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Response to Third-line Endocrine Treatment for Advanced Breast Cancer

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In a retrospective analysis we have identified 55 patients who have received three endocrine treatments for advanced breast cancer. 42% of these patients have benefitted from third-line endocrine treatment in terms of disease stabilisation, symptom relief or objective response and this was translated into statistically significant ($P<0.01$) improved median survival of these patients (34 months) compared with those with progressive disease on third-line treatment (14 months). This suggests that third-line endocrine treatment might be of benefit to a number of patients with advanced breast cancer.
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INTRODUCTION

THE ROLE of endocrine therapy in advanced breast cancer is well established as both first-line and second-line treatment. The most widely used first-line endocrine treatment is tamoxifen because of its low toxicity [1] and a review of pooled data involving 5353 patients showed an overall response rate of 34% [2]. Aminoglutethimide is effective in the treatment of metastatic breast cancer both as first-line treatment and as second-line treatment [3] and a review of 929 patients reported an overall response rate for first-line treatment of 32% [4]. Progestins are also active against breast cancer and a review of 1342 patients with advanced breast cancer showed an overall response rate of 26% [5]. Wilson [6] has reviewed second-line endocrine therapy after first-line oophorectomy or tamoxifen, and described response rates ranging from 19 to 38% for a variety of therapies including adrenalectomy, hypophysectomy, aminoglutethimide [7–9], diethylstilboestrol [10], norethisterone [11], megestrol acetate [12] and medroxyprogesterone acetate [13].

With the availability of an increasing number of simple, low-toxicity medical endocrine therapies including tamoxifen itself, aromatase inhibitors [14], luteinizing hormone releasing hormone agonists [15], progestins and in the future pure anti-oestrogens [16] and anti-progestins [17], options arise for third- and even fourth-line endocrine treatments. Some studies have included a few patients who have received third-line therapy but we are not aware of any report which has looked at this systematically.

PATIENTS AND METHODS

Patients

55 patients with histologically proven breast cancer receiving three or more endocrine treatments have been retrospectively reviewed from the database of patients treated at The Breast Unit, Royal Marsden Hospital, London between 1985 and 1990. At the start of the first endocrine treatment their median age was 55 years (range 35–91), 16 were premenopausal, 7 were perimenopausal (within 2 years of their last menstrual period) and 32 were postmenopausal. Data on the oestrogen receptor (ER) status of the primary tumour was only available for 16 patients and was positive (>10 fmol/mg protein) in 14. The first endocrine treatment was given in an adjuvant setting in 8 patients and the remaining 47 patients received all three endocrine treatments for metastatic disease. Only 1 patient received chemotherapy prior to their first endocrine treatment.

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RESULTS

Objective responders

8 patients (15%) responded to third-line endocrine therapy as defined by UICC criteria [18] (7 partial response [PR] and 1 complete response [CR]). All these patients were on aminoglutethimide, their median age was 61 years (range 35–68) and 2 had ER-positive tumours. Median response duration was 13 months (range 4–36+ months). Median survival from the start of third-line treatment was 28 months (see Fig. 1a). The site of response was local recurrence and/or lymph nodes in 7 patients and bone in 1 patient. Details of first- and second-line treatments together with response are given in Table 1.

Stable disease (SD) /symptomatic response

15 patients (27%) had SD for greater than 6 months with symptomatic improvement of bone pain where this had been a clinical problem in 4 patients. Their median age was 57 years (range 42–81) and 2 had ER-positive tumours and 1 had an ER-negative tumour. Median time to disease progression was 9 months (range 6–29 months) and median survival from the start of third-line treatment was 40 months (range 7–76+ months) (see Fig. 1a). 8 of these patients had disease in bone, 7 had local recurrence/nodal disease and 2 patients were known to have visceral disease in addition.

Of these 15 patients, 9 received aminoglutethimide, 4 received medroxyprogesterone acetate, 1 received 4-hydroxyandrostenedione and 1 had an oophorectomy as their third-line endocrine treatment. Details of first- and second-line treatments together with response are given in Table 1.

Patients progressing on third-line therapy

The 32 patients (58%) who failed to respond to third-line endocrine treatment had a median age of 56 years (range 36–91) and a median survival after treatment of 14 months (range 2–57) (Fig. 1a). 10 had ER-positive tumours and 1 had an ER-negative tumour. Of these patients 10 had local recurrence/nodal disease,

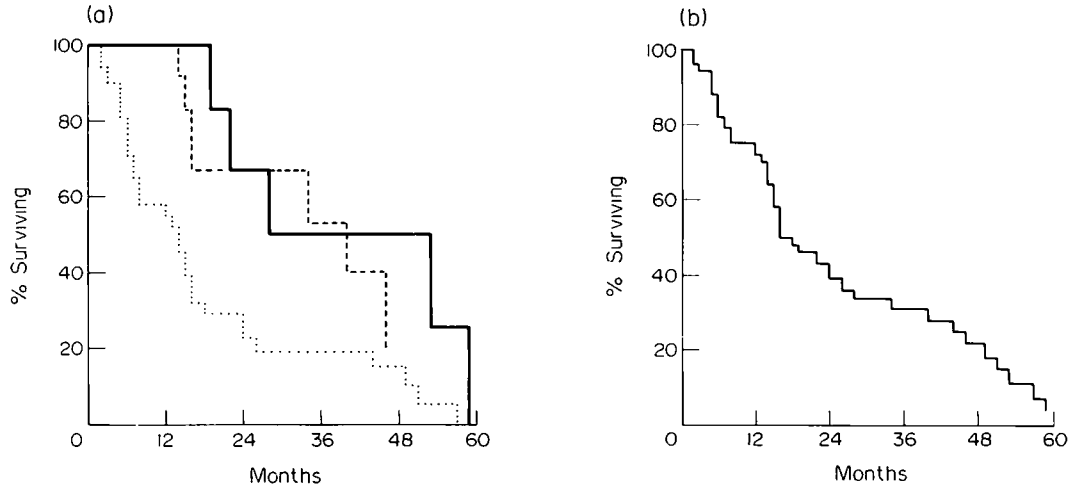

Fig. 1. (a) Survival curves for patients according to response. PR ——, SD ----, PD . . . (b) Survival curve for all patients.

Table 1. First- and second-line endocrine treatments and response to these treatments

Endocrine therapy	First-line response	Second-line response
(a)		
Tamoxifen (20 mg od)	5PR, 1PD	1PR
Adjuvant tamoxifen	1	
Adjuvant oophorectomy	1	
Provera (400 mg od)		1SD, 2PD
Leuprorelin		2SD
Trial aromatase inhibitor		1PD
Flutamide		1PD
(b)		
Tamoxifen (20 mg od)	1CR, 3PR, 4SD, 1PD	2PR, 1NE
Adjuvant tamoxifen	3	
Adjuvant oophorectomy	1	
Provera (400 mg od)	1PR, 1PD	2SD, 4PD
Aminoglutethimide (250 mg bd)		1PR, 1SD, 2NE
Leuprorelin		1SD
Decadurabolin		1PR
(c)		
Tamoxifen (20 mg od)	3CR, 3PR, 6SD, 11PD	2PR, 6PD
Adjuvant tamoxifen	1	
Provera (400 mg od)	2PR, 1SD	1PR, 1SD, 4PD
Aminoglutethimide (250 mg bd)	1CR, 1SD	6SD, 4PD
Leuprorelin	2PD	1SD, 2PD
Adjuvant aminoglutethimide	1	
4-Hydroxyandrostenedione		3PD
Oophorectomy		1SD, 1PD

(a) Patients responding to third-line treatment; (b) patients achieving SD or symptomatic response to third-line treatment; (c) patients with PD on third-line treatment.
CR = Complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

the remaining 22 patients in addition were known to have visceral disease or metastatic bone disease.

Third-line treatment included provera (19 patients), aminoglutethimide (11 patients), decadurabolin (1 patient) and 4-hydroxyandrostenedione (1 patient). Details of first- and second-line treatments together with response are given in Table 1.

DISCUSSION

Response to second-line endocrine therapy is well established in the treatment of advanced breast cancer [6] and third-line endocrine treatment is widely used in clinical practice. We have found it difficult, however, to estimate the efficacy of third-line endocrine treatment from the published literature as there are few studies documenting response to third-line endocrine treatment. The response rates quoted range from 26 to 35% [12, 19, 21] but either the numbers [12, 19] have been small or UICC criteria [21] have not been used to define response.

Retrospective analysis of the 55 patients who received third-line endocrine therapy shows a median overall survival from the start of third-line treatment of 16 months (Fig. 1b). Of these 55

patients 42% achieved clinical benefit from third-line endocrine therapy, with 15% achieving an objective response and a further 27% disease stabilisation and/or symptom relief. The median survival for those achieving an objective response was 28 months and for those who achieved SD was 40 months ($P>0.05$). Taken together these 23 patients had a statistically significant better median overall survival (34 months) than the 32 patients who failed to respond to third-line endocrine therapy (14 months) ($P<0.01$).

It has previously been shown that patients with advanced breast cancer who achieve SD for 6 months or longer survive as long as those achieving an objective response [22] and from our study this appears to be true for third-line endocrine therapy. Although our data suggests that those patients responding to first- or second-line therapy are more likely to gain benefit from third-line therapy the numbers are too small to allow any more precise predictions regarding who is likely to respond to third-line endocrine therapy, although those patients with visceral disease would appear less likely to respond.

17 of the 23 patients (74%) responding or achieving SD to third-line endocrine therapy were treated with aminoglutethimide and hydrocortisone. This is not simply a reflection of our clinical practice, since 51% of patients received aminoglutethimide as third-line endocrine treatment compared with 47% who received provera. Most studies of second-line response to progestins and aminoglutethimide show them to be comparable [12, 13] and there is no obvious reason why the response to aminoglutethimide and progestins should differ for third-line treatment.

With the introduction of an increasing range of new low toxicity endocrine treatments for breast cancer, more treatment options now exist and our data suggest that even with advanced disease many patients may benefit from third-line endocrine treatment.

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