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Patient Acceptability and Practical Implications of Pharmacokinetic Studies in Patients With Advanced Cancer

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We have studied the practical implications and acceptability to patients of pharmacokinetic studies in 34 women receiving anthracyclines for advanced breast cancer. The following parameters were recorded: age, ECOG performance status, psychological state (Rotterdam Symptom Checklist), cytotoxic drug and dose, number of venepunctures for treatment and sampling, and time when the sampling cannula was removed. Immediately after finishing pharmacokinetic sampling, patients completed a questionnaire which revealed that (i) all patients understood sampling was for research, (ii) 35% of patients experienced problems with sampling, (iii) benefits from participation were perceived by 56% of patients. Of 20 patients later questioned after completion of their treatment course, 40% recalled difficulties with blood sampling. Factors identifying in advance those patients who tolerate pharmacokinetic studies poorly were not identified but the number of venepunctures should be minimised. Patients may also perceive benefits from 'non-therapeutic' research.
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INTRODUCTION

BY THEIR very nature, cytotoxic drugs cannot be studied in healthy volunteers, and species differences in drug distribution and metabolism limit the relevance of animal studies. Pharmacokinetic studies have an important place in phase I [1, 2] and phase II [3] trials of cytotoxic agents. In clinical practice the optimal use of carboplatin [4] and etoposide [5] has been influenced by the results of pharmacokinetic studies. These studies are, therefore, essential for the optimal development and use of cytotoxic drugs.

The ethical and practical issues raised by clinical pharmacokinetic studies were discussed by Svensson [6]. These consider-

ations are particularly important in patients with advanced cancer who are often physically unwell and may have clinically significant depression or anxiety [7]. Informed consent is a prerequisite of such studies. Nevertheless, the balance of risk and benefit for the patient remains a major consideration, especially when no direct benefit to an individual patient is anticipated, as is the case for most pharmacokinetic studies. For example, the majority of such studies require blood sampling at regular intervals following treatment. Although venepuncture is generally safe, it carries the risk of pain, phlebitis or rarely, even nerve damage [8].

We have investigated the acceptability and practical implications of pharmacokinetic studies for patients with advanced breast cancer. Firstly, the practical details of each pharmacokinetic study were recorded. Secondly, we assessed the understanding by the patients of their participation in the pharmacokinetic study in order to audit the process of consent. Thirdly, we investigated the problems and benefits which patients expressed immediately following completion of pharmacokinetic sampling and analysed the factors underlying these problems or benefits. Finally, the patient's perception of problems with pharmacokinetic sampling was assessed again upon completion of their treatment course.

PATIENTS AND METHODS

All patients with advanced breast cancer who were eligible for treatment with epirubicin [9] or iododoxorubicin [10] given as single agents were approached to take part in pharmacokinetic studies. Iododoxorubicin is a new anthracycline, structurally closely related to doxorubicin, which is currently under phase II evaluation [11]. The pharmacokinetics of both drugs were studied during the first cycle of treatment.

Details of the treatment programme, including its palliative intent, the drug to be used and its likely side-effects were given to each patient by a consultant. In a separate discussion with the patient, another clinician, who supervised the pharmacokinetic studies, described in detail what the blood sampling would entail. It was emphasised that the blood samples were for research, that having the samples taken would not help the patient directly, that they might have to spend an additional night in hospital, and that if they did not wish to have the blood taken or wished to discontinue sampling this would not affect their treatment. A written information sheet was also provided which was left with the patient and written consent sought, in most cases after the patient had reflected overnight.

The protocol for the pharmacokinetic study was as follows. A treatment cannula was sited by a doctor and removed following administration of the chemotherapy as a slow bolus injection. A second cannula was placed by the doctor and 13 blood samples collected by trained research assistants over the next 48 h. A total of six blood samples were taken during the first hour following treatment, with a further four taken in the first 24 h and the remaining three samples taken before the cannula was removed 48 h following treatment. When the sampling cannula was taken out before 48 h further samples were taken by venepuncture. The number of cannulations and venepunctures required for both chemotherapy and sampling, the number of blood samples obtained and by whom they were taken, as well as when and why the sampling cannula was removed were all recorded.

The questionnaire shown in the Appendix was designed to assess the patients' understanding of their participation in the pharmacokinetic study, and to identify and grade any problems or benefits they felt were associated with the study. After completion of blood sampling and removal of the cannula, the questionnaire was handed to the patient. At the same time, a separate assessment of the difficulty experienced by the patient with the sampling was made by a member of the sampling team. This was graded on a four-point scale of severity of difficulty similar to that completed by the patient.

As part of a separate study evaluating quality of life in patients receiving first-line chemotherapy for advanced breast cancer, the majority of patients completed a Rotterdam Symptom Checklist (RSCL) before treatment [12]. This self rating quality of life questionnaire includes a 7-item psychological subscale which assesses worrying, feeling irritable, feeling nervous, feeling depressed, feeling anxious, feeling tense, and feeling despondent about the future. Each item is scored between 0 (not at all) and 3 (very much). Upon completion of their treatment course, these patients completed a further RSCL and were interviewed regarding quality of life during treatment. As part of this interview patients were asked 'Did the extra blood tests you had taken with your first course of treatment cause you any problems?' The degree of difficulty was scored on a 4-point scale and patients were encouraged to describe any problems which were summarised by the interviewer.

Since treatment toxicity during the 48-h sampling period may influence the tolerability of pharmacokinetics, side-effects which occurred during this period were recorded according to WHO criteria [13]. Subsequent response to chemotherapy was evaluated according to UICC criteria [14].

The effects of discrete variables and continuous variables on the problems or difficulties with pharmacokinetics sampling were evaluated using Fisher's exact test and the Mann–Whitney test, respectively. A multivariate logistic regression analysis was used to investigate which factors independently predicted for problems with the pharmacokinetic sampling. Kappa statistics [15] quantitate the level of agreement when two sets of observations are compared, and the extent by which such agreement is greater than that expected by chance. In this study, Kappa statistics were used firstly to compare observer and patient ratings of problems, and secondly to compare the patient's early and late perceptions of problems with sampling.

RESULTS

Over a 12-month period 35 patients with advanced breast cancer were approached regarding treatment on chemotherapy protocols which included pharmacokinetic studies. 1 patient with poor venous access could not be sampled. The characteristics of the remaining 34 patients and details of their treatments are given in Table 1.

All patients agreed to have pharmacokinetic blood samples taken. The practical aspects of their treatment and pharmacokinetic sampling are shown in Table 2. Nearly half the patients required a single venepuncture for administration of chemotherapy and only 1 venepuncture for all pharmacokinetic blood samples (15/34 = 44%). Patients supervised by a less experienced clinician were subject to a greater number of venepunctures than those managed by more experienced staff

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Table 1. Patient and treatment characteristics

Number of patients	34
Median age (range)	57 years (35–71)
ECOG performance score	
0	6
1	19
2	6
3	3
4	0
Median RSCL psychological subscore (range)*	8.5 (0–20)
No of disease sites:	
1	9
2	10
3	6
> 3	9
Previous chemotherapy	
Adjuvant	4
Locally advanced	2
Metastatic	1
Current chemotherapy	
Epirubicin	
12.5–75 mg/m^2	17
90–120 mg/m^2	3
Iododoxorubicin	
80 mg/m^2	14

*30 patients completed RSCL before treatment.

($P < 0.05$). 3 patients developed local phlebitis related to the sampling cannula, of whom 1 needed antibiotics. There were no other local complications attributable to sampling. The total volume of blood taken from each patient was 120–160 ml. The 34 women spent a total of 19 additional nights (mean 0.56, range 0–2) in hospital as a result of sampling.

Table 2. Practical aspects of treatment and pharmacokinetic study

	Number	
No. of chemotherapy venepunctures		
1	28	(82%)
2	2	(6%)
3	3	(9%)
4	1	(3%)
No. of sampling venepunctures		
1	16	(47%)
2 or 3	5	(15%)
4–12	13	(38%)
Median no. of samples (range)	12 (10–14)	
Samples taken by		
Pharmacokinetic team*	321	(78%)
Others	92	(22%)
Nausea and vomiting at < 48 h† (WHO grade)		
Grade 0	23	
1	4	
2	4	
3	2	
4	1	

*Clinician responsible for pharmacokinetics and trained research assistants. †2 patients had other toxicities. 1 had anthracycline extravasation with pain and erythema but no ulceration; a second patient was drowsy due to antiemetics.

Immediate post study assessment (Appendix)

Question 1. All 34 patients understood that the sampling was for research purposes. One woman also stated that it was to help with her treatment.

Question 2. The majority of patients (22/34 = 65%) reported no problems with blood sampling. 12 patients (35%) had problems associated with pharmacokinetics (8 slight, 3 moderate and 1 with considerable problems). 2 patients recounted 'difficult veins', 3 had 'uncomfortable or painful cannulae', and 7 reported that the 'needle stopped working'. These patient assessments were compared with the evaluation made by the observer doing the blood sampling. There was significant agreement between observer and patient for both the presence of problems ($K = 0.57, P < 0.001$) and the severity of problems ($K = 0.31$, $P = 0.05$). However, 3 patients who did not themselves describe problems with the blood sampling were perceived as having 'slight' problems by the observer. The 7 patients whom the observer considered to have moderate or considerable difficulties were all given the chance to stop the sampling; this offer was accepted by only 1 patient.

In the multivariate logistic regression analysis the only factor which predicted for problems with blood sampling was the number of venepunctures required for blood sampling ($P = 0.0017$). Early treatment-related toxicity, drug and dose administered, ECOG performance status, the age of the patient and the score on the RSCL psychological subscale did not carry independent predictive capacity (all P values > 0.05).

Question 3. A total of 19 (56%) patients reported benefits from the pharmacokinetic sampling (11 some and 8 a lot of benefit). The benefits experienced were described by 16 patients. 12 reported that sampling might help them or others in the future; 4 women felt the sampling had provided them with extra support. Benefits were reported with equal frequency by patients who also expressed problems as by those who did not (7/12 and 12/22, respectively; $P = 1.0$). There was no significant relationship between reported benefits and age, ECOG performance score, RSCL psychological subscale score, number of treatment or sampling venepunctures, cannula longevity, treatment toxicity, chemotherapy drug or dose (all P values > 0.05).

Late assessment

20 of the 34 patients were questioned about problems with the pharmacokinetic blood sampling upon completion of the treatment programme, median of 18 weeks (range 6–23) after sampling. The incidence of problems among these 20 patients at the immediate post sampling assessment was similar to that for the whole group of 34 women ($P = 0.62$, McNemar's test). 14 patients did not undergo a late assessment since they did not meet the criteria for a second interview as part of a separate study.

A total of 8 of the 20 patients questioned (40%) described difficulties with the pharmacokinetic sampling at the late assessment (2 slight, 1 moderate and 5 considerable). One woman, who had experienced considerable problems, voiced concern at having spent an additional night in hospital although she would have remained in hospital regardless of pharmacokinetic sampling because of scheduled clinical investigations. Of the remaining 7 women with problems, 4 expressed difficulties related to the cannulae and 3 expressed a general regret at having had the samples taken. There was no relationship between response to treatment and perception of problems at the later assessment

($P = 0.6$). Neither the early nor the late RSCL psychological subscale scores predicted for problems at the late assessment ($P = 0.12$ and $P = 0.85$, respectively).

The problems described by the patients immediately after sampling and at this later assessment were compared using Kappa statistics. There was a significant level of agreement ($K = 0.57, P = 0.003$) regarding whether or not problems were described on both occasions. However, when the severity of problems experienced was compared, the level of agreement between the early and late perceptions was not significant ($K = 0.36$, $P = 0.07$). 2 patients described their problems as greater on the initial than on the late questionnaire; 5 women described their problems as worse when questioned later.

DISCUSSION

Clinical pharmacokinetic studies are important in the development of new cytotoxic agents but they depend on the participation of patients who in most cases will not benefit from having taken part. Pharmacokinetic studies raise important ethical and practical questions. It is essential that the patient should understand the reasons for blood sampling. Pharmacokinetic studies should be designed so as to provide useful information and be acceptable to the patient. It would also be valuable to identify in advance those patients most likely to experience problems with sampling so they may be spared unnecessary distress. This prospective study into patients perceptions and the practicalities of such studies addressed these questions.

In the current study consent was obtained according to the guidelines laid down in the Declaration of Helsinki [16] and by the Royal College of Physicians [17]. All patients indicated on the questionnaire performed shortly after the completion of pharmacokinetic sampling that they understood the sampling was for research and not therapeutic purposes. This is encouraging since Cassileth *et al.* [18] showed that less than two thirds of cancer patients who signed consent forms subsequently understood the nature and aims of their treatment. Lynoe *et al.* [19] studied the quality of information given to women undergoing laparoscopy as a research procedure. They concluded that deficiencies in patients' understanding primarily reflected variations in the information given to them. Obtaining informed consent in the current study did not lead to refusal to participate, emphasising that the requirement for informed consent is not an obstacle to pharmacokinetic studies.

On completion of the pharmacokinetic sampling one third of the patients reported difficulties with the sampling. The pharmacokinetic samplers were effective at identifying these patients. The possibility of discontinuing sampling where problems are identified by the sampler but not by the patients, should be considered. However, in the current study this would also have led to the unnecessary termination of sampling in 3 women who themselves at no point reported difficulties.

All patients who described problems at the immediate post study assessment cited difficulties with the cannula. This was underlined by the correlation between the problems experienced and the number of venepunctures. One of the recognised drawbacks of most pharmacokinetic studies is the need for repeated blood sampling. The possibility of damaging a vein is particularly important since it may not be possible to use that vein for future treatments [20]. We aimed to use only one venepuncture for sampling, in addition to the chemotherapy needle, but in 53% of patients this was not possible. Experienced staff should conduct these studies, and the number of blood samples taken should be limited wherever possible [21]. The 'life' of cannulae may be prolonged by the use of heparin–steroid infusions or local application of glyceryl trinitrate [22]. Although only 20 patients were questioned, it is nevertheless disappointing that at the late assessment 5 patients perceived problems with the pharmacokinetics as being worse than they had at the end of sampling. Their comments, however, related to general regret at having participated or spending additional time in hospital and not to problems with venepunctures.

This study has not enabled us to identify in advance those patients who do not tolerate pharmacokinetic sampling. However, there is no evidence in this study to suggest that elderly patients, those with a poor performance status or a high RSCL psychological subscale score should not be approached about participation in pharmacokinetic studies.

Interestingly, the current study has shown that many patients perceived benefits from participating in the pharmacokinetic sampling even though they understood it was not going to help them. This is important because a primary ethical concern with 'non-therapeutic' research is that the patient derives no direct benefit. Under those circumstances the risks, albeit small [23], of participating in such studies are inevitably considered to outweigh the benefits. Our findings suggest that this may be a misconception and that there may be benefits from 'non-therapeutic' studies which should be balanced against the risks. A study from the U.S.A. investigated the attitudes of cancer patients and other volunteers to clinical trials [24]. They showed that a desire to help other patients is a significant motive for participation in clinical trials. Similarly, a desire to contribute to medical progress was a motive for many patients in their decision to take part in a phase I study [25]. Taken with the findings in the current study this suggests a degree of altruism in a patient's decision to participate in clinical trials.

In conclusion, this study has confirmed that patients will give informed consent to participate in 'non-therapeutic' clinical pharmacokinetic studies. The majority of patients experience no problems with blood sampling and it is not possible to identify in advance those patients who were likely to have difficulties. Where problems occur they are largely related to excessive venepunctures which pharmacokinetics studies should be designed to minimise. Importantly, half the patients may feel they benefitted from participation in 'non-therapeutic' pharmacokinetic sampling.

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APPENDIX

Immediate post study assessment questionnaire

We are interested to know what you felt about having your blood samples taken to measure the chemotherapy drug in your blood. Please circle your response to each question.

1. Why do you think the blood sampling was done?

   A To help with my treatment
   B For research and to help other patients in the future
   C Don't know
   D Other reasons (please specify below):

   _____

2. Did you have any problems with the blood sampling?

   A None
   B Slight
   C Moderate
   D Considerate

   Please describe any problems:

   _____

   _____

   _____

3. Did you feel there was any benefit for you in having these samples taken?

   A None
   B Some
   C A lot

   Please describe any benefits:

   _____

   _____

   _____