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Results of Endocrine Therapy do not Predict Response to Chemotherapy in Advanced Breast Cancer

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Abstract—*One hundred and four patients with advanced breast cancer treated with adriamycin +/- vincristine had had prior endocrine therapy. Of* 28 *responders to prior endocrine therapy a response to subsequent chemotherapy occurred in* 15 (54%); *the response frequency in the* 76 *non-responders to endocrine therapy was* 51% (39 *patients). The median time to treatment failure was not significantly different between responders to prior endocrine treatment and non-responders* (7 months *vs* 5 months; P = 0.136). *Although the median survival from starting chemotherapy tended to be longer in the endocrine responders* (18 months) *than in the non-responders* (12 months), *there was no significant difference between the two groups* ($\chi = 2.749$; P = 0.097). *In a subgroup of* 31 *non-responders to endocrine therapy who had had stable disease* (≥6 months) *the median time to treatment failure was* 6 months *and median survival* 13 months. *This lack of differences existed for each subgroup of endocrine therapy. Response to prior endocrine treatment was not shown to be a determinant of response to subsequent chemotherapy.*

INTRODUCTION

RECENTLY attempts have been made to identify prognostic factors for response to chemotherapy in advanced breast cancer [1, 2]. There have been conflicting reports on the effect of prior endocrine treatment on the response to subsequent chemotherapy [3–7]. This report concerns an analysis of patients with advanced breast cancer who were treated with chemotherapy after previous endocrine therapy, the response to hormone treatment being correlated with the response to subsequent chemotherapy.

MATERIALS AND METHODS

Patients

The 104 patients had either locally advanced inoperable or disseminated breast cancer which on progression had been treated with primary endocrine therapy. Pre-menopausal women had ovarian ablation either surgically or by irradiation +/- prednisolone 5 mg b.d. (41 patients). Post-menopausal patients received either tamoxifen 10 mg b.d. +/- prednisolone 5 mg b.d. (46 patients), oestrogens (stilboestrol 50 mg daily or ethinyloestradiol 1 mg daily) or androgens (fluoroxymesterone 10 mg b.d. or t.d.s.). On progression of disease endocrine treatment was stopped and a period of 1 month with no treatment followed to exclude a withdrawal response before commencing chemotherapy. Ninety-three patients (89%) received chemotherapy after progression on first endocrine treatment. Only 11 (11%) had two successive different endocrine treatments before proceeding to chemotherapy.

Subsequently, on further progressive disease chemotherapy was given in a prospective randomised clinical trial designed to assess the contribution of vincristine to adriamycin [8]. Patients were randomly allocated to receive adriamycin 70 mg/m² i.v. (60 mg/m² if age ≥60 yr) on day 1 of a 3-weekly cycle either alone or in combination with vincristine 1.4 mg/m² (maximum 2 mg) on days 1 and 8. After 8 cycles of treatment, or earlier in the event of progressive disease, treatment was continued with cyclophosphamide 100 mg/m²/day p.o. (maximum 150 mg/day) on days 1–14 of a 4-weekly cycle with

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methotrexate 30 mg/m² i.v. (maximum 50 mg) and 5-fluorouracil 600 mg/m² i.v. (maximum 1000 mg) on days 1 and 8. In patients 60 yr old or more the dose of cyclophosphamide was reduced to a maximum 100 mg/day p.o., methotrexate to 20 mg/m² i.v. (maximum 40 mg) and 5-fluorouracil to 400 mg/m² i.v. (maximum 1000 mg). This regimen (CMF) was given at 4-weekly intervals until progression of disease.

Because no significant differences in response frequency (57 vs 52%), time to treatment failure and survival were found between the two regimens [8] the 104 patients were pooled for the purpose of the present analysis. Only 4 patients achieved an improved response category on CMF and these were included in the analysis.

Before commencing endocrine and chemotherapy all patients had evidence of progressive disease. They were assessed clinically, measurements being taken of all visible and palpable lesions. A bone survey (radiological and/or isotopic) and chest X-ray were done in all cases, and isotopic liver scans were carried out when indicated. The patients were assessed periodically at either 3- or 4-weekly intervals, according to the chemotherapy schedule being given.

The response to endocrine and cytotoxic chemotherapy was assessed according to the criteria recommended by the UICC [9, 10], the records of all patients being reviewed by two independent extramural assessors.

Response categories

Complete response (CR): disappearance of all known disease. In the case of lytic bone metastases, these were shown radiologically to have recalcified; partial response (PR): >50% decrease in the product of perpendicular diameters of measurable lesions and objective improvement in other assessable lesions, these observations being confirmed on two successive occasions at least 1 month apart with no new lesions appearing; no change (NC): lesions unchanged (i.e. <50% decrease or <25% increase in the size of measurable lesions) for a period of at least 6 months; progressive disease (PD): progression of some or all lesions and/or appearances of new lesions.

Time to treatment failure (TTF)

This was the time from the start of therapy until either new lesions appeared or any existing lesion increased by 25% or more above its smallest size recorded. TTF is equivalent to the duration of response in patients with CR or PR [10].

Oestrogen receptors

Oestrogen receptor content of primary or metastatic tissue was estimated by the method of King *et al.* [11]. A value of less than 5 fmol receptor/mg cytosol protein was regarded as negative (ER−) and any value greater than this was positive (ER+).

Statistical methods

Survival and time to treatment failure were analysed by the log-rank method [12]. The significance of differences between binary variables was calculated by the chi-square test for one degree of freedom.

RESULTS

Of 104 patients analysed in this study 41 were pre-menopausal and 63 post-menopausal at the start of primary endocrine therapy. The characteristics of patients in the different response categories to prior endocrine treatment are detailed in Table 1, from which it is seen that the sites of involvement were generally similar in the three groups. The median age at diagnosis, the age at start of endocrine therapy and the sites of involvement were similar. Responders to endocrine treatment tended to have a longer median post-operative disease-free interval than those with no change or non-responders respectively (22 vs 19 vs 17 months). A simiar trend was seen for the interval between start of endocrine treatment and start of chemotherapy. In the 28 responders to endocrine therapy (response rate 27%) no complete responses were seen.

Subsequent chemotherapy with adriamycin or adriamycin + vincristine yielded a response frequency of 54% (15/28) in patients who had a partial response to prior endocrine treatment, a response frequency of 51% (39/76) being observed in those patients with no prior response (NC + PD) to primary endocrine therapy.

Median time to failure from start of chemotherapy was 7 months (range 1–28+) in the responders to prior endocrine treatment and 5 months (range 1–27) in the non-responders ($\chi^2 = 2.222$; $P = 0.136$). There was a trend for median survival time from start of chemotherapy to be longer in responders to hormonal therapy (18 vs 12 months), but this was not statistically significant ($\chi^2 = 2.749$; $P = 0.097$) (Fig. 1). In the subgroup of patients who had had stable disease for ≥6 months ($n = 31$) the median time to treatment failure was 6 months (range 3–31+ months) from the start of chemotherapy.

This lack of differences existed for each subgroup of endocrine therapy (Table 2). There was a minor tendency for pre-menopausal patients to respond more frequently to sub-

Table 1. Characteristics of patients in the different response categories to prior endocrine treatment

	Response ($n = 28$)	No change ($n = 31$)	Progressive disease ($n = 45$)
Median age at diagnosis (yr)	48	48	48
Stage at diagnosis (no patients)			
operable (I, II)	21	21	36
inoperable (III, IV)	7	10	9
Median (and range) of post-operative disease-free interval (months)	22 (0–184)	19 (0–233)	17 (0–125)
Median age at start endocrine therapy (yr)	52	54	52
Median age at start chemotherapy (yr)	56	55	52
Oestrogen receptor status at diagnosis			
$\geqslant 5$ fmol/mg protein	12	13	14
<5 fmol/mg protein	3	2	15
unknown	13	16	16
Sites of involvement at start of chemotherapy (no patients)			
bone	15 (58%)	20 (65%)	21 (45%)
lymph nodes	13 (50%)	16 (52%)	34 (72%)
skin	14 (54%)	20 (65%)	31 (66%)
lung and/or pleura	13 (50%)	11 (35%)	22 (47%)
liver	1 (4%)	2 (6%)	5 (11%)

Table 2. Response to chemotherapy related to prior responses to primary endocrine therapy

		Prior response to endocrine therapy	Subsequent response to chemotherapy*
1 Ovarian ablation ($n = 41$)	PR	12 (29%)	6/12 (50%)
	NC+PD	29 (71%)	12/29 (41%)
2 Androgens/oestrogens ($n = 17$)	PR	7 (41%)	4/7 (57%)
	NC+PD	10 (59%)	6/10 (60%)
3 Tamoxifen ($n = 46$)	PR	9 (20%)	5/9 (56%)
	NC+PD	37 (80%)	21/37 (57%)

*Numerator = No. responding to chemotherapy; denominator = No. receiving chemotherapy.

Table 3. Response to chemotherapy related to ER status

	No. of patients (%)		
Response to chemotherapy	ER+ ($n = 39$)	ER- ($n = 20$)	ER unknown ($n = 45$)
CR+PR	24 (62%)	12 (60%)	22 (49%)
PD+NC	15 (38%)	8 (40%)	23 (51%)

sequent chemotherapy after prior response to ovarian ablation. The response to chemotherapy according to ER status is shown in Table 3. There was no difference in the objective regression rate between ER-positive and ER-negative tumours. However, the group of patients in whom no receptor data were available is relatively large (43%).

DISCUSSION

Endocrine therapy is the first-choice systemic treatment for most patients with advanced breast cancer, chemotherapy usually being administered after endocrine treatment has failed [13]. It has been reported that patients who respond to prior hormonal treatment have a significantly longer duration of response as well as a longer survival

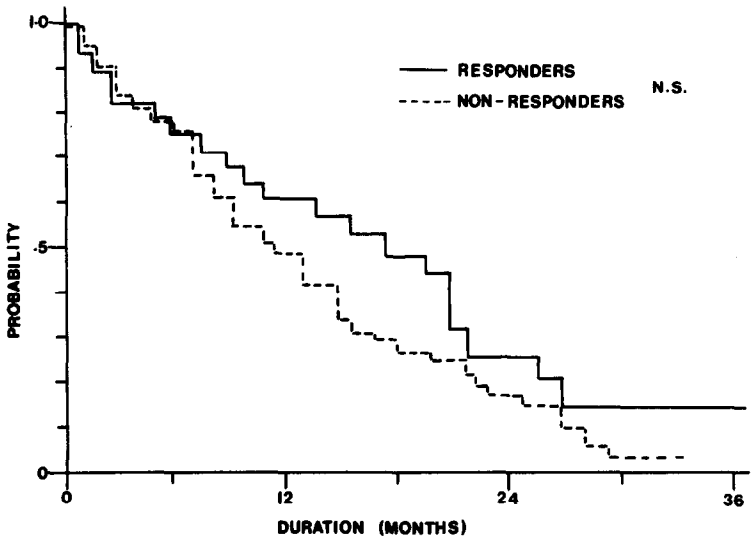

Fig. 1. Probability of survival from start chemotherapy in responders (n = 28) (————) *vs non-responders* (n = 76) (--------) *to prior endocrine therapy* ($\chi^2 = 2.795$; P = 0.09).

from start of chemotherapy than non-responders, although the response frequency to chemotherapy is similar for both groups [4, 5, 7]. Valagussa *et al.* [3] found that prior endocrine therapy was associated with a poor response to subsequent chemotherapy.

The data reported here indicate that the outcome of subsequent chemotherapy is not influenced significantly by the previous response to primary endocrine treatment for advanced breast cancer. This result is consistent with a previous report which showed that oestrogen receptor status is not a determinant of response to chemotherapy [6].

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