

# Tamoxifen versus Aminoglutethimide versus Combined Tamoxifen and Aminoglutethimide in the Treatment of Advanced Breast Carcinoma<sup>1</sup>

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## Abstract

In a control randomized cross-over trial, 117 patients with advanced breast cancer were treated initially either with tamoxifen (10 mg p.o. twice daily) or aminoglutethimide (250 mg p.o. 4 times daily) with hydrocortisone (20 mg twice daily). Patients failing to respond or relapsing were switched to the alternative treatment. Eighteen (30%) of the 60 patients initially treated with tamoxifen achieved an objective response, and 11 (18%) achieved stable disease. Seventeen (30%) of the 57 patients treated initially with aminoglutethimide achieved an objective response, and 13 (23%) achieved stable disease. Aminoglutethimide achieved a 35% objective response and a further 26% subjective bone pain relief in patients with bone metastases (overall, 61%) compared with a 17% objective response and a further 17% objective bone pain relief with tamoxifen (total, 34%). None of six premenopausal patients responded to aminoglutethimide compared with two of four responding to tamoxifen. The median response duration to aminoglutethimide was 16 months compared with 20 months for tamoxifen. Side effects for aminoglutethimide (including lethargy, rash, and depression) were more common than for tamoxifen, and 7% of aminoglutethimide-treated patients had to discontinue treatment because of these compared with 0% on tamoxifen. In cross-over studies, 6 of 12 tamoxifen responders who relapsed achieved a second response to aminoglutethimide (50%), as did 6 of 29 patients who initially failed to respond to tamoxifen (21%). In contrast, none of 11 patients relapsing after response to aminoglutethimide achieved a second response to tamoxifen; only 1 of 18 nonresponders to aminoglutethimide subsequently responded to tamoxifen (6%).

In a subsequent study in which 62 patients were treated with combined tamoxifen and aminoglutethimide, the overall response rate of 37% was not significantly better than that for either agent used alone.

## Introduction

Two important new forms of medical endocrine therapy have recently been introduced in the treatment of advanced breast cancer. The first, tamoxifen, is an antiestrogen which has been shown to be as effective as other forms of hormone therapy but with a very low incidence of side effects (6, 7). The second, aminoglutethimide, is an inhibitor of adrenal steroid synthesis (2) and therefore may act as a "medical adrenalectomy," although it is also a powerful inhibitor of the aromatase enzyme involved in the conversion of androgens to estrogens in peripheral tissues (3). In a recent control randomized trial, aminoglutethimide has been shown to be as effective as surgical

adrenalectomy in the treatment of advanced breast cancer (9). Both drugs have the advantage of their effects being readily reversible if treatment proves ineffective.

The relative efficacies of these 2 agents and the extent to which they show cross-resistance have not yet been clearly established. To assess this, we have therefore carried out a control randomized cross-over trial of tamoxifen and aminoglutethimide in 117 patients with advanced breast cancer. Preliminary results have already been reported (11). We report here a more detailed update with a follow-up of up to 33 months.

Because of the different mechanisms of action of the 2 agents, we have also studied their effects used as combination therapy in a sequential study of 62 patients matched for prognostic variables with patients in the earlier trial. Preliminary results are reported here.

## Patients and Methods

One hundred seventeen patients presenting to the Breast Unit, Royal Marsden Hospital (Fulham Road), with histologically proven advanced breast cancer were entered into the comparative randomized trial between January 1979 and March 1980. Sixty-two subsequent patients were entered into the combined tamoxifen and aminoglutethimide study between April 1980 and April 1981. Details of age, menstrual status, major sites of disease involvement, and previous therapy are given for all patients in Table 1. Our policy was to enter all patients presenting to the unit with advanced breast cancer into these trials, except those with symptomatic liver metastases or carcinomatous lymphangitis of the lungs who were treated immediately with combination chemotherapy. Patients previously treated with adrenalectomy or hypophysectomy were likewise excluded.

**Trial Design.** In the control randomized trial, patients were allocated to initial treatment either with tamoxifen or with aminoglutethimide. Treatment was continued until there was obvious evidence of progressive disease, whereupon patients were switched to the other treatment arm. In the combination study, patients were continued on treatment until they showed clear evidence of progressive disease.

**Dosage.** Tamoxifen was given in a dose of 10 mg p.o. twice daily.

Aminoglutethimide was given in a dose of 250 mg p.o. 3 times daily with hydrocortisone (20 mg twice daily) for the first 2 weeks; the dose of aminoglutethimide was subsequently increased to 250 mg p.o. 4 times daily except in patients experiencing persistent side effects (see below).

**Staging.** Patients were staged by full clinical examination, full peripheral blood count, serum biochemistry and liver function tests, bone scan, and radiological skeletal survey. Where clinically indicated, bone marrow aspirate, trephine, and iso-

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topic liver scan were also carried out. Staging investigations were repeated after 2 months of treatment and then at 6 monthly intervals or as clinically appropriate.

**Response Criteria.** Tumor response was assessed objectively according to standard UICC criteria for advanced breast carcinoma (5). Chest X-rays and radiological skeletal surveys were assessed independently by a consultant radiologist. Patients were defined as showing stable disease if they showed both no evidence of disease progression for at least 2 months after starting treatment and also relief of symptoms (if initially present) during this period.

**Results**

**Response.** Eighteen (30%) of the 60 patients initially randomized who received tamoxifen achieved an objective response and a further 11 patients (18%) showed stable disease. Seventeen (30%) of the 57 patients initially randomized to receive aminoglutethimide achieved an objective response, and a further 13 patients (23%) achieved stable disease.

Twenty-three (37%) of the 62 patients treated with combined tamoxifen and aminoglutethimide achieved an objective response, and a further 7 patients (11%) achieved stable disease.

**Response by Site.** Details of response by site of disease for each initial form of treatment are given in Table 2. The only major difference found was in the treatment of bone metastases. Eleven (35%) of 31 patients initially treated with aminoglutethimide achieved an objective response in bone, and a further 8 (26%) showed subjective relief of bone pain (total benefit, 61%). In contrast, only 5 (17%) of 29 patients treated with tamoxifen achieved an objective response and a further 5 (17%) had subjective relief of bone pain (total, 34%). When the drugs were used in combination, 8 (28%) of 29 patients achieved an objective response, and a further 6 (21%) had bone pain relief (total benefit, 49%). No other differences in sites of response for the different treatments were seen.

**Response by Menopausal Status.** None of the 6 premenopausal patients initially treated with aminoglutethimide achieved a response compared with 2 of 4 premenopausal patients treated with tamoxifen. Two of 6 premenopausal patients responded to combined tamoxifen plus aminogluteth-

imide. No differences in response rates for the different treatments were seen in perimenopausal or postmenopausal patients.

**Response Duration and Survival.** The predicted median duration of response for each initial treatment is shown in Chart 1. Median response duration for tamoxifen was 20 months compared with 16 months for aminoglutethimide (no significant difference). Median duration of survival (life table analysis) for all patients whether responding or not is shown in Chart 2. Median survival duration was 20 months for both initial treatments.

Comparable response duration and survival data are not yet available for patients treated with combined tamoxifen and aminoglutethimide.

**Cross-Resistance and Cross-Sensitivity.** Of the 29 patients initially failing to respond to tamoxifen, 6 (21%) achieved a subsequent objective response to aminoglutethimide. Of 8 patients whose disease remained stable on tamoxifen for at least 3 months and then progressed, 2 (25%) subsequently responded to aminoglutethimide. For the 12 patients responding to tamoxifen who have thus far relapsed, 6 (50%) have subsequently responded to aminoglutethimide.

In contrast, of the 18 patients who failed to respond to aminoglutethimide, only one (6%) subsequently responded to tamoxifen. Of the 13 patients whose disease remained stable on aminoglutethimide, only one (8%) responded to tamoxifen. Of the 11 patients who have thus far responded to aminoglutethimide and then relapsed, none subsequently responded to tamoxifen.

**Side Effects.** The main side effects seen in patients treated with tamoxifen, aminoglutethimide, or both agents in combination are listed in Table 3. Side effects were much more common for aminoglutethimide than for tamoxifen and included, in particular, lethargy and drowsiness, rash, and depression. In the majority of patients, these side effects were transient and settled within 1 or 2 weeks of starting treatment. However, 7% of patients could not tolerate treatment on aminoglutethimide, whereas no patient had to discontinue treatment because of side effects with tamoxifen. Side effects for combination therapy were the same as those for aminoglutethimide alone, and 6% of patients had to discontinue treatment.

Table 1  
Patient characteristics for each treatment

	No. of patients	Median age (yr)	Premenopausal	Perimenopausal	Previous endocrine therapy	Previous chemotherapy	Liver metastases
Tamoxifen	60	57 (34-83) <sup>a</sup>	4	8	15	23	6
Aminoglutethimide	57	55 (31-76)	6	10	15	26	4
Tamoxifen + aminoglutethimide	62	56 (31-77)	6	8	14	18	6

<sup>a</sup> Numbers in parentheses, range.

Table 2  
Response by site of disease

	Bone				Lung	Pleura	Liver
	Soft tissue	Objective	Subjective	Total			
Tamoxifen	12/38 (32) <sup>a</sup>	5/29 (17)	5/29 (17)	10/29 (34)	2/8 (25)	2/5	1/6
Aminoglutethimide	10/26 (38)	11/31 (35)	8/31 (26)	19/31 (61)	2/9 (22)	2/5	0/4
Tamoxifen + aminoglutethimide	12/25 (48)	8/29 (28)	6/29 (21)	14/29 (49)	5/16 (31)	3/7	2/6

<sup>a</sup> Numbers in parentheses, percentage.

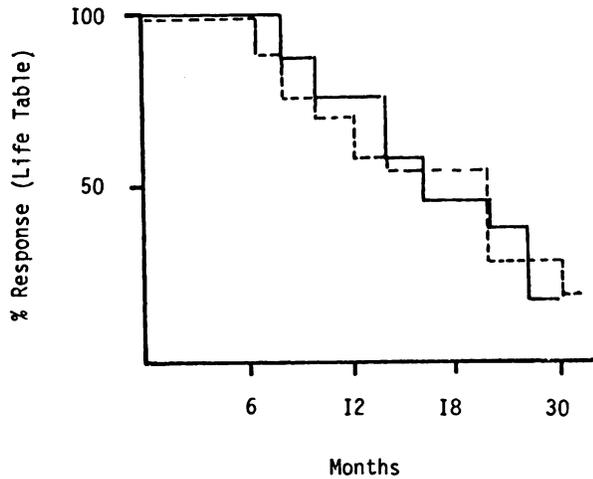


Chart 1. Remission duration (life table analysis) of patients receiving aminoglutethimide (—) or tamoxifen (---) as first-line treatment.

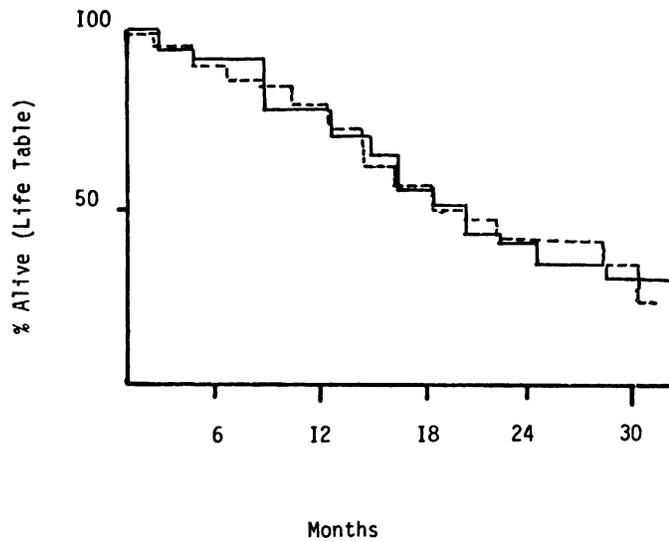


Chart 2. Survival (life table analysis) of patients receiving aminoglutethimide (—) or tamoxifen (---) as first-line treatment.

**Discussion**

These results demonstrate that aminoglutethimide and tamoxifen are equally effective in the treatment of advanced breast cancer, both in response rates achieved and in duration of response. The trial further confirmed an observation which we had made from an earlier Phase II study of aminoglutethimide (10). This drug appears to be very effective in the management of painful bone metastases and seems to be superior to tamoxifen both in achieving objective evidence of resclerosis on X-ray and in relieving bone pain. In this difficult area of breast cancer therapy, it is to be noted that 61% of patients had worthwhile bone pain relief.

Tamoxifen has already been reported to be effective in premenopausal patients (12), and our studies confirm this. In contrast, no responses to aminoglutethimide were seen in premenopausal patients, and we have confirmed its ineffectiveness in a larger group of premenopausal patients (4). Aminoglutethimide has a further disadvantage compared with tamoxifen, and that is in its significantly greater incidence of side

Table 3  
Main side effects of treatment

	% of patients				
	Lethargy or drowsiness	Rash	Nausea	Depression	Not tolerated
Tamoxifen			6		
Aminoglutethimide	37	30	8	4	7
Tamoxifen + aminoglutethimide	35	27	11	18	6

effects. A significant minority of patients were troubled in the early stages of treatment with drowsiness, lethargy, and a rash. Usually, this was self-limiting, but in a few patients treatment had to be stopped.

It was of considerable interest to find in cross-over studies that aminoglutethimide was effective as second-line therapy in 50% of patients who had responded to tamoxifen and even in 20% of nonresponders, whereas the converse was not true. Thus far, we have seen very little evidence of responses to tamoxifen as second-line therapy after aminoglutethimide. At present, we cannot fully explain this, but the observation may have important therapeutic implications for the future.

The results with combination therapy were disappointing. Combination chemotherapy has been clearly shown to be superior to single-agent therapy in the treatment of advanced breast cancer (1). Since tamoxifen and aminoglutethimide have different mechanisms of action, we hoped that the same might be true here, but these results suggest that combining the 2 agents does not significantly improve response rate. Follow-up data on response duration of combined endocrine therapy are required before the overall therapeutic effect of this approach can be fully evaluated.

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