	1	
		Yes-permanently*	2	43
		No-never	3	
	*IF YES			
(b)	What did you do?	contact own GP	1	44
		contact hospital doctor	1	45
		nothing	1	46
		other*		47

*Other-please specify

THE FOLLOWING QUESTIONS REFER TO THE ADVICE YOU MAY HAVE BEEN GIVEN WHEN YOU STARTED YOUR MEDICINES.

10.	Who explained to you about these medicines?	Doctor	1	48
		Pharmacist	1	49
		Nurse	1	50
		Other patient	1	51
		Nobody	1	52
11.	What were you told about your ..... medicines?	When to take them	1	53
		How often to take them	1	54
		How long you will have to take them for	1	55
		Any other information about the medicine itself	1	56
		The importance of not stopping them	1	57
		other*		58

*Other-please specify

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12.	Were you supplied with enough medicine to last you until this appointment by:	hospital pharmacy		1	59
		own GP via local pharmacy*		2	

*If supply from local pharmacy:

Address of local pharmacy.....

.....

13(a)	Does this cause you any problems?	Yes*		1	60
		No		2	

*IF YES

(b)	How many times have you run out of tablets before the clinic appointment and missed doses?			☐☐	61-62

14.	Have you either taken your medicines today or the last dose that was due yesterday?	Yes		1	63
		No		2	

			Yes	No	
15.	Have you ever stopped your medicines?	When you felt better	1	2	64
		When you felt worse	1	2	65
		When you felt the same	1	2	66

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16. Do you ever forget to take or miss out your medicines at the usual time?

Yes	1	
No	2	67

*IF YES GO TO 17
*IF NO GO TO 20

17. How many times have you missed out or forgotten your medicines in the last week? ☐☐ 68-69

18. When are you most likely to forget or miss your medicines?

Morning	1	
Afternoon	2	70
Evening	3	
None of these	4	
Don't know	5	

19. If you remember that you have missed taking your medicines do you?

Take them as soon as you remember	1	71
Miss out that dose	1	72
Take twice as much next time	1	73

FOR OFFICE USE ONLY

QUESTIONNAIRE NUMBER | | | | 2 | 1-4

Code

20.	How do you remember to take your medicines?	Do you take them in relation to food?	Before With After	1 2 3	5
		Do you put them out so that you do not forget them?		1	6
		Do you rely on your own memory?		1	7
		Does somebody remind you to take them?		1	8
		Do you use a calendar or diary as a reminder?		1	9
		Do you use any other aids?		1	10
		Do you take them in relation to waking up or going to bed?		1	11
		other*			12

*Other-please specify.....

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21.	Do you live with	husband	1	13
		other family members	1	14
		others	1	15
		alone	1	16
22.	Are you	working (full or part-time)	1	17
		not working	2	

23. Would you mind if I visited you at home? Yes / No*

*IF NO

I would contact you first by telephone or by post card. TELEPHONE NUMBER .....

24. Any questions you would like to ask me? Will you bring your medicines with you next time please?

THANK YOU AGAIN FOR YOUR HELP

25.	Interviewers comments:		Yes	No	
	Evidence of	Intellectual impairment	1	2	18
		Poor vision	1	2	19
		Diminished hearing	1	2	20
	Did the patient answer the questions herself?		1	2	21
	Is the patient in charge of her medicines?		1	2	22

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QUESTIONNAIRE NUMBER [ ][ ][ ][3] Code 1-4

CLINIC NUMBER [ ] 5

TYPE OF CLINIC

Surgery	1	6
Radiotherapy	1	7
Oncology	1	8

NAME: ADDRESS

DATE OF BIRTH: AGE(in years): [ ][ ][ ] 9-11

HOSPITAL UNIT NUMBER .....

NAME AND ADDRESS OF GP

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Duration of symptoms before presentation to clinic (in months)	☐☐☐		12-14
Date of presentation to clinic	.....		
Duration of illness (in months)	☐☐☐		15-17
Any other serious illness in addtion to cancer	Yes	1	
	No	2	18
Any indications of a history of psychological problems	Yes	1	
	No	2	19
Any drugs being taken which might impair mental ability	Yes	1	
	No	2	20
Any evidence of recurrence of the cancer	Scar	1	21
	Axilla or SCF nodes	1	22
	Bone	1	23
	Others*	1	24
*Others-give details			
Any evidence of non-compliance with a therapy	Yes*	1	
	No	2	25
*Yes-give details			

			FOR OFFICE USE ONLY
PREVIOUS TREATMENT:			
	Surgery	1	26
	Radiotherapy	1	27
	Hormone Therapy*	1	28
	Chemotherapy	1	29

*HORMONE THERAPY-give details

TYPE OF HORMONE THERAPY:			
	Tamoxifen	1	30
	Aminoglutethimide	1	31
	Hydrocortisone	1	32
	Medroxyprogesterone acetate	1	33
	Norethisterone acetate	1	34
	Megestrol acetate	1	35
	Other	1	36
HORMONE THERAPY BEING USED FOR:			
	Primary treatment	1	
	Adjuvant treatment	2	37
	Recurrence	3	

				FOR OFFICE USE ONLY
CURRENT TREATMENT:		Yes	No	
	Radiotherapy	1	2	38
	Chemotherapy	1	2	39
TYPE OF HORMONE THERAPY		Yes	No	
	Tamoxifen	1	2	40
	Duration of therapy in months		☐☐☐	41-43
	Aminoglutethimide	1	2	44
	Duration of therapy in months		☐☐☐	45-47
	Hydrocortisone	1	2	48
	Duration of therapy in months		☐☐☐	49-51
	Medroxyprogesterone acetate	1	2	52
	Duration of therapy in months		☐☐☐	53-55
HORMONE THERAPY BEING USED FOR:				
	Primary treatment		1	
	Adjuvant treatment		2	56
	Recurrence		3	

APPENDIX IIIA

Full "Chi-Square" test of association between stopping therapy and all other variables.

Variables	Value	Number N	% of N Stopping	Chi Square	Degrees of Freedom	Probability
Appointment Frequency	every 3 months	75	6.7			
	every 6 months	39	10.3			
	Not known	7	14.3	0.904	4	0.924
	Discharged	1	0.0			
	other	26	7.7			
Missed Appointments	Once	10	0.0			
	More than once	4	0.0	1.477	2	0.478
	Never	135	9.6			
Reminded Appointment due	Yes	27	0	3.124	1	0.077
	No	123	10.6			
Present Radiotherapy	Yes	2	0.0			
	No	148	8.8	0.192	1	0.661
Present Chemotherapy	Yes	2	0.0			
	No	148	8.8	0.192	1	0.661
Present Oral therapy	Yes	149	8.7	0.096	1	0.757
	No	1	0.0			
Ever refused Surgery	Yes	2	0.0	0.194	1	0.660
	No	147	8.8			
Ever refused Radiotherapy	Yes	4	0.0	0.393	1	0.531
	No	145	9.0			
Can patient list medicines	Yes	128	7.8	0.949	1	0.330
	No	21	14.3			
Total number of medicines	1	59	11.9			
	2	41	9.8			
	3	28	3.6			
	4	9	0.0			
	>4	13	7.7	2.612	4	0.625
Know when to take medicines	Yes	142	8.5	0.157	1	0.692
	No	8	12.5			

NOTE: Missing data are not included, therefore the numbers in the columns do not always agree with the numbers of patients interviewed.

APPENDIX IIIA continued

Variables	Value	Number N	% of N Stopping	Chi Square	Degrees of Freedom	Probability
Need to refer to label	Yes	9	11.1	0.065	1	0.799
	No	139	8.6			
Number of dose taken per day	1	23	0.0			
	2	45	13.3			
	3	16	12.5			
	4	16	6.3			
	>4	48	6.3	4.504	5	0.479
Unable to sleep	Yes	1	0.0			
	No	142	9.2	0.101	1	0.751
Lack energy	Yes	6	50.0			
	No	120	6.7	13.467	1	< 0.001
Feel tired	Yes	10	20.0			
	No	119	7.6	1.829	1	0.176
Feel irritable	Yes	6	16.7			
	No	130	9.2	0.367	1	0.545
Feel dizzy	Yes	9	33.3			
	No	132	6.8	7.608	1	0.006
Feel depressed	Yes	6	33.3			
	No	114	7.9	4.430	1	0.035
Hot Flush	Yes	31	19.4			
	No	102	5.9	5.257	1	0.022
Rash	Yes	1	0.0			
	No	145	9.0	0.098	1	0.754
Headache	Yes	1	0.0			
	No	142	8.5	0.092	1	0.761
Bone pain	Yes	7	0.0			
	No	122	9.0	0.690	1	0.406
Altered vision	Yes	2	50.0			
	No	130	8.5	4.112	1	0.043

APPENDIX IIIA continued

Variables	Value	Number N	% of N Stopping	Chi Square	Degrees of Freedom	Probability
Feel sick	Yes	13	7.7			
	No	133	9.0	0.026	1	0.872
Be sick	Yes	2	0.0			
	No	145	9.0	0.197	1	0.657
Diarhoea	Yes	4	0.0			
	No	141	9.2	0.405	1	0.525
Constipation	Yes	11	0.0			
	No	135	9.6	1.163	1	0.281
Appetite change	Yes	17	11.8			
	No	130	8.5	0.203	1	0.652
Weight change	Yes	33	6.1			
	No	104	9.6	0.396	1	0.529
Advised by Doctor	Yes	145	9.0	0.491	1	0.484
	No	5	0.0			
Advice from Pharmacist	Yes	42	9.5	0.054	1	0.816
	No	108	8.3			
Advice from Nurse	Yes	1	8.7	0.096	1	0.757
	No	149	0.0			
Advice from other patient	Yes	13	15.4	0.812	1	0.368
	No	137	8.0			
Advice from nobody	Yes	2	0.0	0.192	1	0.661
	No	148	8.8			
When to take drugs	Yes	73	6.8	0.593	1	0.441
	No	77	10.4			
How often to take drugs	Yes	147	8.8	0.290	1	0.590
	No	3	0			
How long to take drugs	Yes	53	3.8	2.480	1	0.115
	No	97	11.3			

APPENDIX IIIA continued

Variables	Value	Number N	% of N Stopping	Chi Square	Degrees of Freedom	Probability
Important not to stop drugs	Yes	111	7.2	1.149	1	0.284
	No	39	12.8			
Other information	Yes	32	6.3	0.300	1	0.584
	No	118	9.3			
Supply	Hosp.pharm.	8	25.0	2.812	1	0.094
	GP-Loc.pharm.	141	7.8			
Supply a problem	Yes	7	14.3	0.285	1	0.593
	No	142	8.5			
Number times run out	0	144	6.9	17.280	2	<0.001
	1	5	40.0			
	2	1	100.0			
Taken last dose due	Yes	124	6.5	4.434	1	0.035
	No	26	19.2			
Ever forget or miss	Yes	43	11.6	0.668	1	0.414
	No	107	7.5			
Remember drugs with food	No	72	8.3	10.104	3	0.018
	Before	13	30.8			
	With	19	0.0			
	After	46	6.5			
Remember by putting out	Yes	72	6.9	0.519	1	0.471
	No	78	10.3			
Memory	Yes	103	11.7	3.697	1	0.055
	No	47	2.1			
Somebody reminds	Yes	49	4.1	1.933	1	0.165
	No	101	10.9			
Use of calendar or diary	Yes	5	0.0	0.491	1	0.484
	No	145	9.0			
On waking or going to bed	Yes	32	6.3	0.300	1	0.584
	No	118	9.3			

APPENDIX IIIA continued

Variables	Value	Number N	% of N Stopping	Chi Square	Degrees of Freedom	Probability
Evidence of intellectual impairment	Yes	18	16.7	1.654	1	0.198
	No	132	7.6			
Poor Vision	Yes	7	0.0	0.697	1	0.404
	No	143	9.1			
Diminished hearing	Yes	23	8.7	0.000	1	0.996
	No	127	8.7			
Answered questions herself	Yes	141	9.2	0.909	1	0.341
	No	9	0.0			
In charge of Medicine	Yes	141	9.2	0.909	1	0.341
	No	9	0.0			
Lives with	Husband	86	9.3	0.103	1	0.748
	Family	48	10.4	0.273	1	0.601
	Others	5	0.0	0.491	1	0.484
	Alone	42	9.5	0.054	1	0.816
Working	Yes	39	5.1	0.834	1	0.361
	No	111	9.9			
Clinic Number	1	76	5.3			
	2	25	0.0			
	3	48	18.8	9.745	2	0.008
Age/years	< 50	14	7.1			
	50-60	37	10.8			
	61-70	40	7.7			
	71-80	45	11.1			
	> 80	13	0.0	1.851	4	0.763
Duration symptoms before presentation /months	0-1	53	13.2			
	2-6	47	4.3			
	>6	19	15.8	3.013	2	0.222
Duration illness since treatment commenced /months	0-12	43	9.3			
	13-24	30	6.7			
	25-36	14	7.1			
	37-48	11	9.1			
	49-60	11	0.0			
	>60	34	14.7	2.677	5	0.750

APPENDIX IIIA continued

Variables	Value	Number N	% of N Stopping	Chi Square	Degrees of Freedom	Probability
Other illness	Yes	46	13.0	2.072	1	0.150
	No	100	6.0			
Psychological Problems	Yes	18	16.7	1.870	1	0.172
	No	126	7.1			
Drugs which impair mental ability	Yes	7	0.0	0.669	1	0.413
	No	137	8.8			
Previous non-compliance	Yes	19	36.8	20.818	1	<0.001
	No	126	4.8			
Previous Surgery	Yes	122	9.8	1.129	1	0.288
	No	28	3.6			
Previous Radiotherapy	Yes	66	12.1	1.777	1	0.183
	No	84	6.0			
Previous Hormonal Therapy	Yes	6	16.7	0.505	1	0.477
	No	144	8.3			
Previous Chemotherapy	Yes	14	7.1	0.045	1	0.832
	No	136	8.8			
Previous Tamoxifen	Yes	3	33.3	2.353	1	0.125
	No	147	8.2			
Duration Tamoxifen treatment /months	1-6	63	3.2	4.317	3	0.229
	7-24	47	12.8			
	25-48	30	13.3			
	> 48	8	12.5			
Hormones used as treatment	Primary	31	3.2	3.022	2	0.221
	Adjuvant	41	14.6			
	Recurrence	76	7.9			

APPENDIX IIIB

Full "chi-square" test of association between forgetting or missing dose and all other variables.

Variables	Value	Number N	% of N who forget/miss	Chi Square	Degrees of Freedom	Probability
Appointment Frequency	every 3 months	76	28.9			
	every 6 months	39	25.6			
	Not known	7	28.6	0.625	4	0.960
	Discharged	1	0.0			
	other	26	30.8			
Missed Appointments	Once	10	40.0			
	More than once	4	25.0	0.689	2	0.708
	Never	136	27.9			
Reminded Appointment due	Yes	27	14.8	3.013	1	0.083
	No	124	31.5			
Present Radiotherapy	Yes	2	50.0	0.461	1	0.497
	No	149	28.2			
Present Chemotherapy	Yes	2	0.0	0.807	1	0.369
	No	149	28.9			
Present Oral therapy	Yes	150	28.7	0.401	1	0.527
	No	1	0.0			
Ever refused Surgery	Yes	2	50.0	0.451	1	0.502
	No	148	28.4			
Ever refused Radiotherapy	Yes	4	0.0	1.652	1	0.199
	No	146	29.5			
Can patient list medicines	Yes	129	30.2	2.278	1	0.131
	No	21	14.3			
Total number of medicines	1	59	25.4			
	2	42	33.3			
	3	28	25.0			
	4	9	33.3			
	>4	13	30.8	1.060	4	0.901
Know when to take medicines	Yes	143	29.4	1.059	1	0.304
	No	8	12.5			

APPENDIX IIIB continued

Variables	Value	Number N	% of N who forget/miss	Chi Square	Degrees of Freedom	Probability
Need to refer to label	Yes	9	22,2	0.168	1	0.682
	No	140	28.6			
Number of dose taken per day	1	23	13.0			
	2	45	37.8			
	3	17	35.3			
	4	16	18.8			
	>4	48	29.2	6.114	5	0.295
Unable to sleep	Yes	1	0.0			
	No	143	28.7	0.401	1	0.527
Lack energy	Yes	6	16.7			
	No	121	26.4	0.284	1	0.594
Feel tired	Yes	10	30.0			
	No	120	25.8	0.083	1	0.773
Feel irritable	Yes	6	0.0			
	No	131	28.2	2.322	1	0.128
Feel dizzy	Yes	9	55.6			
	No	133	26.3	3.562	1	0.059
Feel depressed	Yes	6	50.0			
	No	115	26.1	1.644	1	0.200
Hot Flush	Yes	31	48.4			
	No	103	22.3	7.963	1	0.005
Rash	Yes	1	100.0			
	No	146	28.8	2.435	1	0.119
Headache	Yes	1	0.0			
	No	143	28.7	0.401	1	0.527
Bone pain	Yes	7	0.0			
	No	123	30.9	3.056	1	0.080
Altered vision	Yes	2	50.0			
	No	130	30.8	0.340	1	0.560

APPENDIX IIIB continued

Variables	Value	Number N	% of N who forget/miss	Chi Square	Degrees of Freedom	Probability
Feel sick	Yes	13	30.8			
	No	134	28.4	0.034	1	0.854
Be sick	Yes	2	0.0			
	No	146	28.8	0.803	1	0.370
Diarhoea	Yes	4	50.0			
	No	142	28.2	0.905	1	0.342
Constipation	Yes	11	18.2			
	No	136	28.7	0.557	1	0.455
Appetite change	Yes	17	52.9			
	No	131	26.0	5.317	1	0.021
Weight change	Yes	33	36.4			
	No	105	24.8	1.694	1	0.193
Advised by Doctor	Yes	146	28.1	0.337	1	0.562
	No	5	40.0			
Advice from Pharmacist	Yes	42	26.2	0.149	1	0.699
	No	109	29.4			
Advice from Nurse	Yes	1	100.0	2.528	1	0.112
	No	150	28.0			
Advice from other patient	Yes	13	38.5	0.696	1	0.404
	No	138	27.5			
Advice from nobody	Yes	2	50.0	0.461	1	0.497
	No	149	28.2			
When to take drugs	Yes	73	20.5	4.362	1	0.037
	No	78	35.9			
How often to take drugs	Yes	148	29.1	1.219	1	0.270
	No	3	0.0			
How long to take drugs	Yes	53	22.6	1.365	1	0.243
	No	98	31.6			

APPENDIX IIIB continued

Variables	Value	Number N	% of N who forget/miss	Chi Square	Degrees of Freedom	Probability
Important not to stop drugs	Yes	112	28.6	0.002	1	0.965
	No	39	28.2			
Other information	Yes	32	21.9	0.869	1	0.351
	No	119	30.3			
Supply	Hosp.pharm.	8	25.0	0.056	1	0.814
	GP-Loc.pharm.	142	28.9			
Supply a problem	Yes	7	28.6	0.000	1	0.995
	No	143	28.7			
Number times run out	0	145	27.6	2.894	2	0.235
	1	5	40.0			
	2	1	100.0			
Taken last dose due	Yes	125	28.0	0.081	1	0.776
	No	26	30.8			
Remember drugs with food	No	72	31.9	3.293	3	0.349
	Before	13	15.4			
	With	19	15.8			
	After	47	31.9			
Remember by putting out	Yes	72	22.2	2.643	1	0.104
	No	79	34.2			
Memory	Yes	104	30.8	0.862	1	0.353
	No	47	23.4			
Somebody reminds	Yes	49	24.5	0.566	1	0.452
	No	102	30.4			
Use of calendar or diary	Yes	5	20.0	0.182	1	0.669
	No	146	28.8			
On waking or going to bed	Yes	32	28.1	0.002	1	0.960
	No	119	28.6			

APPENDIX IIIB Continued

Variables	Value	Number N	% of N who forget/miss	Chi Square	Degrees of Freedom	Probability
Evidence of intellectual impairment	Yes	18	22.2	0.393	1	0.531
	No	133	29.3			
Poor Vision	Yes	7	28.6	0.000	1	0.996
	No	144	28.5			
Diminished hearing	Yes	23	17.4	1.637	1	0.201
	No	128	30.5			
Answered questions herself	Yes	142	29.6	1.417	1.	0.234
	No	9	11.1			
In charge of Medicine	Yes	142	29.6	1.417	1	0.234
	No	9	11.1			
Lives with	Husband	87	26.4	0.419	1	0.517
	Family	48	41.7	6.011	1	0.014
	Others	5	20.0	0.182	1	0.669
	Alone	42	26.2	0.149	1	0.699
Working	Yes	39	38.5	2.574	1	0.109
	No	112	25.0			
Clinic Number	1	76	36.8			
	2	26	19.2	5.269	2	0.072
	3	49	20.4			
Age/years	< 50	14	21.4			
	50-60	37	37.8			
	61-70	40	25.0			
	71-80	45	24.4			
	> 80	13	38.5	3.131	4	0.536
Duration symptoms before presentation /months	0-1	53	32.1			
	2-6	47	23.4			
	>6	20	55.0	6.392	2	0.041
Duration illness since treatment commenced /months	0-12	43	25.6			
	13-24	30	26.7			
	25-36	15	33.3			
	37-48	11	18.2			
	49-60	11	45.5			
	>60	34	32.4	2.706	5	0.745

APPENDIX IIIB continued

Variables	Value	Number N	% of N who forget/miss	Chi Square	Degrees of Freedom	Probability
Other illness	Yes	46	37.0	1.920	1	0.166
	No	101	25.7			
Psychological Problems	Yes	19	26.3	0.041	1	0.839
	No	126	28.6			
Drugs which impair mental ability	Yes	8	25.0	0.045	1	0.832
	No	137	28.5			
Previous non-compliance	Yes	20	30.0	0.042	1	0.837
	No	126	27.8			
Previous Surgery	Yes	122	31.1	2.225	1	0.136
	No	29	17.2			
Previous Radiotherapy	Yes	66	36.4	3.581	1	0.059
	No	85	22.4			
Previous Hormonal Therapy	Yes	6	16.7	0.428	1	0.513
	No	145	29.0			
Previous Chemotherapy	Yes	14	35.7	0.397	1	0.529
	No	137	27.7			
Previous Tamoxifen	Yes	3	33.3	0.035	1	0.851
	No	148	28.4			
Duration Tamoxifen treatment /months	1-6	63	25.4	0.873	3	0.832
	7-24	47	31.9			
	25-48	31	29.0			
	> 48	8	37.5			
Hormones used as treatment	Primary	32	18.8	3.637	2	0.162
	Adjuvant	41	24.4			
	Recurrence	76	35.5			

APPENDIX IIIC

Full "chi-square" tests of association between not taking last dose and all other variables.

Variables	Value	Number N	% of N not taken last dose	Chi Square	Degrees of Freedom	Probability
Appointment Frequency	every 3 months	76	15.8			
	every 6 months	39	17.9			
	Not known	7	28.6	1.022	4	0.907
	Discharged	1	0.0			
	other	26	19.2			
Missed Appointments	Once	10	30.0			
	More than once	4	0.0	1.975	2	0.373
	Never	136	16.9			
Reminded Appointment due	Yes	27	14.8	0.133	1	0.715
	No	124	17.7			
Present Radiotherapy	Yes	2	0.0	0.421	1	0.516
	No	149	17.4			
Present Chemotherapy	Yes	2	50.0	1.528	1	0.216
	No	149	16.8			
Present Oral therapy	Yes	150	16.7	4.840	1	0.028
	No	1	100.0			
Ever refused Surgery	Yes	2	50.0	1.510	1	0.219
	No	148	16.9			
Ever refused Radiotherapy	Yes	4	0.0	0.862	1	0.353
	No	146	17.8			
Can patient list medicines	Yes	129	18.6	2.492	1	0.114
	No	21	4.8			
Total number of medicines	1	59	13.6			
	2	42	23.8			
	3	28	10.7			
	4	9	22.2			
	>4	13	23.1	3.136	4	0.535
Know when to take medicines	Yes	143	18.2	1.757	1	0.185
	No	8	0.0			

APPENDIX IIIC continued

Variables	Value	Number N	% of N not taken last dose	Chi Square	Degrees of Freedom	Probability
Need to refer to label	Yes	9	0.0	2.025	1	0.155
	No	140	18.6			
Number of dose taken per day	1	23	8.7			
	2	45	17.8			
	3	17	29.4			
	4	16	18.8			
	>4	48	16.7	3.182	5	0.672
Unable to sleep	Yes	1	100.0	4.570	1	0.033
	No	143	17.5			
Lack energy	Yes	6	16.7			
	No	121	15.7	0.004	1	0.950
Feel tired	Yes	10	10.0			
	No	120	16.7	0.303	1	0.582
Feel irritable	Yes	6	16.7			
	No	131	19.1	0.022	1	0.883
Feel dizzy	Yes	9	11.1			
	No	133	15.8	0.141	1	0.707
Feel depressed	Yes	6	0.0			
	No	115	21.7	1.644	1	0.200
Hot Flush	Yes	31	19.4			
	No	103	18.4	0.013	1	0.909
Rash	Yes	1	0.0			
	No	146	17.8	0.216	1	0.642
Headache	Yes	1	0.0			
	No	143	18.2	0.222	1	0.638
Bone pain	Yes	7	14.3			
	No	123	19.5	0.116	1	0.733
Altered vision	Yes	2	0.0			
	No	130	18.5	0.451	1	0.502

APPENDIX IIIC continued

Variables	Value	Number N	% of N not taken last dose	Chi Square	Degrees of Freedom	Probability
Feel sick	Yes	13	15.4			
	No	134	17.9	0.052	1	0.820
Be sick	Yes	2	0.0			
	No	146	17.8	0.432	1	0.511
Diarhoea	Yes	4	0.0			
	No	142	17.6	0.850	1	0.357
Constipation	Yes	11	18.2			
	No	136	17.6	0.002	1	0.964
Appetite change	Yes	17	23.5			
	No	131	16.0	0.603	1	0.438
Weight change	Yes	33	12.1			
	No	105	15.2	0.197	1	0.657
Advised by Doctor	Yes	146	17.1	0.028	1	0.867
	No	5	20.0			
Advice from Pharmacist	Yes	42	21.4	0.724	1	0.395
	No	109	15.6			
Advice from Nurse	Yes	1	100.0	4.840	1	0.028
	No	150	16.7			
Advice from other patient	Yes	13	0.0	2.959	1	0.085
	No	138	18.8			
Advice from nobody	Yes	2	0.0	0.422	1	0.516
	No	149	17.4			
When to take drugs	Yes	73	20.5	1.099	1	0.295
	No	78	14.1			
How often to take drugs	Yes	148	16.9	0.558	1	0.455
	No	3	33.3			
How long to take drugs	Yes	53	13.2	0.922	1	0.337
	No	98	19.4			

APPENDIX IIIC continued

Variables	Value	Number N	% of N not taken last dose	Chi Square	Degrees of Freedom	Probability
Important not to stop drugs	Yes	112	13.4	4.453	1	0.035
	No	39	28.2			
Other information	Yes	32	12.5	0.634	1	0.426
	No	119	18.5			
Supply	Hosp.pharm.	8	37.5	2.399	1	0.121
	GP-Loc.pharm.	142	16.2			
Supply a problem	Yes	7	14.3	0.048	1	0.827
	No	143	17.5			
Number times run out	0	145	17.2	0.235	2	0.889
	1	5	20.0			
	2	1	0.0			
Ever forget or miss	Yes	43	18.6	0.081	1	0.776
	No	108	16.7			
Remember drugs with food	No	72	15.3	2.585	3	0.460
	Before	13	30.8			
	With	19	10.5			
	After	47	19.1			
Remember by putting out	Yes	72	15.3	0.364	1	0.547
	No	79	19.0			
Memory	Yes	104	20.2	2.073	1	0.150
	No	47	10.6			
Somebody reminds	Yes	49	10.2	2.504	1	0.114
	No	102	20.6			
Use of calendar or diary	Yes	5	20.0	0.028	1	0.867
	No	146	17.1			
On waking or going to bed	Yes	32	3.1	5.658	1	0.017
	No	119	21.0			

APPENDIX IIIC continued

Variables	Value	Number N	% of N not taken last dose	Chi Square	Degrees of Freedom	Probability
Evidence of intellectual impairment	Yes	18	27.8	0.868	1	0.352
	No	133	15.8			
Poor Vision	Yes	7	28.6	0.664	1	0.415
	No	144	16.7			
Diminished hearing	Yes	23	21.7	0.389	1	0.533
	No	128	16.4			
Answered questions herself	Yes	142	18.3	1.991	1	0.158
	No	9	0.0			
In charge of Medicine	Yes	142	17.6	0.250	1	0.617
	No	9	11.1			
Lives with	Husband	87	16.1	0.044	1	0.834
	Family	48	12.5	1.099	1	0.294
	Others	5	40.0	1.883	1	0.170
	Alone	42	19.0	0.137	1	0.712
Working	Yes	39	10.3	1.788	1	0.181
	No	112	19.6			
Clinic Number	1	76	18.4			
	2	26	26.9	3.486	2	0.175
	3	49	10.2			
Age/years	< 50	14	14.3			
	51-60	37	8.1			
	61-70	40	20.0			
	71-80	45	22.2			
	> 80	13	23.1	3.517	4	0.475
Duration symptoms before presentation /months	0-1	53	13.2			
	2-6	47	19.1			
	>6	20	20.0	0.825	2	0.662
Duration illness since treatment commenced /months	0-12	43	16.3			
	13-24	30	10.0			
	25-36	15	20.0			
	37-48	11	18.2			
	49-60	11	18.2			
	>60	34	26.5	3.073	5	0.689

APPENDIX IIIC continued

Variables	Value	Number N	% of N not taken last dose	Chi Square	Degrees of Freedom	Probability
Other illness	Yes	46	28.3	6.008	1	0.014
	No	101	11.9			
Psychological Problems	Yes	19	15.8	0.032	1	0.857
	No	126	17.5			
Drugs which impair mental ability	Yes	8	25.0	0.357	1	0.550
	No	137	16.8			
Previous non-compliance	Yes	20	30.0	2.353	1	0.125
	No	126	15.9			
Previous Surgery	Yes	122	18.0	0.295	1	0.587
	No	29	13.8			
Previous Radiotherapy	Yes	66	16.7	0.025	1	0.874
	No	85	17.6			
Previous Hormonal Therapy	Yes	6	33.3	1.138	1	0.286
	No	145	16.6			
Previous Chemotherapy	Yes	14	7.1	1.099	1	0.295
	No	137	18.2			
Previous Tamoxifen	Yes	3	66.7	5.251	1	0.022
	No	148	16.2			
Duration Tamoxifen treatment /months	1-6	63	17.5	0.220	3	0.974
	7-24	47	17.0			
	25-48	31	19.4			
	> 48	8	12.5			
Hormones used as treatment	Primary	32	21.9	2.396	2	0.302
	Adjuvant	41	9.8			
	Recurrence	76	19.7			

APPENDIX IIID

Full "chi-square" test of association between clinic number and all other variables.

Variables	Value	Clinic Number			Chi Square	Degrees of Freedom	Probability
		1	2	3			
Appointment Frequency	every 3 months	54	2	20			
	every 6 months	14	11	14			
	Not known	1	3	3	36.441	8	<0.001
	Discharged	1	0	0			
	other	6	9	11			
Missed Appointments	Once	5	3	2			
	More than once	4	0	0	5.639	4	0.228
	Never	66	23	47			
Reminded Appointment due	Yes	16	4	7			
	No	60	22	42	1.062	2	0.588
Present Radiotherapy	Yes	1	1	0			
	No	75	25	49	1.923	2	0.382
Present Chemotherapy	Yes	1	1	0			
	No	75	25	49	1.923	2	0.382
Present Oral therapy	Yes	76	25	49			
	No	0	1	0	4.840	2	0.089
Ever refused Surgery.	Yes	1	1	0			
	No	75	24	49	2.014	2	0.365
Ever refused Radiotherapy	Yes	2	2	0			
	No	74	23	49	4.083	2	0.123
Can patient list medicines	Yes	67	23	39			
	No	8	3	10	2.494	2	0.287
Total number of medicines	1	26	11	22			
	2	26	8	8			
	3	12	4	12			
	4	5	1	3	6.179	8	0.627
	>4	2	2	4			
Know when to take medicines	Yes	72	25	46			
	No	4	1	3	0.176	2	0.916

APPENDIX IIID continued

Variables	Value	Clinic Number			Chi Square	Degrees of Freedom	Probability
		1	2	3			
Need to refer to label	Yes	2	2	5	3.074	2	0.215
	No	72	24	44			
Number of dose taken per day	1	13	8	2			
	2	20	3	22			
	3	11	4	2	22.884	10	0.011
	4	7	5	4			
	> 4	24	6	18			
Unable to sleep	Yes	0	1	0	5.584	2	0.061
	No	74	21	28			
Lack energy	Yes	2	2	2			
	No	61	21	40	1.268	2	0.530
Feel tired	Yes	6	2	2			
	No	58	22	40	0.777	2	0.678
Feel irritable	Yes	2	1	3			
	No	65	23	43	0.818	2	0.664
Feel dizzy	Yes	4	1	4			
	No	68	22	43	0.601	2	0.740
Feel depressed	Yes	3	0	3			
	No	57	22	36	1.466	2	0.413
Hot Flush	Yes	17	1	13			
	No	50	22	31	5.771	2	0.056
Rash	Yes	1	0	0			
	No	74	25	47	0.967	2	0.617
Headache	Yes	1	0	0			
	No	73	25	45	0.953	2	0.621
Bone pain	Yes	4	1	2			
	No	66	18	39	0.036	2	0.982
Altered vision	Yes	0	0	2			
	No	66	23	41	4.203	2	0.122

APPENDIX IIID continued

Variables	Value	Clinic Number			Chi Square	Degrees of Freedom	Probability
		1	2	3			
Feel sick	Yes	8	3	2			
	No	65	23	46	1.942	2	0.379
Be sick	Yes	2	0	0			
	No	72	26	48	2.027	2	0.363
Diarhoea	Yes	1	0	3			
	No	73	25	44	3.581	2	0.167
Constipation	Yes	4	1	6			
	No	69	25	42	2.665	2	0.264
Appetite change	Yes	11	4	2			
	No	64	21	46	3.777	2	0.151
Weight change	Yes	13	8	12			
	No	54	16	35	1.987	2	0.370
Advised by Doctor	Yes	73	26	47			
	No	3	0	2	1.077	2	0.584
Advice from Pharmacist	Yes	24	9	9			
	No	52	17	40	3.313	2	0.191
Advice from Nurse	Yes	1	0	0			
	No	75	26	49	0.993	2	0.609
Advice from other patient	Yes	5	1	7			
	No	71	25	42	3.155	2	0.207
Advice from nobody	Yes	1	0	1			
	No	75	26	48	0.541	2	0.763
When to take drugs	Yes	32	19	22	7.786	2	0.020
	No	44	7	27			
How often to take drugs	Yes	76	24	48			
	No	0	2	1	5.888	2	0.053
How long to take drugs	Yes	24	12	17			
	No	52	14	32	1.812	2	0.404

APPENDIX IIID continued

Variables	Value	Clinic Number			Chi Square	Degrees of Freedom	Probability
		1	2	3			
Important not to stop drugs	Yes	56	20	36			
	No	20	6	13	0.125	2	0.940
Other information	Yes	22	4	6			
	No	54	22	43	5.611	2	0.061
Supply	Hosp.pharm.	2	2	4			
	GP-Loc.pharm.	73	24	45	2.120	2	0.346
Supply a problem	Yes	2	2	3			
	No	73	24	46	1.443	2	0.486
Number times run out	0	75	24	46			
	1	1	2	2			
	2	0	0	1	4.707	4	0.319
Taken last dose due	Yes	62	19	44			
	No	14	7	5	3.486	2	0.175
Ever forget or miss	Yes	28	5	10			
	No	48	21	39	5.269	2	0.072
Remember drugs with food	No	39	11	22			
	Before	4	3	6			
	With	11	2	6			
	After	22	10	15	3.732	6	0.713
Remember by putting out	Yes	36	12	24			
	No	40	14	25	0.060	2	0.970
Memory	Yes	49	18	37			
	No	27	8	12	1.695	2	0.429
Somebody reminds	Yes	25	8	16			
	No	51	18	33	0.041	2	0.980
Use of calendar or diary	Yes	3	2	0			
	No	73	24	49	3.333	2	0.189
On waking or going to bed	Yes	14	7	11			
	No	62	19	38	0.907	2	0.635

APPENDIX IIID continued

Variables	Value	Clinic Number			Chi Square	Degrees of Freedom	Probability
		1	2	3			
Evidence of intellectual impairment	Yes	10	1	7			
	No	66	25	42	1.986	2	0.370
Poor Vision	Yes	5	0	2			
	No	71	26	47	1.947	2	0.378
Diminished hearing	Yes	15	3	5			
	No	61	23	44	2.429	2	0.297
Answered questions herself	Yes	69	26	47			
	No	7	0	2	3.389	2	0.184
In charge of Medicine	Yes	70	26	46			
	No	6	0	3	2.158	2	0.340
Lives with	Husband	42	17	28	0.819	2	0.664
	Family	21	7	20	2.731	2	0.255
	Others	4	1	0	2.606	2	0.272
	Alone	21	7	14	0.026	2	0.987
Working	Yes	22	8	9			
	No	54	18	40	2.141	2	0.343
Age/years	< 51	6	2	6			
	51-60	19	6	12			
	61-70	12	10	18			
	71-80	28	6	11			
	> 80	19	2	1	14.219	8	0.076
Duration symptoms before presentation /months	0-1	28	7	18			
	2-6	25	6	16			
	>6	14	1	5	2.197	4	0.670
Duration illness since treatment commenced /months	0-12	27	2	14			
	13-24	11	4	15			
	25-36	4	0	11			
	37-48	4	5	2			
	49-60	8	2	1			
	>60	20	9	5	36.854	10	< 0.001

APPENDIX IIID continued

Variables	Value	Clinic Number			Chi Square	Degrees of Freedom	Probability
		1	2	3			
Other illness	Yes	30	2	14			
	No	44	24	33	9.729	2	0.008
Psychological Problems	Yes	10	3	6			
	No	62	23	41	0.100	2	0.951
Drugs which impair mental ability	Yes	4	1	2			
	No	68	25	44	0.207	2	0.902
Previous non-compliance	Yes	8	2	10			
	No	65	24	37	3.540	2	0.170
Previous Surgery	Yes	62	22	38			
	No	14	4	11	0.607	2	0.738
Previous Radiotherapy	Yes	20	13	33			
	No	56	13	16	20.891	2	<0.001
Previous Hormonal Therapy	Yes	4	0	2			
	No	72	26	47	1.409	2	0.494
Previous Chemotherapy	Yes	12	0	2			
	No	64	26	47	8.064	2	0.018
Previous Tamoxifen	Yes	1	0	2			
	No	75	26	47	1.807	2	0.405
Duration Tamoxifen treatment /months	1-6	42	5	16			
	7-24	15	11	21			
	25-48	15	5	11			
	> 48	3	5	0	26.206	6	<0.001
Hormones used as treatment	Primary	17	4	11			
	Adjuvant	9	6	26			
	Recurrence	49	16	11	30.692	4	<0.001

Appendix IV - Patient characteristics for all patients in the mitozolomide phase I/II clinical trial.

Trial Number	Age	Sex	Tumour Type	Previous Treatment	Previous Mitozolamide	Present Treatment Date	Surface Area (m2)	Dose (mg)	Dose (mg/m2)	Route of Administration
MITPO01	58	FEMALE	LUNG	NONE	NO	4/7/85	1.512	150	100.0	PO
MITPO02	55	FEMALE	MELANOMA	SURGERY RADIOTHERAPY CHEMOTHERAPY	NO	22/10/85	1.454	130	89.4	PO
MITPO03	53	FEMALE	OVARY		NO	1/11/85	1.637	140	85.5	PO
MITPO04	51	FEMALE	PANCREAS		NO	27/11/85	1.529	120	78.5	PO
MITPO05	43	MALE	PAROTID		NO	27/11/85	2.066	180	87.1	PO
MITPO06	72	FEMALE	OVARY		NO	14/11/85	1.494	110	73.6	PO
MITPO07	68	FEMALE	LUNG	RADIOTHERAPY	NO	29/11/85	1.596	160	100.3	PO
MITPO08	65	MALE	UNKNOWN		NO	12/12/85	1.631	140	85.8	PO

Appendix IV - continued

Trial Number	Age	Sex	Tumour Type	Previous Treatment	Previous Mitozolamide	Present Treatment Date	Surface Area (m2)	Dose (mg)	Dose (mg/m2)	Route of Administration
MITPO09	69	MALE	MELANOMA		NO	9/1/86	1.768	160	90.5	PO
MITPO10	43	MALE	PAROTID		YES 27/11/85-PO 180mg	8/1/86	2.066	180	87.1	IV
MITPO11	51	FEMALE	PANCREAS		YES 27/11/85-PO 120MG	5/2/86	1.475	120	81.3	IV
MITPO12	48	FEMALE	OVARY	SURGERY CHEMOTHERAPY	NO	13/2/86	1.600	140	87.5	PO
MITPO13	23	MALE	ASTROCYTOMA	RADIOTHERAPY	NO	5/3/86	1.986	180	90.6	PO
MITPO14	69	FEMALE	BREAST	SURGERY RADIOTHERAPY HORMONE THERAPY	NO	19/3/86	1.517	140	92.3	PO
MITPO15	61	FEMALE	OVARY	SURGERY CHEMOTHERAPY	NO	9/4/86	1.800	160	88.9	PO
MITPO16	48	FEMALE	OVARY	SURGERY CHEMOTHERAPY	YES 140MG-PO 13/2/86	26/3/86	1.629	140	85.9	IV

Appendix IV - continued

Trial Number	Age	Sex	Tumour Type	Previous Treatment	Previous Mitozolamide	Present Treatment Date	Surface Area (m2)	Dose (mg)	Dose (mg/m2)	Route of Administration
MITPO17	23	MALE	ASTROCYTOMA	RADIOTHERAPY	YES 180MG-PO 5/3/86	16/4/86	1.986	180	90.6	IV
MITPO19	69	FEMALE	BREAST	SURGERY RADIOTHERAPY HORMONE THERAPY	YES 140MG-PO 19/3/86	30/4/86	1.399	140	100.1	IV
MITPO20	77	FEMALE	BREAST	SURGERY HORMONE THERAPY CHEMOTHERAPY	NO	15/5/86	1.393	130	93.3	PO
MITPO21	23	MALE	ASTROCYTOMA		YES 180MG-PO 5/3/86 180MG-IV 16/4/86	4/6/86	2.005	180	89.8	PO
MITPO22	60	FEMALE	LUNG		NO	2/5/86	1.435	140	97.5	PO
MITPO23	45	FEMALE	MELANOMA		NO	3/6/86	1.690	150	88.8	PO
MITPO24	74	MALE	BLADDER		NO	29/5/86	1.848	170	92.0	PO
MITPO25	38	MALE	LUNG		NO	4/6/86	1.914	170	88.8	PO

Appendix V - Plasma mitozolomide levels for all patients in the phase I/II trial.

Patient Number	Dose (mg)	Dose (mg/m2)	Route of Administration	Infusion Time (hr)	Pharmacokinetic Data													
MITPO01	150	100.0	PO	-	Time after Drug Administration (hr)	0.00	0.50	1.00	1.50	2.00	2.50	3.00	4.00	6.00	8.00				
					Actual Plasma Concentration (mg/L)	0.000	0.332	1.677	2.487	1.887	1.399	1.146	0.719	0.147	0.018				
					Fitted Plasma Concentration (mg/L)	0.000	0.294	1.880	2.168	1.939	1.557	1.178	0.610	0.135	0.027				
MITPO02	130	89.4	PO	-	Time after Drug Administration (hr)	0.00	0.50	1.00	1.50	2.00	2.67	3.00	4.00	6.00	8.00				
					Actual Plasma Concentration (mg/L)	0.000	1.693	2.728	2.493	2.004	1.604	1.396	0.894	0.384	0.251				
					Fitted Plasma Concentration (mg/L)	0.000	1.692	2.735	2.462	2.052	1.575	1.380	0.924	0.414	0.186				
MITPO03	140	85.5	PO	-	Time after Drug Administration (hr)	0.00	0.50	1.00	1.50	2.00	2.50	3.00	4.00	6.00	8.00				
					Actual Plasma Concentration (mg/L)	0.000	0.000	0.327	0.602	0.971	1.114	1.034	1.500	0.875	0.411				
					Fitted Plasma Concentration (mg/L)	0.000	0.000	0.246	0.693	0.974	1.134	1.206	1.186	0.883	0.560				
MITPO04	120	78.5	PO	-	Time after Drug Administration (hr)	0.00	0.27	0.50	0.73	1.00	1.35	1.67	2.05	2.48	3.07	4.27	6.05	8.00	11.97
					Actual Plasma Concentration (mg/L)	0.000	0.243	2.023	6.211	4.316	3.695	2.906	2.034	1.695	1.235	0.697	0.227	0.000	0.000
					Fitted Plasma Concentration (mg/L)	0.000	0.000	2.024	5.823	4.784	3.699	2.923	2.211	1.611	1.044	0.432	0.117	0.000	0.000
MITPO05	180	87.1	PO	-	Time after Drug Administration (hr)	0.00	0.27	0.48	0.77	1.02	1.35	1.67	2.03	2.50	3.05	4.25	6.05	8.00	11.98
					Actual Plasma Concentration (mg/L)	0.000	0.000	0.000	0.403	6.703	6.517	4.886	3.575	3.268	2.485	0.900	0.451	0.000	0.000
					Fitted Plasma Concentration (mg/L)	0.000	0.000	0.000	0.400	6.742	6.200	5.082	4.026	2.969	2.078	0.954	0.297	0.000	0.000
MITPO06	110	73.6	PO	-	Time after Drug Administration (hr)	0.00	0.50	1.00	1.50	2.00	2.50	3.00	4.00	6.00	8.00				
					Actual Plasma Concentration (mg/L)	0.000	1.983	2.338	2.210	1.503	1.130	0.876	0.478	0.099	0.000				
					Fitted Plasma Concentration (mg/L)	0.000	1.975	2.400	2.065	1.596	1.179	0.852	0.434	0.109	0.000				
MITPO07	160	100.3	PO	-	Time after Drug Administration (hr)	0.00	0.58	1.08	1.50	2.00	2.50	3.00	4.00	8.00					
					Actual Plasma Concentration (mg/L)	0.000	0.000	0.000	0.000	1.975	3.210	3.111	1.794	0.247					
					Fitted Plasma Concentration (mg/L)	0.000	0.000	0.000	0.000	1.968	3.259	3.024	1.866	0.162					
MITPO08	140	85.8	PO	-	Time after Drug Administration (hr)	0.00	0.20	0.52	0.83	1.12	1.42	1.67	2.00	2.47	2.98	4.00	5.97	7.98	11.78
					Actual Plasma Concentration (mg/L)	0.000	0.000	0.000	0.969	2.778	2.781	1.991	1.622	1.532	0.882	0.608	0.217	0.000	0.000
					Fitted Plasma Concentration (mg/L)	0.000	0.000	0.000	0.968	2.812	2.529	2.187	1.791	1.346	0.986	0.530	0.160	0.000	0.000

Appendix V - continued

Patient Number	Dose (mg)	Dose (mg/m2)	Route of Administration	Infusion Time (hr)	Pharmacokinetic Data															
MITPO09	160	90.5	PO	-	Time after Drug Administration (hr)	0.00	0.50	1.00	1.50	2.00	2.50	3.00	4.00	6.00	8.00						
					Actual Plasma Concentration (mg/L)	0.834	0.825	1.760	1.862	3.820	3.382	2.032	1.566	0.907	0.449						
					Fitted Plasma Concentration (mg/L)	0.000	0.604	2.033	2.681	2.856	2.761	2.523	1.909	0.891	0.364						
MITPO10	180	87.1	IV	0.55	Time after Drug Administration (hr)	0.00	0.28	0.50	0.57	0.73	1.00	1.23	1.50	1.77	2.00	2.50	2.98	3.98	5.98	8.00	12.10
					Actual Plasma Concentration (mg/L)	0.000	3.892	4.985	7.296	3.842	2.488	2.832	2.116	1.714	1.715	1.290	0.998	0.395	0.000	0.000	0.000
					Fitted Plasma Concentration (mg/L)	0.000	3.441	5.500	5.776	4.857	3.625	2.825	2.108	1.573	1.226	0.713	0.424	0.143	0.000	0.000	0.000
MITPO11	120	81.3	IV	1.12	Time after Drug Administration (hr)	0.00	0.23	0.50	0.77	0.98	1.12	1.30	1.50	1.72	1.97	2.50	2.98	4.03	6.03	8.03	
					Actual Plasma Concentration (mg/L)	0.000	2.800	3.647	3.920	4.931	3.591	2.339	2.516	2.189	1.583	1.475	0.963	0.635	0.000	0.000	
					Fitted Plasma Concentration (mg/L)	0.000	1.637	2.960	3.843	4.321	4.565	3.486	2.583	1.857	1.276	0.577	0.281	0.058	0.000	0.000	
MITPO12	140	87.5	PO	-	Time after Drug Administration (hr)	0.00	0.16	0.77	0.93	1.10	1.32	1.68	1.98	2.48	2.92	3.98	6.03	7.63	11.52		
					Actual Plasma Concentration (mg/L)	0.000	0.000	0.201	0.267	0.313	0.351	0.392	0.672	0.589	0.490	0.333	0.195	0.198	0.000		
					Fitted Plasma Concentration (mg/L)	0.000	0.000	0.163	0.259	0.340	0.416	0.491	0.520	0.523	0.499	0.404	0.230	0.142	0.000		
MITPO13	180	90.6	PO	-	Time after Drug Administration (hr)	0.00	0.23	0.52	0.75	1.00	1.25	1.48	1.77	2.00	2.48	2.98	3.95	6.03	8.00	11.90	
					Actual Plasma Concentration (mg/L)	0.000	1.177	2.839	2.974	2.420	2.660	2.056	2.675	2.538	2.575	1.906	0.972	0.286	0.015	0.000	
					Fitted Plasma Concentration (mg/L)	0.000	1.533	2.252	2.576	2.749	2.790	2.745	2.613	2.471	2.123	1.751	1.128	0.377	0.122	0.000	
MITPO14	140	92.3	PO	-	Time after Drug Administration (hr)	0.00	0.27	0.52	0.77	1.00	1.27	1.48	1.73	1.98	2.48	3.00	4.02	5.98	7.73	11.77	
					Actual Plasma Concentration (mg/L)	0.000	0.593	3.563	4.803	4.226	4.588	3.934	2.976	2.746	1.709	1.289	0.852	0.333	0.264	0.109	
					Fitted Plasma Concentration (mg/L)	0.000	2.362	3.510	4.011	4.105	3.940	3.694	3.332	2.943	2.195	1.549	0.721	0.141	0.030	0.001	
MITPO15	160	88.9	PO	-	Time after Drug Administration (hr)	0.00	0.27	0.50	0.75	0.98	1.25	1.51	1.77	2.00	2.52	3.05	4.08	6.07	7.92	11.80	
					Actual Plasma Concentration (mg/L)	0.000	0.921	2.990	4.533	6.184	5.571	4.644	4.147	3.646	2.872	1.920	1.219	0.578	0.331	0.000	
					Fitted Plasma Concentration (mg/L)	0.000	0.682	3.481	4.903	5.334	5.251	4.866	4.356	3.877	2.869	2.049	1.028	0.261	0.073	0.000	
MITPO16	140	85.9	IV	0.70	Time after Drug Administration (hr)	0.00	0.27	0.45	0.73	1.00	1.27	1.52	1.77	2.02	2.57	3.02	4.15	6.05	7.92	11.92	
					Actual Plasma Concentration (mg/L)	0.141	3.234	4.554	5.648	4.637	3.455	2.528	2.394	1.948	1.674	1.296	0.759	0.318	0.194	0.177	
					Fitted Plasma Concentration (mg/L)	0.000	1.876	3.000	4.347	3.824	3.364	2.988	2.653	2.356	1.815	1.466	0.857	0.348	0.143	0.021	

Appendix V - continued

Patient Number	Dose (mg)	Dose (mg/m2)	Route of Administration	Infusion Time (hr)	Pharmacokinetic Data														
MITPO17	180	90.6	IV	0.73	Time after Drug Administration (hr)	0.00	0.22	0.52	0.75	1.03	1.25	1.52	1.73	2.02	2.50	2.98	4.00	6.00	7.95	11.88
					Actual Plasma Concentration (mg/L)	0.000	1.455	4.319	4.937	3.546	2.775	2.185	2.171	1.830	1.442	0.942	0.555	0.163	0.050	0.000
					Fitted Plasma Concentration (mg/L)	0.000	1.783	3.745	4.800	3.803	3.167	2.530	2.125	1.670	1.120	0.752	0.322	0.061	0.012	0.000
MITPO19	140	100.1	IV	0.52	Time after Drug Administration (hr)	0.00	0.25	0.53	0.75	1.00	1.25	1.53	1.77	2.00	2.50	2.97	4.00	5.98	8.07	11.95
					Actual Plasma Concentration (mg/L)	0.000	4.319	8.880	7.866	7.233	6.872	5.633	4.856	4.248	3.067	2.230	1.489	0.435	0.232	0.000
					Fitted Plasma Concentration (mg/L)	0.000	4.682	9.007	8.054	7.093	6.247	5.418	4.796	4.266	3.309	2.605	1.543	0.564	0.195	0.000
MITPO20	130	93.3	PO	-	Time after Drug Administration (hr)	0.00	0.27	0.50	0.73	1.00	1.28	1.50	1.78	2.00	2.47	3.00	3.98	5.95	7.92	12.05
					Actual Plasma Concentration (mg/L)	0.092	0.083	1.304	2.382	2.318	4.225	3.332	3.712	3.680	3.748	2.750	1.672	0.590	0.258	0.078
					Fitted Plasma Concentration (mg/L)	0.000	1.211	1.968	2.523	2.966	3.239	3.351	3.393	3.366	3.185	2.865	2.182	1.068	0.466	0.000
MITPO21	180	89.8	PO	-	Time after Drug Administration (hr)	0.00	0.23	0.50	0.75	1.00	1.27	1.50	1.77	2.00	2.50	3.02	4.03	6.00	7.95	11.92
					Actual Plasma Concentration (mg/L)	0.000	0.000	0.820	1.717	2.572	3.421	3.756	3.160	3.050	2.734	1.768	1.183	0.496	0.286	0.000
					Fitted Plasma Concentration (mg/L)	0.000	0.000	0.625	2.018	2.818	3.231	3.335	3.269	3.113	2.625	2.072	1.190	0.341	0.090	0.000
MITPO22	140	97.5	PO	-	Time after Drug Administration (hr)	0.00	0.50	1.00	1.50	2.00	2.50	3.08	4.00	6.08	8.08					
					Actual Plasma Concentration (mg/L)	0.147	0.544	1.664	2.451	2.182	1.499	1.039	0.663	0.283	0.162					
					Fitted Plasma Concentration (mg/L)	0.000	0.477	1.935	2.216	2.004	1.633	1.198	0.669	0.145	0.029					
MITPO23	150	88.8	PO	-	Time after Drug Administration (hr)	0.00	0.50	1.00	1.50	2.00	2.50	3.00	4.00	6.00	8.00					
					Actual Plasma Concentration (mg/L)	0.042	0.600	2.323	1.800	1.537	1.262	1.016	0.453	0.186	0.094					
					Fitted Plasma Concentration (mg/L)	0.000	0.600	2.320	1.883	1.492	1.181	0.935	0.586	0.231	0.091					
MITPO24	170	92.0	PO	-	Time after Drug Administration (hr)	0.00	0.50	1.00	1.50	2.00	2.50	3.08	4.00	6.08	8.08					
					Actual Plasma Concentration (mg/L)	0.040	0.624	3.156	2.407	1.951	1.578	1.148	0.386	0.229	0.112					
					Fitted Plasma Concentration (mg/L)	0.000	0.625	3.149	2.502	1.900	1.439	1.090	0.625	0.206	0.158					
MITPO25	170	88.8	PO	-	Time after Drug Administration (hr)	0.00	0.50	1.00	1.50	2.00	2.50	3.00	4.00	6.00	8.00					
					Actual Plasma Concentration (mg/L)	0.094	6.449	3.325	2.143	1.585	1.350	1.050	0.322	0.231	0.138					
					Fitted Plasma Concentration (mg/L)	0.000	3.496	2.912	2.341	1.879	1.508	1.211	0.780	0.324	0.135					

Appendix VI - Pharmacokinetic parameters of mitozolomide for all patients in the phase I/II trial.

Patient Number	Dose (mg)	Dose (mg/m2)	Pharmacokinetic Parameters	Total AUC (mg hr/L)	AUC > 1mg/L (mg hr/L)	AUC > 2mg/L (mg hr/L)	AUC > 4mg/L (mg hr/L)	Peak Plasma Level (mg)
MITPO01	150	100.0	Trapezoidal	6.141	1.700	0.170	0.000	2.487
			Fitted	5.947				2.172
MITPO02	130	89.4	Trapezoidal	8.720	2.960	0.560	0.000	2.716
			Fitted	8.981				2.735
MITPO03	140	85.5	Trapezoidal	6.692	0.740	0.000	0.000	1.486
			Fitted	8.494				1.219
MITPO04	120	78.5	Trapezoidal	9.925	5.000	2.670	0.512	6.497
			Fitted	9.225				6.117
MITPO05	180	87.1	Trapezoidal	13.089	7.850	5.110	1.660	7.102
			Fitted	13.047				6.856
MITPO06	110	73.6	Trapezoidal	6.152	2.070	0.232	0.000	2.274
			Fitted	6.098				2.410
MITPO07	160	100.3	Trapezoidal	9.903	4.240	1.340	0.000	3.127
			Fitted	8.804				3.277
MITPO08	140	85.8	Trapezoidal	5.866	1.760	0.370	0.000	2.796
			Fitted	5.692				2.813

Appendix VI continued

Patient Number	Dose (mg)	Dose (mg/m2)	Pharmacokinetic Parameters	Total AUC (mg hr/L)	AUC > 1mg/L (mg hr/L)	AUC > 2mg/L (mg hr/L)	AUC > 4mg/L (mg hr/L)	Peak Plasma Level (mg)
MITPO09	160	90.5	Trapezoidal	12.168	4.910	1.560	0.000	3.820
			Fitted	12.943				2.857
MITPO10	180	87.1	Trapezoidal	8.278	3.910	2.120	0.460	5.878
			Fitted	7.230				5.903
MITPO11	120	81.3	Trapezoidal	8.616	4.180	2.010	0.740	4.931
			Fitted	6.286				4.565
MITPO12	140	87.5	Trapezoidal	2.595	0.000	0.000	0.000	0.672
			Fitted	2.860				0.527
MITPO13	180	90.6	Trapezoidal	9.899	4.000	1.310	0.000	2.770
			Fitted	10.322				2.791
MITPO14	140	92.3	Trapezoidal	11.781	5.500	3.060	0.330	4.954
			Fitted	10.771				4.107
MITPO15	160	88.9	Trapezoidal	15.847	8.430	5.050	1.240	6.479
			Fitted	13.759				5.359
MITPO16	140	85.9	Trapezoidal	12.037	5.710	3.080	0.680	5.712
			Fitted	10.917				4.410

Appendix VI continued

Patient Number	Dose (mg)	Dose (mg/m2)	Pharmacokinetic Parameters	Total AUC (mg hr/L)	AUC > 1mg/L (mg hr/L)	AUC > 2mg/L (mg hr/L)	AUC > 4mg/L (mg hr/L)	Peak Plasma Level (mg)
MITPO17	180	90.6	Trapezoidal	8.824	4.170	1.970	0.230	4.543
			Fitted	7.819				4.868
MITPO19	140	100.1	Trapezoidal	19.976	13.130	9.190	4.410	8.781
			Fitted	20.282				9.067
MITPO20	130	93.3	Trapezoidal	14.177	7.180	3.380	0.010	3.906
			Fitted	14.006				3.735
MITPO21	180	89.8	Trapezoidal	11.334	4.760	1.920	0.000	3.738
			Fitted	10.332				3.336
MITPO22	140	97.5	Trapezoidal	6.777	1.860	0.240	0.000	2.458
			Fitted	6.305				2.218
MITPO23	150	88.8	Trapezoidal	5.676	1.400	0.040	0.000	2.323
			Fitted	6.122				2.374
MITPO24	170	92.0	Trapezoidal	6.876	2.540	0.250	0.000	3.207
			Fitted	7.278				3.195
MITPO25	170	88.8	Trapezoidal	9.318	4.800	2.640	0.735	6.405
			Fitted	9.646				3.523

Appendix VI continued

Patient Number	Dose (mg)	Dose (mg/m2)	Pharmacokinetic Parameters	Volume Distribution (L)	Clearance (L/hr)	Elimination Half-Life (hr)	Elimination Rate Constant (/hr)	Absorption Half-Life (hr)	Absorption Rate Constant(/hr)	Lag Time (hr)
MITPO01	150	100.0	Trapezoidal	30.793	25.845	0.826	0.839	0.489	1.416	0.468
			Fitted	29.205		0.803	0.864	0.599	1.157	0.448
MITPO02	130	89.4	Trapezoidal	38.620	14.176	1.888	0.367	0.136	5.100	0.357
			Fitted	36.074		1.727	0.401	0.193	3.586	0.312
MITPO03	140	85.5	Trapezoidal	64.805	20.975	2.141	0.324	1.089	0.636	0.788
			Fitted	43.902		1.846	0.375	1.708	0.406	0.794
MITPO04	120	78.5	Trapezoidal	25.606	14.321	1.239	0.559	0.278	2.495	0.249
			Fitted	17.690		0.943	0.735	0.027	26.123	0.486
MITPO05	180	87.1	Trapezoidal	23.821	13.297	1.242	0.558	0.033	20.832	0.767
			Fitted	21.272		1.069	0.649	0.080	8.622	0.764
MITPO06	110	73.6	Trapezoidal	27.161	18.551	1.015	0.683	0.330	2.098	0.097
			Fitted	26.062		1.001	0.692	0.345	2.007	0.110
MITPO07	160	100.3	Trapezoidal	35.541	17.615	1.398	0.496	0.213	3.251	1.809
			Fitted	29.319		1.118	0.620	0.329	2.107	1.766
MITPO08	140	85.8	Trapezoidal	45.274	23.867	1.315	0.527			
			Fitted	40.398		1.138	0.609	0.085	8.192	0.789

Appendix VI continued

Patient Number	Dose (mg)	Dose (mg/m2)	Pharmacokinetic Parameters	Volume Distribution (L)	Clearance (L/hr)	Elimination Half-Life (hr)	Elimination Rate Constant (/hr)	Absorption Half-Life (hr)	Absorption Rate Constant(/hr)	Lag Time (hr)
MITPO09	160	90.5	Trapezoidal	42.966	14.899	1.998	0.347	1.011	0.686	0.220
			Fitted	20.701		1.608	0.597	1.150	0.603	0.359
MITPO10	180	87.1	Trapezoidal	32.808	21.744	1.046	0.663			
			Fitted	22.970		0.640	1.084			
MITPO11	120	81.3	Trapezoidal	22.449	13.636	1.141	0.607	0.201	3.449	0.000
			Fitted	12.733		0.462	1.499			
MITPO12	140	87.5	Trapezoidal	207.387	48.578	2.959	0.234	0.738	0.939	0.356
			Fitted	156.457		2.215	0.313	0.696	0.996	0.561
MITPO13	180	90.6	Trapezoidal	27.534	20.469	0.932	0.743	0.394	1.760	0.112
			Fitted	27.984		1.112	0.623	0.784	0.885	0.000
MITPO14	140	92.3	Trapezoidal	35.363	12.321	1.989	0.348	0.056	12.476	0.000
			Fitted	12.541		0.669	1.036	0.669	1.037	0.000
MITPO15	160	88.9	Trapezoidal	26.052	10.979	1.644	0.421	0.278	2.490	0.204
			Fitted	16.804		1.002	0.692	0.361	1.922	0.204
MITPO16	140	85.9	Trapezoidal	40.178	11.631	2.394	0.290			
			Fitted	27.013		1.460	0.475			

Appendix VI continued

Patient Number	Dose (mg)	Dose (mg/m2)	Pharmacokinetic Parameters	Volume Distribution (L)	Clearance (L/hr)	Elimination Half-Life (hr)	Elimination Rate Constant (/hr)	Absorption Half-Life (hr)	Absorption Rate Constant(/hr)	Lag Time (hr)
MITPO17	180	90.6	Trapezoidal	35.416	21.248	1.155	0.600	0.047	14.682	0.197
			Fitted	27.686		0.834	0.831			
MITPO19	140	100.1	Trapezoidal	13.955	7.008	1.380	0.502			
			Fitted	13.579		1.364	0.508			
MITPO20	130	93.3	Trapezoidal	26.573	10.513	1.752	0.396	0.511	1.355	0.257
			Fitted	12.792		0.955	0.726	0.957	0.724	0.316
MITPO21	180	89.8	Trapezoidal	43.247	17.726	1.691	0.410	0.465	1.490	0.347
			Fitted	24.449		0.973	0.713	0.620	1.118	0.418
MITPO22	140	97.5	Trapezoidal	61.177	22.745	1.864	0.372	0.226	3.061	0.410
			Fitted	23.183		0.724	0.958	0.726	0.954	0.410
MITPO23	150	88.8	Trapezoidal	52.334	25.144	1.442	0.481	0.082	8.456	0.472
			Fitted	52.482		1.485	0.467	0.093	7.416	0.468
MITPO24	170	92.0	Trapezoidal	52.859	24.726	1.482	0.468			
			Fitted	42.009		1.247	0.556	0.111	6.245	0.473
MITPO25	170	88.8	Trapezoidal	43.269	18.245	1.644	0.422			
			Fitted	40.097		1.577	0.440	0.099	7.007	0.001

Appendix VII - Haematological toxicity for all patients in the mitozolomide phase I/II clinical trial.

Patient Number	Dose (mg)	Dose (mg/m2)	Haematological Toxicity Values ($\times 10^9$/L)	Initial	Time to Nadir (days)	Nadir	% Fall from Initial Value
MITPO01	150	100.0	Platelets	620	28	115.0	81.5
			White Blood Cells	38.2	14	8.2	78.5
MITPO02	130	89.4	Platelets	400	22	90.0	77.5
			White Blood Cells	7.1	22	3.9	45.1
MITPO03	140	85.5	Platelets	365	29	70.0	80.8
			White Blood Cells	7.7	36	5.4	29.9
MITPO04	120	78.5	Platelets	322	25	25.0	92.2
			White Blood Cells	7.2	43	2.7	62.5
MITPO05	180	87.1	Platelets				
			White Blood Cells				
MITPO06	110	73.6	Platelets	261	26	107.0	59
			White Blood Cells	5.4	26	4.9	14.8
MITPO07	160	100.3	Platelets	446	21	66.0	85.2
			White Blood Cells	7.1	35	1.0	85.9
MITPO08	140	85.8	Platelets				
			White Blood Cells				

Appendix VII continued

Patient Number	Dose (mg)	Dose (mg/m2)	Haematological Toxicity Values ($\times 10^9$/L)	Initial	Time to Nadir (days)	Nadir	% Fall from Initial Value
MITPO09	160	90.5	Platelets	230	20	79.0	65.6
			White Blood Cells	6.3	41	2.3	63.5
MITPO10	180	87.1	Platelets				
			White Blood Cells				
MITPO11	120	81.3	Platelets				
			White Blood Cells				
MITPO12	140	87.5	Platelets	174	30	132.0	24.1
			White Blood Cells				
MITPO13	180	90.6	Platelets	285	24	98.9	65.3
			White Blood Cells	4.72	24	3.3	30.9
MITPO14	140	92.3	Platelets				
			White Blood Cells				
MITPO15	160	88.9	Platelets	308	24	19.0	93.8
			White Blood Cells	4.43	42	1.6	64.6
MITPO16	140	85.9	Platelets	193	23	13.0	93.3
			White Blood Cells	4.81	37	0.7	86.3

Appendix VII - continued

Patient Number	Dose (mg)	Dose (mg/m2)	Haematological Toxicity Values ($x 10^9/L$)	Initial	Time to Nadir (days)	Nadir	% Fall from Initial Value
MITPO17	180	90.6	Platelets	439	30	226.0	48.5
			White Blood Cells	4.88	23	4.0	18.2
MITPO19	140	100.1	Platelets	739	21	60.0	91.9
			White Blood Cells	17.79	21	8.7	50.9
MITPO20	130	93.3	Platelets	220	30	22.0	90
			White Blood Cells	6.43	43	1.6	75.1
MITPO21	180	89.8	Platelets				
			White Blood Cells				
MITPO22	140	97.5	Platelets	204	20	12.0	94.1
			White Blood Cells	7.6	32	2.1	72.1
MITPO23	150	88.8	Platelets	1163	28	28.0	97.6
			White Blood Cells	15.6	39	3.1	80.1
MITPO24	170	92.0	Platelets	492	28	105.0	78.7
			White Blood Cells	10.3	35	9.4	8.7
MITPO25	170	88.8	Platelets	426	26	30.0	93
			White Blood Cells	8.2	40	2.20	73.2

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