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Tamoxifen versus aminoglutethimide in advanced breast carcinoma: a randomised cross-over trial

IAN E SMITH, ADRIAN L HARRIS, MICHAEL MORGAN, HUBERT T FORD, JEAN-CLAUDE GAZET, CLIVE L HARMER, HARVEY WHITE, COLIN A PARSONS, ANTONIO VILLARDO, GERALDINE WALSH, J ALAN McKINNA

Abstract

Altogether 117 patients with advanced breast cancer were treated with either tamoxifen 10 mg by mouth twice daily or aminoglutethimide 250 mg by mouth four times daily with hydrocortisone 20 mg twice daily in a randomised cross-over trial in which patients who failed to respond to the first treatment or relapsed while receiving it were switched to the other. Eighteen (30%) out of 60 patients initially treated with tamoxifen achieved an objective response and 11 (18%) showed stable disease. Seventeen (30%) out of 57 patients treated initially with aminoglutethimide achieved an objective response and 13 (23%) achieved stable disease. Objective responses in bone metastases were achieved more commonly with aminoglutethimide (11 patients (35%)) than with tamoxifen (five (17%)). The predicted median duration of response for tamoxifen was 15 months and for aminoglutethimide over 15 months (no significant difference). Five (15%) out of 34 patients who failed to respond to tamoxifen and four out of six patients who relapsed after responding to tamoxifen subsequently responded to aminoglutethimide. In contrast, only two (6%) out of 31 patients who failed to respond to aminoglutethimide and none out of four patients who relapsed while receiving aminoglutethimide subsequently responded to tamoxifen. The main side effects occuring in the 97 patients who received aminoglutethimide as first- or second-line treatment were lethargy and drowsiness (36 patients) and rash (29); seven patients had to stop treatment because of side effects. In contrast, side effects were rare and mild with tamoxifen and no patient had to stop treatment because of them.

Both tamoxifen and aminoglutethimide appear from this study to be equally effective in the medical endocrine treatment of advanced breast cancer.

Breast Unit, Royal Marsden Hospital, London SW3 6JJ
IAN E SMITH, MD, MRCP, consultant medical oncologist
ADRIAN L HARRIS, DPHIL, MRCP, lecturer in medicine
MICHAEL MORGAN, FRCS, consultant surgeon
HUBERT T FORD, FRCR, consultant radiotherapist
JEAN-CLAUDE GAZET, MS, FRCS, consultant surgeon
CLIVE L HARMER, FRCR, consultant radiotherapist
HARVEY WHITE, MCH, FRCS, consultant surgeon
COLIN A PARSONS, FRCS, FRCR, consultant radiologist
ANTONIO VILLARDO, MD, visiting research fellow
GERALDINE WALSH, research secretary
J ALAN McKINNA, FRCS, consultant surgeon

Introduction

In the past few years traditional approaches to the endocrine management of patients with advanced breast cancer have been challenged by two important new forms of medical endocrine treatment. The first, tamoxifen, is an anti-oestrogen already in widespread clinical use. The second, aminoglutethimide, inhibits adrenal steroid synthesis and therefore may act as a "medical adrenalectomy," though it also has other actions including inhibition of the aromatase enzyme involved in the conversion of androgens to oestrogens in peripheral tissues.[2] At present aminoglutethimide is still a trial drug and is less widely used than tamoxifen, but both appear to be as effective as the more traditional forms of endocrine treatment in achieving and maintaining tumour regression.[3–5] In addition both drugs are easily administered even to ill patients, and their effects are readily reversible if treatment proves ineffective.

So far no randomised comparative trial of these two agents has been reported, and thus their relative efficacies and the extent to which they show cross-resistance have not yet been properly established. We therefore carried out a randomised cross-over trial of tamoxifen and aminoglutethimide in 117 patients with advanced breast cancer. The trial was started in January 1979 and we report our first results here.

Patients and methods

One hundred and seventeen patients (116 women, one man) who presented to the breast unit with histologically proved advanced breast cancer were entered into this trial between January 1979 and March 1980. Table I gives details of age, menstrual state, and previous endocrine treatment and chemotherapy. Fifty-five patients had received no previous systemic treatment of any sort. Our policy was to enter all patients into this trial except those with symptomatic liver metastases or carcinomatous lymphangitis of the lungs, who were treated immediately with combination chemotherapy. Patients who had previously been treated with adrenalectomy or hypophysectomy were likewise excluded.

TABLE I—*Details of patients in each group*

	Tamoxifen	Aminoglutethimide
No of patients	60	57
Median age (range) (years)	57 (34–83)	55 (31–76)
No premenopausal	4	6
No perimenopausal	8	10
No who had undergone oophorectomy	8	5
No postmenopausal	40	36
Previous endocrine treatment	15	15
Previous chemotherapy	23	22
No previous systemic treatment	29	26

Design of trial—This was a randomised cross-over trial in which patients were randomly allocated to be treated with either tamoxifen or aminoglutethimide. Treatment was continued for at least two months unless there were clear clinical grounds for changing sooner. Patients whose disease progressed while they were receiving the first treatment were changed to the second. Patients whose tumour responded or whose disease remained stable continued the treatment until relapse and were then also changed to the other treatment arm.

Dosage—In the first treatment arm patients received tamoxifen 10 mg by mouth twice daily. In the second treatment arm they received aminoglutethimide 250 mg by mouth three times daily with hydrocortisone 20 mg twice daily for the first two weeks; the dose of aminoglutethimide was subsequently increased to 250 mg by mouth four times daily except in patients aged over 70 years or in those who experienced persistent side effects (see below).

Staging—The disease was staged according to the results of full clinical examination, full blood count, serum biochemistry, liver function tests (bilirubin concentration and activities of alanine transaminase, alkaline phosphatase, and γ-glutamyl transferase), bone scan, and radiological skeletal survey. When clinically indicated bone-marrow aspiration, trephine biopsy, and isotopic liver scan were also carried out. Staging investigations were repeated after two months of treatment and then at six-monthly intervals or as clinically appropriate.

Response criteria—Tumour response at each site of advanced disease was assessed objectively according to standard criteria (International Union against Cancer) for advanced breast carcinoma.[6] Chest *x*-ray films and radiological skeletal surveys were assessed independently by a consultant radiologist. Patients were defined as having stable disease if they showed no evidence of disease progression for at least three months after starting treatment and also relief of symptoms (if initially present) during this period.

Results

Response—Eighteen (30%) of the 60 patients initially randomised to receive tamoxifen achieved an objective response. A further 11 patients (18%) showed stable disease. Thirty-one patients (52%) showed progressive disease. None of the patients had to stop treatment because of toxicity. Seventeen (30%) of the 57 patients initially randomised to receive aminoglutethimide achieved an objective response. A further 13 patients (23%) achieved stable disease. Twenty-two patients (39%) showed progressive disease during the first two months of treatment. Five patients (9%) had to stop treatment because of toxicity.

Response by site—Table II gives details of the response by site of disease for each initial treatment. The only major difference observed was in the effect on bone metastases. Five (17%) out of 29 patients treated initially with tamoxifen achieved an objective response in bone and a further five (17%) had subjective relief of bone pain and stable disease but without objective *x*-ray changes. In contrast, 11 (35%) out of 31 patients initially treated with aminoglutethimide achieved an objective response in bone and a further eight (26%) showed subjective relief of bone pain and stabilisation of disease.

TABLE II—*Response of patients by site*

Site	Tamoxifen		Aminoglutethimide	
	No of patients	Response	No of patients	Response
Soft tissues	38	12 (32%)	26	10 (38%)
Bone:				
Objective response	29	5 (17%)	31	11 (35%)
Subjective response		5 (17%)		8 (26%)
Total		10 (34%)		19 (61%)
Lung	8	2	9	2
Pleura	5	2	5	2
Liver	6	1	4	

Response by menopausal state—None of the six premenopausal patients initially treated with aminoglutethimide achieved a response compared with two of the four premenopausal patients treated with tamoxifen. Two of the 10 perimenopausal patients (under two years from last menopausal period) treated with aminoglutethimide responded compared with two of the eight receiving tamoxifen. Fifteen (37%) of the 41 patients treated with aminoglutethimide who were postmenopausal or had undergone oophorectomy responded compared with 14 (29%) of the 48 receiving tamoxifen.

Duration of response and survival—Figure 1 shows the duration of response predicted by life-table analysis for each initial treatment. The predicted median duration for tamoxifen was 15 months and that for aminoglutethimide over 15 months. No significant difference in duration of response was seen. Figure 2 gives survival predicted by life-table analysis in all patients, whether responding or not, according to the initial treatment. No significant difference was seen between the two treatment arms.

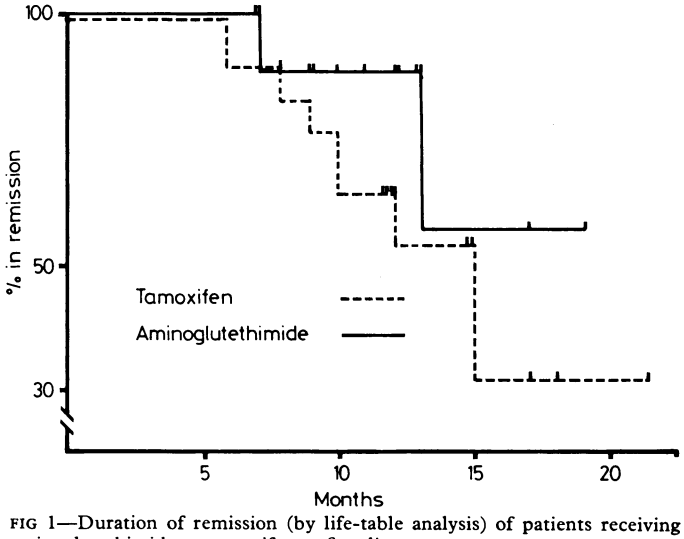

FIG 1—Duration of remission (by life-table analysis) of patients receiving aminoglutethimide or tamoxifen as first-line treatment.

Cross-resistance and cross-sensitivity—Of the 34 patients who initially failed to respond to tamoxifen, five (15%) achieved a subsequent objective response to aminoglutethimide. Of the six patients who initially responded to tamoxifen and subsequently relapsed, four subsequently responded to aminoglutethimide. Of the 31 patients who initially failed to respond to aminoglutethimide, two (6%) subsequently responded to tamoxifen. One of these two patients had failed to complete an adequate course of aminoglutethimide because of toxicity. The other was the one man in the study: his progressive lung metastases initially failed to respond to aminoglutethimide but subsequently responded to tamoxifen. Of the four patients who initially responded to aminoglutethimide and then relapsed, none subsequently responded to tamoxifen.

Side effects—Side effects in the 95 patients who received tamoxifen either as initial treatment or as second-line cross-over treatment after

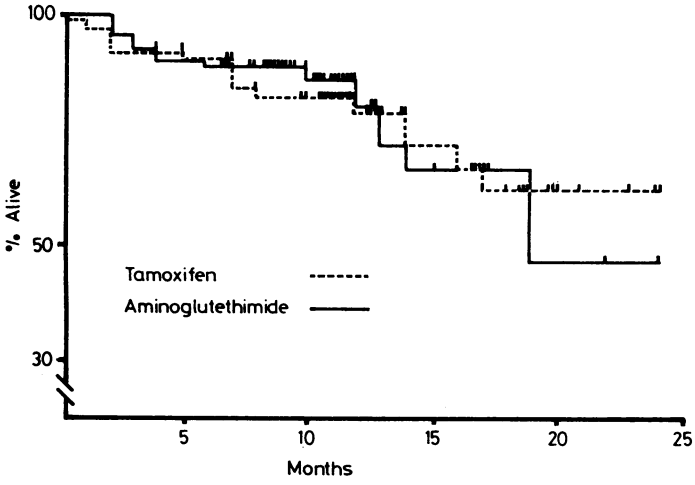

FIG 2—Survival (by life-table analysis) of patients receiving aminoglutethimide or tamoxifen as first-line treatment.

aminoglutethimide comprised nausea (six patients), hypercalcaemia (two), vaginal discharge (two), hot flushes (two), fever (one), and dizziness (one). Eighty-one patients (85%) had no side effects, and no patients had to stop treatment because of undue toxicity. Side effects in the 97 patients who received aminoglutethimide either as initial treatment or as second-line cross-over treatment comprised lethargy and drowsiness (36 patients), a rash (29), nausea (eight), depression (four), menorrhagia (two), and headache (one). The rash, which characteristically appeared eight or nine days after the start of treatment, was erythematous, maculopapular, and sometimes associated with general malaise and fever; in a few patients it was severe, semiconfluent, and occasionally associated with facial and periorbital oedema; and in all but one patient it was self-limiting within five to seven days. Forty-one patients (42%) had no appreciable side effects. In seven patients side effects were severe enough to warrant stopping treatment (four because of lethargy and drowsiness, two because of nausea, and one because of depression).

Discussion

These results show that aminoglutethimide, a fairly new agent for treating advanced breast cancer, is as effective as tamoxifen in achieving and maintaining tumour regression. In addition, the trial confirms an observation that we made in an early study of aminoglutethimide[4]: this agent is particularly effective in the management of painful bone metastases and appears to be better than tamoxifen both in relieving pain and in achieving objective evidence of re-sclerosis on *x*-ray films.

This potential advantage of aminoglutethimide is offset by two factors. Firstly, no responses were seen in premenopausal patients, and we subsequently confirmed in a larger study that aminoglutethimide is ineffective in such patients.[7] In contrast, responses were seen in premenopausal patients treated with tamoxifen, and others have suggested that this agent is as effective as oophorectomy.[8] The second disadvantage of aminoglutethimide compared with tamoxifen was its considerably greater incidence of side effects. These have already been described in some detail[4 5] and include in particular drowsiness and lethargy and a rash. In most patients these side effects are self-limiting, and the drowsiness is dose related; in this trial, however, the side effects were severe enough in some patients to necessitate stopping treatment, whereas this never happened with tamoxifen. These side effects should, however, be kept in perspective: while they confer a disadvantage on aminoglutethimide compared with tamoxifen, they are nevertheless mild compared with those of most forms of combination chemotherapy.

Interestingly, we found aminoglutethimide to be effective in some patients who had failed to respond to tamoxifen and in others who had responded and then relapsed. This lack of complete cross-resistance offers important therapeutic possibilities in the management of patients with advanced breast cancer and may relate to the different mechanisms of action of these two drugs. The converse may not be true: so far the trial has shown little evidence of response to tamoxifen given as second-line treatment to patients initially treated with aminoglutethimide. It might be that this is an unimportant "small numbers" effect that will disappear as the trial continues, but others have made the same observation in the preliminary stages of a similar trial (R J Santen, personal communication). Further information will become available as our trial proceeds to determine whether this potentially important difference between the two drugs is a real one.

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HEART'S EASE is that herb which such physicians as are licensed to blaspheme by authority, without danger of having their tongues burned through with an hot iron, called an herb of the Trinity. It is also called by those that are more moderate, Three Faces in a Hood, Live in Idleness, Cull me to you; and in Sussex we call them Pancies.

Besides those which are brought up in gardens, they grow commonly wild in the fields, especially in such as are very barren: sometimes you may find it on the tops of the high hills. They flower all the Spring and Summer long.

The herb is really saturnine, something cold, viscous, and slimy. A strong decoction of the herbs and flowers (if you will, you may make it into syrup) is an excellent cure for the French pox, the herb being a gallant antivenereal: and that antivenereals are the best cure for that disease, far better and safer than to torment them with the flux, divers foreign physicians have confessed. The spirit of it is excellently good for the convulsions in children, as also for the falling sickness, and a gallant remedy for the inflammation of the lungs and breasts, pleurisy, scabs, itch, &c. It is under the celestial sign Cancer. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)