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Combination of Tamoxifen, Aminoglutethimide, Danazol and Medroxyprogesterone Acetate in Advanced Breast Cancer

Janet R. Hardy, Trevor J. Powles, Ian R. Judson, H. Dudley Sinnett, Sue E. Ashley, R. Charles Coombes and Caroline L. Ellin

Seventy-four post-menopausal women with metastatic breast cancer were treated with a combination hormonal regimen consisting of tamoxifen, aminoglutethimide danazol and medroxyprogesterone acetate (POND). 72% of the patients had received no previous treatment. The overall response rate (complete and partial remission) was 43.5% with a median response duration of 19 months and a median survival of 27 months. The most common sites of response were in regional nodes and local chest wall disease. The major side-effects were those expected from the individual agents: nausea, lethargy, rash and oedema.
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INTRODUCTION

In chemotherapy of metastatic breast cancer, higher response rates are achieved with a combination of agents, presumably because of their different mechanisms of cytotoxic action [1]. Dosages of individual drugs can be reduced and the toxicity 'spread' over different organ systems.

In an attempt to improve the response rate to standard hormonal treatment in breast cancer, Powles *et al.* [2] used a combination of drugs each of which has a different mechanism of 'endocrine action'. The combination of tamoxifen [3], aminoglutethimide [4], danazol [5] and hydrocortisone (TAD) had a significantly better response (43%) than tamoxifen alone (31%). Medroxyprogesterone acetate (MPA), a synthetic progestin [6, 7], gave an objective response rate of 20–40% when used as first-line hormonal therapy in patients with disseminated breast cancer [8]. To improve the response rate, duration of response and survival of patients treated with a combination regimen, we have used MPA in combination with tamoxifen, aminoglutethimide and danazol (POND). The glucocorticoid effect of MPA is sufficient to suppress endogenous cortisol production such that hydrocortisone is not required when MPA is used in combination with aminoglutethimide [9].

PATIENTS AND METHODS

All post-menopausal patients with assessable metastatic breast cancer for whom endocrine therapy was considered the treatment of choice were eligible. Those patients who had previously received tamoxifen, danazol, aminoglutethimide or MPA were excluded. Cytotoxic chemotherapy within 3 weeks of entry, abnormal cardiac and renal function and a life expectancy of less than 3 months were exclusion criteria.

Patients received the four agents as follows: tamoxifen 20 mg in the morning, aminoglutethimide 250 mg in the morning and 500 mg at night, danazol 100 mg in the morning, 200 mg at night and MPA 500 mg, twice a day.

Before the start of therapy all patients underwent clinical examination and disease assessment. Staging investigations included haematological and biochemical profile, bone scan, chest X-ray and limited skeletal survey. These were repeated at the time of maximum disease response, disease progression or every 3–6 months in the case of static disease. Response was judged according to UICC criteria [10]. Survival and response duration were measured from time of entry. Toxicity was graded according to standard WHO criteria [11]. Information on oestrogen receptor status was not available in most patients.

RESULTS

Seventy-four patients were started on POND between August 1983 and September 1986 (Table 1). POND was first-line treatment in most cases (72%). 9 patients with advanced disease had been previously treated with chemotherapy and 9 had received hormones other than those in POND or had undergone oophorectomy. 6 patients had received adjuvant treatment. Bone, chest wall and regional nodes were the most common sites of metastatic disease.

10 patients (14%) achieved a complete response on POND and 22 (30%) a partial response, giving an overall response rate of 43% and an assessable response rate of 51% (Table 2). The most common sites of response were in regional nodes and local chest wall disease (Table 3). 10 patients had stable disease on treatment. 11 patients were not assessable for disease response because of early death, non-compliance or loss to follow-up. The median duration of response was 19 months (range 3–50), the median time to progression 8 months (2–50 or longer), and the median survival from start of treatment 27 months (1–54) (Figs 1–3).

The most common side-effects were nausea, lethargy, constipation and rash (Table 4). 41% of patients had a dose modification during treatment with reduction or discontinuation of one or more drugs because of toxicity (generally lethargy, rash, weight gain, hirsutism or voice change).

Correspondence to T.J. Powles, Department of Medicine, Royal Marsden Hospital, Downs Road, Sutton, Surrey, SM2 5PT, U.K.
J.R. Hardy, T.J. Powles, I.R. Judson and C.L. Ellin are at the Department of Medicine, H.D. Sinnett is at the Department of Surgery, S.E. Ashley is at the Department of Computing, Royal Marsden Hospital, Surrey and R.C. Coombes is at the Department of Oncology, St George's Hospital, London, SW17, U.K.

Table 1. Patients' characteristics

Median age (range) (No. of patients) (yr)	63 (45–85)
Adjuvant treatment	
Endocrine (including oophorectomy)	5
Chemotherapy	1
Previous treatment for advanced disease	
Endocrine (including oophorectomy)	9
Chemotherapy	9
Median disease-free interval (mon)	23
Site of metastatic disease	
Local	31 (42%)
Skin	4 (5%)
Nodes	26 (35%)
Lung	19 (26%)
Liver	14 (16%)
Bone	33 (45%)
Other	14 (19%)

DISCUSSION

Because of differences in distribution of steroid receptors in tumours and the differences in endocrine effect and pharmacology of the various hormones, combinations of hormones might give better response rates than those of the individual hormones used alone. The fact that about 20% of patients who fail to respond to one type of endocrine therapy subsequently respond to alternative hormonal treatment [12] supports this theory. In this study we confirmed the original finding of Powles *et al.* [2] that a high response can be achieved with a combination hormonal regimen in the treatment of advanced breast cancer. Response rates have been below 33% with single agents in this unit [13–15] and yet response rates over 40% have been achieved with both TAD and POND. Although the previous trial of TAD versus tamoxifen [2] had shown that more patients receiving the combination achieved a response and that this response was achieved more quickly, it became apparent after a follow-up of about 2 years that the duration of remission and survival was longer in those patients receiving tamoxifen alone [16]. This was thought to indicate that endocrine resistance is acquired more rapidly with combination treatment.

Survival benefit with hormonal treatment only occurs when treating advanced life-threatening disease. Most of the patients receiving the combination treatment did so at an early stage when they were unlikely to have widespread, potentially life-threatening metastatic disease. The duration of response in these patients ended when tumour cells became resistant to any one of four agents. Conversely those patients whose disease became resistant to tamoxifen could be treated by another single agent with a 20% chance of further response and survival advantage if the disease by this stage had become life-threatening. We had planned a randomized phase III trial of TAD versus POND. However, when it became apparent that there was a significant survival difference in favour of the single agent [16], the planned trial was abandoned.

Table 2. Response

Response*	No.
CR	10 (13.5%)
PR	22 (30%)
NC	10 (13%)
PD	21 (29%)
NA	11 (15%)
Overall	32/74 (43%)
Assessable	32/63 (51%)

*CR = complete and PR = partial response; NC = no change; PD = progressive disease; and NA = not assessable.

Table 3. Response by site

Site of metastasis	CR	PR	NC	PD	NA	Assessable response
Local	7	7	4	9	4	61%
Skin	1	0	1	2	0	—
Nodes	9	3	5	9	0	50%
Lung	1	5	5	6	2	32%
Liver	0	2	1	6	3	22%
Bone	1	12	9	4	7	50%
Other	0	1	1	2	10	—

Since palliation is the primary aim when treating disseminated breast cancer, the toxicity of any treatment is of major concern. The toxicity of the combination treatment in this trial was that expected from the additive toxicity of the individual agents. The dose modification rate of 41% for POND is high compared with the 4.5% in patients treated with tamoxifen alone [2], suggesting that the combination of four hormones is not well-tolerated by patients. Some studies have even suggested that any potential therapeutic advantage of a combination regimen is outweighed by the increase in toxicity [17, 18].

Both Rose *et al.* [17] and Ingle *et al.* [18] found no difference between aminoglutethimide and tamoxifen versus tamoxifen alone when treating disseminated breast cancer. Mouridsen *et al.* compared tamoxifen with tamoxifen plus MPA [19] and tamoxifen with tamoxifen plus diethylstilboestrol [20], but failed to show any advantage for the combinations. The addition of fluoxymesterone to aminoglutethimide and hydrocortisone did not add to the response rate or duration of response of aminoglutethimide and hydrocortisone used alone [21]. However, tamoxifen combined with fluoxymesterone gave significantly

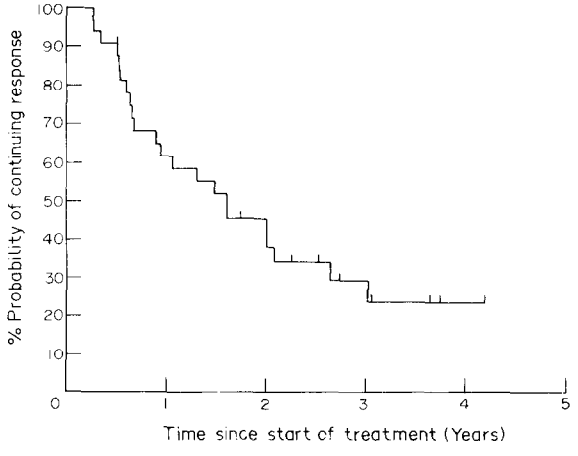

Fig. 1. Duration of response to POND.

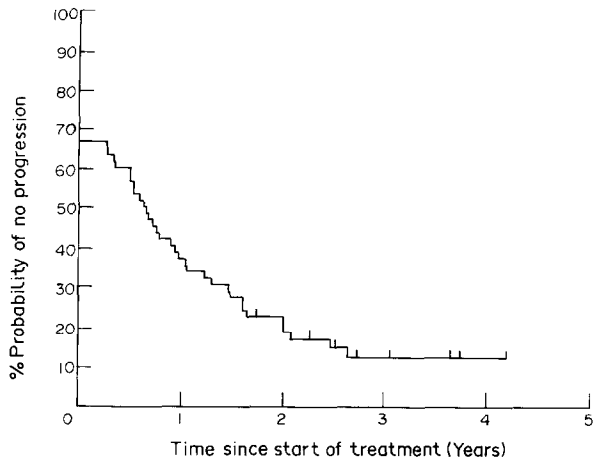

Fig. 2. Time to progression.

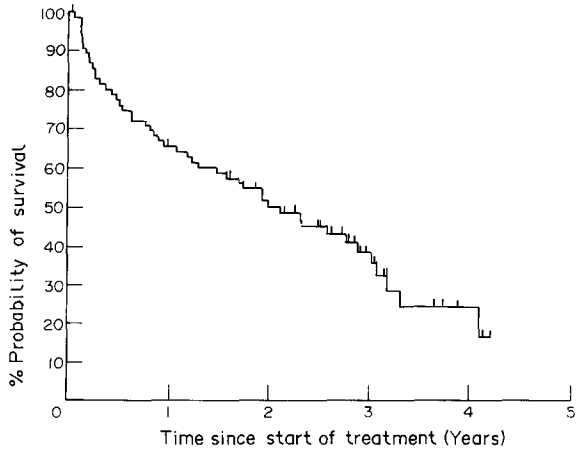

Fig. 3. Survival from start of POND.

Table 4. *Toxicity**

WHO grade	0	1	2	>3
Nausea	60	10	4	0
Vomiting	70	3	1	0
Alopecia	67	3	4	0
Neuropathy	74	0	0	0
Stomatitis	73	0	1	0
Constipation	60	6	7	1
Diarrhoea	74	0	0	0
Lethargy	40	15	11	8
Rash	57	6	6	5
Oedema	67	2	4	1
Ataxia	69	3	2	0
Other	46	8	12	8

*Maximum toxicity grade documented for each patient during treatment.

better response rates than tamoxifen alone [22] and Rubens [23] has reported an increased reponse rate following the use of prednisolone after oophorectomy or in combination with tamoxifen.

Thus, our results are consistent with the previous observation that combination hormonal therapy does give higher response rates than single agent treatment in disseminated breast cancer. The addition of MPA to tamoxifen/aminoglutethimide/danazol combination did not add to the response rates, duration of response or survival attained with TAD in previous trials. Moreover, follow-up has shown that survival is longer in those patients treated with single hormonal agents rather than with combinations and that the toxicity of the combination is greater.

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Sonography Versus Palpation in the Detection of Regional Lymph-Node Metastases in Patients with Malignant Melanoma

Lucas Prayer, Hedy Winkelbauer, Norbert Gritzmann, Fritz Winkelbauer, Michael Helmer and Hubert Pehamberger

High-resolution real-time sonography was done in 217 patients with malignant melanoma to compare its value in detecting regional lymph-node metastases with that of palpation. Lymph-node metastases were found in 29 patients by ultrasound whereas, by palpation, metastases were detected in 15 patients only. The presence of metastases was proven by histopathology after surgical lymphadenectomy in these ultrasound positive cases. Thus sonography was superior to palpation, and in addition permitted distinction between metastatic changes and inflammatory lymph-node enlargement. Ultrasound is recommended for preoperative staging as well as in postoperative monitoring of patients with malignant melanoma.
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INTRODUCTION

ALTHOUGH THE incidence of malignant melanoma is increasing worldwide [1–3], prognosis and survival rates are improving [1] primarily because the tumour is being recognized in earlier phases. The presence of lymph-node metastases correlates with the depth of invasion of the primary tumour; these factors are the most important prognostically. Thus early detection of lymph-node metastases is critical in the management of melanoma patients [4–6]. Palpation of regional lymph nodes has a high rate of error, with a reported frequency of false negative findings of up to 39% [7]. Our aim was to evaluate the use of high-resolution real-time sonography in the detection of regional lymph-node metastases, to compare sonography with palpation and to determine whether sonograms in preoperative staging and postoperative care of melanoma patients are routinely indicated.

Correspondence to L. Prayer, Alserstrasse 4, Central Institute of Radiodiagnosis, University of Vienna 1090 Vienna, Austria.
Lucas Prayer, Norbert Gritzmann, Fritz Winkelbauer and Michael Helmer are at the Central Institute of Radiodiagnosis, University of Vienna, and the Ludwig Boltzmann Institute of Radiological and Physical Tumor Diagnosis, Vienna; Hedy Winkelbauer and Hubert Pehamberger are at the Department of Dermatology I, University of Vienna, Austria.

PATIENTS AND METHODS

We studied 217 patients with primary malignant melanoma (Table 1). Primary lymph nodes, dependent on tumour localisation, were examined by palpation and by high-resolution real-time sonography. Lymph nodes were investigated either before or after removal of the primary melanoma in postoperative follow-up.

Sonography was done with an ATL 'Ultramark 8' with a 7.5 MHz anular array; a detachable elastomere (hydrated polyacrylamide-agar) was used to reduce artefacts. The visible lymph nodes were documented in longitudinal and cross sections. Circular and oval masses with poor echo were regarded as indicative of metastatic changes; on the other hand, longitudinally configurated lymph nodes, the hilum of which appeared