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Patient Treatment Preference in Advanced Breast Cancer: a Randomized Cross-over Study of Doxorubicin and Mitozantrone

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Abstract—*Twenty-two patients with advanced breast cancer participated in a randomized cross-over study of one cycle each of doxorubicin followed 3 weeks later by mitozantrone or vice versa. Before further treatment, patients selected which drug they wished to continue. Of 18 patients completing the study, 13 chose to continue mitozantrone, 2 doxorubicin and 3 had no preference ($P = 0.007$).*

Patients were told to assume similar efficacy of the two drugs and drug preference was based primarily on side-effects. Patient self-assessment of quality of life and physician assigned toxicity scores both indicated that nausea and vomiting, appetite and alopecia were significantly worse following doxorubicin than after mitozantrone. Except for alopecia, no significant period or carry-over effects were noted although the power of the study to detect such interactions was low. This study design may prove useful in enabling patients to select their preference between two treatments of similar efficacy.

INTRODUCTION

METASTATIC breast cancer is not curable with currently available chemotherapy [1]. Recent interest in the management of advanced breast cancer has, therefore, focussed on the side-effects of chemotherapy and their impact on patients' "quality of life".

Doxorubicin is frequently used to treat patients with advanced breast cancer. Although the acute dose-limiting toxicity is myelosuppression, it also causes alopecia, nausea, vomiting and stomatitis, and cardiomyopathy is associated with high cumulative dosage. Mitozantrone, an anthracenedione, has structural similarities to doxorubicin. Early phase II studies of this drug demonstrated activity in advanced breast cancer and suggested that some side-effects, especially alopecia and nausea and vomiting, were less frequent and less severe than usually seen with doxorubicin [2]. Large randomized phase II studies comparing doxorubicin and mitozantrone in advanced breast cancer are in progress. Preliminary results from these studies have not shown statistically significant differences in the antitumour activity of the two drugs, but demonstrate a lower incidence of alopecia, nausea and vomiting and, possibly, stomatitis with mitozantrone [3, 4].

We have assessed patient preference for doxorubicin or mitozantrone in advanced breast cancer using a randomized, cross-over study design [5]. No attempt has been made to compare the efficacy of the two drugs in inducing tumour response. We exposed patients to each drug in random order. Patients were told to assume that both drugs had similar antitumour activity and asked to choose which drug they wished to continue.

MATERIALS AND METHODS

Between June 1984 and August 1985, 22 female patients requiring chemotherapy for advanced breast cancer were entered into the study. Ages at entry ranged from 33–68 years (median 54 years). Eleven had received chemotherapy previously (8 adjuvant, 3 for advanced disease), 8 prior radiotherapy, but 5 were previously untreated. Patients were ineligible if they had received either of the trial drugs, had an elevated bilirubin, had an ECOG performance status greater than 2 or if English was not their

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primary language. The nature of the study and its objectives were fully explained to patients and each gave written informed consent before entering the study. The consent form stated that the two drugs were thought to have similar antitumour activity and that patients would be asked which drug they preferred.

Patients were stratified to one of two dosage schedules according to toxicity experienced during prior chemotherapy or radiotherapy. Seven patients, who had poor tolerance to prior chemotherapy, or who were > 65 years or had a low pre-treatment white cell count (WBC) (3–4 × 10^9/l.) were classified as "poor risk" and received 50 mg/m^2 of doxorubicin and 12 mg/m^2 of mitozantrone. The remaining 15 patients were classified as "good risk" and received 60 mg/m^2 of doxorubicin and 14 mg/m^2 of mitozantrone, respectively. Patients were randomized to receive doxorubicin or mitozantrone first and then the other drug for their second treatment 3 weeks later. Twelve patients (8 "good risk") received doxorubicin first and 10 (7 "good risk") received mitozantrone first. At the time for the third treatment, patients were asked to select which drug they wished to continue. Any not expressing a preference continued the drug they had received second. Treatment then proceeded for a further six cycles unless unacceptable toxicity or disease progression occurred. Side-effects were recorded and graded [6] by the patient's physician throughout the study. During the study all patients were given metoclopramide tablets as antiemetic treatment and the number of tablets used was recorded.

Prior to each of the first three treatments and 48 hr after each of the first two treatments, patients completed a "quality of life" questionnaire. This was similar to questionnaires we have used previously [7] and consisted of six linear analogue self-assessment (LASA) scales measuring physical well-being, mood, pain, nausea and vomiting, appetite and overall quality of life. In addition to the above, at the time for the third treatment, patients completed a preference questionnaire which asked them which drug they preferred and the reasons for their choice. They were also asked to list and grade the side-effects from each treatment and complete additional LASA scales comparing nausea and vomiting, loss of hair and tiredness experienced with each treatment.

STATISTICAL ANALYSIS

Patient drug preference was the primary endpoint of the study and was analysed using McNemar's test [8]. LASA scores were measured in cm from the left end of the line, which corresponded to the highest possible quality of life.

In analysing this cross-over design, treatment effects may be confounded by changes in patient outcomes over time (period effects) or by the sequence of drug administration (carry-over effects). Treatment effects, period effects and carry-over effects were searched for using parametric methods as described by Hills and Armitage [8]. No adjustment of P-values was made for multiple tests. Group comparisons, based on first treatment received, were analysed using an exact Wilcoxon rank sum test [9].

RESULTS

Drug preference

Patient preferences for doxorubicin or mitozantrone are shown in Table 1. Four of the 22 patients were not assessable for drug preference: one patient was withdrawn after the first treatment for urgent radiotherapy; one failed to complete the preference questionnaire and two refused the second drug because the first had not caused alopecia (both had received mitozantrone). Of the remaining 18 patients, 13 preferred mitozantrone, 2 chose to continue doxorubicin and 3 had no preference ($P = 0.007$).

Reasons for drug selection are also shown in Table 1. All patients preferring mitozantrone included fewer or less severe side-effects as a reason. The three patients who expressed no preference all believed that the choice of drug should be made by their physician. One patient who preferred doxorubicin cited fewer and less severe side-effects and also "feeling better".

Thirteen patients noted that side-effects were worse with doxorubicin and all chose to continue mitozantrone. Two thought side-effects were worse with mitozantrone: one of these chose to continue doxorubicin but the other had no preference. Three thought the drugs possessed equal side-effects; one of these chose doxorubicin but two had no preference.

Although this study was not designed to compare the antitumour activity of the drugs, response data are included in Table 1 because of their possible influence on drug selection. After the first two treatments, partial response (PR) was recorded in 5 patients, stable disease in 15 and progression in two [6]. However, because of the cross-over design of the study it was only possible to ascribe response to a particular drug if tumour response was observed after the first treatment. Following the first cycle PR was documented in two patients and a minor response in skin in a third patient.

One of these three patients, who received mitozantrone first experienced no side-effects and refused to cross over to doxorubicin and, thus, was not eligible for preference. The other two crossed over from doxorubicin to mitozantrone and went on to

Table 1. Doxorubicin–mitozantrone preferences

Patient No.	Sequence* (1st drug)	Response†	Worse side effects*	Reasons for preference‡
Patients preferring mitozantrone (13)§				
1	DOX	SD	DOX	A
3	DOX	SD	DOX	A B
7	MIT	SD	DOX	A
9	DOX	SD‖	DOX	A
11	MIT	SD	DOX	A B
14	DOX	SD	DOX	A B C
16	MIT	SD	DOX	A C
17	DOX	PR¶	DOX	A B
18	DOX	SD	DOX	A B C
19	DOX	SD	DOX	A B C
20	DOX	SD	DOX	A
21	MIT	PR	DOX	A B C
22	MIT	PR	DOX	A B
Patients expressing no preference (3)				
4	MIT	PR	Equal	—
8	DOX	SD	MIT	—
13	DOX	SD	Equal	—
Patients preferring doxorubicin (2)				
2	DOX	SD	Equal	B
10	MIT	PD	MIT	A
Patients not assessable for preference (4)				
5	DOX	SD	Lost to follow up	
6	MIT	SD	Refused 2nd drug (DOX)	
12	MIT	PD	Given radiotherapy after first drug	
15	MIT	PR¶	Refused 2nd drug (DOX)	

*MIT—mitozantrone; DOX—doxorubicin.
†Objective response after two treatments.
‡A—Fewer/less severe side effects; B—feeling better with treatment; C—treatment better/more effective.
§P = 0.007; McNemar's test.
‖Minor response (skin) after 1st drug.
¶Partial response after 1st drug.

indicate a preference for mitozantrone on the basis of less toxicity.

Quality of life assessments

Data from the LASA scales of the 18 patients assessable for preference were expressed as differences between the LASA scores following doxorubicin and mitozantrone for each patient. Data were incomplete from four patients at 48 hr following chemotherapy. Among the remaining 14 patients, scores after doxorubicin were significantly worse for nausea and vomiting ($P < 0.01$) and appetite ($P < 0.01$). LASA scores recorded 3 weeks after each treatment were available for analysis from all 18 patients, but no statistically significant differences between the two treatments were observed for any endpoint. Throughout these analyses, no significant period or carry-over effects were detected.

LASA scales from the preference questionnaire given on completion of both cycles of treatment indicated a significant treatment effect for nausea and vomiting ($P < 0.05$) and hair loss ($P < 0.04$) which were worse following doxorubicin. Although a significant period effect was detected for hair loss [worse in the second period ($P < 0.05$)], no other significant period or carry-over effects were detected.

The questionnaire also asked patients to list and grade side-effects they experienced. Most frequently listed were: nausea (doxorubicin 72%, mitozantrone 61%), vomiting (doxorubicin 50%, mitozantrone 22%), hair loss (doxorubicin 69%, mitozantrone 31%) and sore mouth (doxorubicin 39%, mitozantrone 22%). Side-effects tended to be more severe following doxorubicin. Although nausea and vomiting were worse after doxorubicin, the numbers of metoclopramide tablets used by patients were very similar for each drug.

Table 2. Physician assessed toxicity

Toxicity	*n*	Drug*	Toxicity grade (WHO) 0	1	2	3	*P*-value†
Nausea/ vomiting	19	DOX:	2	8	1	8	0.005
		MIT:	6	6	5	2	
Alopecia	17‡	DOX:	2	7	5	3	NA§
		MIT:	3	4	7	3	
Stomatitis	19	DOX:	12	5	2	0	NS
		MIT:	15	3	1	0	
Diarrhoea	19	DOX:	17	0	2	0	NS
		MIT:	19	0	0	0	

*DOX—doxorubicin; MIT—mitozantrone.
†Analysis using cross-over design; NS—not significant: $P > 0.05$.
‡Two patients inevaluable because of pre-existing alopecia.
§NA—Not applicable (significant carry-over effect).

Physicians' toxicity assessment

Results of the physicians' toxicity scores collected after both treatments were grouped according to drug received and are summarized in Table 2. Nineteen patients (including one who failed to complete the preference questionnaire) were evaluable although hair loss could not be assessed in two patients because of pre-existing alopecia. Analysis utilizing the cross-over design demonstrated that nausea and vomiting were significantly worse following doxorubicin ($P < 0.005$), but no significant differences for other toxicities were noted. Haematological toxicities were very similar for both drugs and were consistent with the selection of equimyelotoxic drug doses. A significant carry-over effect for alopecia precluded a within patient comparison of treatments for this toxicity. Therefore, a group comparison of the first treatment for all 22 patients was undertaken and showed that alopecia was significantly worse after doxorubicin ($P < 0.01$).

DISCUSSION

This cross-over study demonstrated that a significant majority of patients with advanced breast cancer, after experiencing both drugs, preferred mitozantrone to doxorubicin as continuing treatment for their disease. Mitozantrone caused significantly less nausea and vomiting and alopecia than doxorubicin. Patients' reasons for preference were based primarily on less side-effects from mitozantrone, given the assumption that the two drugs had similar antitumour activity. The preference results are based on only 18 of the 22 patients, but 2 of the 4 patients excluded refused the second drug (doxorubicin) because of lack of side-effects of the first.

The use of this study design in cancer therapy trials is novel and allows patients to play an active role in decision making about their future therapy. It is similar to the randomized trial design for individual patients [10, 11], but differs in that antitumour activity cannot be compared. Analysis of a cross-over design may be confounded by carry-over effects. Such an effect was demonstrated for alopecia in our study. Furthermore, patients' perception of side-effects may be modified by whether they achieve a symptomatic response from the treatment. The design of the current study is valid only if the treatments possess similar antitumour activity as appeared to be the case at the inception of this study. More recent data suggest that the response rate to mitozantrone as a single agent in advanced breast cancer may be somewhat less than that for doxorubicin [12, 13]. However, it should be noted that even though one of these studies included a total of 172 evaluable patients [12], neither showed a statistically significant difference in response rates for the two drugs and further randomized studies will be necessary to establish their comparative efficacy. Nevertheless, we suspect that the response rate to mitozantrone in advanced breast cancer is likely to be lower than for doxorubicin and we are currently exploring research methods which extend the basic cross-over design so that patients can select their preferred drug when choosing between treatments which may differ in both antitumour activity and side-effects.

Attempts to incorporate patient preferences into clinical decisions about cancer treatment have been made previously [14, 15]. These studies attempted to elicit individual preferences as to how much importance the various goals of treatment should be given. Nevertheless, these and other examples are limited by the fact that that patients faced with the decision of selecting chemotherapy usually have no first hand experience of the side-effects of the treatment on which to base their decision. The present study gave patients the opportunity to select their own cytotoxic chemotherapy after experiencing each of the two drugs. As the majority of

cytotoxic chemotherapy is administered with palliative intent, we believe that similar studies of single agents or combination regimens could be attempted in other solid tumours.

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