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Short communication

A randomised trial of tamoxifen versus tamoxifen with aminoglutethimide in post-menopausal women with advanced breast cancer

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Summary. *Sixty-six post-menopausal women with metastatic breast cancer were randomised to receive tamoxifen or tamoxifen with aminoglutethimide. The women in the tamoxifen group were virtually free of toxicity, whilst 45% of patients in the aminoglutethimide group had toxicity and 13% discontinued the drug because of this. Responses were seen in 19% of patients receiving tamoxifen alone and 23% of those receiving both drugs. There is no indication that the increased toxicity seen with the addition of aminoglutethimide to tamoxifen in this situation is justified by an increased response rate.*

Introduction

Advanced breast cancer has long been known to respond to a variety of hormonal manipulations. The anti-oestrogen tamoxifen [5] and the aromatase inhibitor aminoglutethimide [2] have both seen shown to induce responses in advanced breast cancer, by differing modes of action. Up to 20% of patients primarily resistant to tamoxifen will respond to aminoglutethimide [4], and therefore the combination of the two agents might be expected to produce a higher response rate. Therefore, a randomised trial of tamoxifen (TAM) versus tamoxifen with aminoglutethimide (TAG) was undertaken.

Patients and methods

All patients were post-menopausal and had measurable metastatic breast cancer. None had had previous hormonal treatment. Bone scan evidence of metastases was not accepted without confirmatory X-ray changes. The dose of tamoxifen in both groups was 10 mg b.d. and that of aminoglutethimide, 250 mg t. d. s. for 2 weeks, increasing to 250 mg q. d. s. thereafter. In addition, hydrocortisone 10 mg b. d. was given to the TAG group. The two groups were comparable in age, performance status and time to first recurrence (Table 1). Oestrogen receptor data were only available in a minority of cases.

Patients were assessed monthly for response and toxicity. Those patients failing to complete a month of treatment for reasons other than drug toxicity were considered non-evaluable. Patients were assessed for response at 3 months. The criteria used were those of the UICC, with response being maintained for at least 4 weeks [3]. Complete response was taken as disappearance of all evidence of disease, as judged clinically and by serial investigations. Partial response was a reduction of 50% or more in the measurable lesions with no new lesions appearing. No change was defined as a less than 50% reduction or 25% increase in measurable lesions with no new lesions appearing and progressive disease as a greater than 25% increase in measurable lesions or the appearance of a new lesion.

Patients who had a response continued with the treatment until progression occurred, as did those with no change in their disease. Patients with progressive disease were withdrawn from the study. Those who developed toxicity attributable to aminoglutethimide either continued the treatment at a reduced dose or continued with tamoxifen alone. They are included in the assessment of response in the group to which they were randomised.

Table 1. Patient details

	TAM	TAG
No. of patients	35	31
Median age (range) (years)	63 (46–77)	57 (49–79)
ECOG 0	5	5
Performance 1	20	17
status		
2	2	4
3	8	5
Median time to first relapse (weeks)	92	67
Oestrogen receptor status		
Positive	5	7
Negative	11	2
Unknown	19	22
Previous chemotherapy	12	7

Results

In all, 14 patients were considered non-evaluable for response. In the TAM group eight patients died within a month of starting treatment and 1 was found to have previously received tamoxifen. In the TAG group three patients died within a month, one never received aminoglutethimide because of problems with hypertension and one was found to have previously received tamoxifen. This left 26 evaluable patients in each group.

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Table 2. Sites of response

	TAM	TAG
Skin	3	1
Nodes	1	2
Lung	1	1 (documented on CXR)
Breast	1	
Liver		1 (documented on ultrasound)
Bone		1 (documented on X-rays)

Table 3. Toxicity of TAG regimen

TAG toxicity	No. of patients
Drowsiness	10
Rash	7
Nausea and vomiting	4
Hypotension	1

There were five partial responses in the TAM group (19%) and six partial responses in the TAG group (23%), out of 26 evaluable patients in each group. Excluding only patients who had previously received tamoxifen the partial response rate was 15% for the TAM group and 20% for the TAG group. The six responders in the TAG group include three patients who, after an initial response in soft tissue, had to discontinue aminoglutethimide owing to toxicity and continued to respond to tamoxifen alone. The sites of response are shown in Table 2. The response durations for the TAM group were 16, 84, 86, 88, and 156+ weeks and those for the TAG group, 16, 45, 56, 57, 82+, and 96 weeks.

Toxicity

Only one of the TAM patients had nausea and she was able to continue taking the drug. By contrast, 14 (45%) of the TAG group had some toxicity attributable to the aminoglutethimide. This is detailed in Table 3. Although toxicity was not usually severe, four patients (13%) stopped aminoglutethimide and continued with tamoxifen alone. Of these two had a skin rash and two drowsiness.

Discussion

Both tamoxifen and aminoglutethimide have induced responses in a proportion of patients with advanced breast cancer. The response rate in each group was lower than some other groups have reported [2, 5], but the oestrogen receptor status of most patients was not known and some patients had been heavily pretreated with cytotoxic drugs. Despite the different modes of action of the two drugs, the TAG combination did not yield a higher response rate. Although the number of patients in each arm is small this result is in accordance with both other randomised studies [1, 4] and those using historical controls [6, 7]. The toxicity due to the addition of aminoglutethimide was, however, considerable and four patients had to stop the drug. With increasing clinical experience of aminoglutethimide it has become clear that side-effects may be dose-related or self-limiting [2]. Nevertheless, the four patients concerned were not prepared to continue with the drug after having experienced toxicity. In post-menopausal patients with metastatic breast cancer there appears to be no therapeutic benefit to justify the increased toxicity seen when tamoxifen and aminoglutethimide are combined in the doses used in this study.

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