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Oestrogen Receptors and Response to Cytotoxic Chemotherapy in Advanced Breast Cancer

R. D. Rubens[1], R. J. B. King[2], Sheila Sexton[1], M. J. Minton[1], and J. L. Hayward[1]

[1] Imperial Cancer Research Fund Breast Cancer Unit, Guy's Hospital, London, SE1 9RT, England
[2] Department of Hormone Biochemistry, Imperial Cancer Research Fund Laboratories, Lincoln's Inn Fields, London, WC2A 3PX, England

Summary. *Of 54 patients with advanced breast cancer, 21/37 (57%) with oestrogen receptor-positive (ER+) tumours and 11/17 (65%) with oestrogen receptor-negative (ER−) tumours responded to cytotoxic chemotherapy. These data and a survey of the literature indicate that oestrogen receptor status is not a determinant of response to chemotherapy. However, ER+ tumours seem to grow more slowly than ER− ones and the response to chemotherapy tends to be longer in ER+ patients.*

Introduction

Breast cancers that lack high-affinity cytoplasmic oestrogen-binding proteins (oestrogen receptors) tend to be less well-differentiated histologically and have higher thymidine labelling indices than tumours containing these receptors [9]. This has led to speculation that oestrogen receptor-negative tumours may be more sensitive to cytotoxic chemotherapy, but evidence for this hypothesis is conflicting [7, 5]. This report is of a retrospective analysis of patients with advanced breast cancer treated by cytotoxic chemotherapy in the Guy's Hospital Breast Unit on whom oestrogen receptor information is available.

Patients and Methods

All patients with breast cancer of known oestrogen receptor (ER) status who had received cytotoxic chemotherapy for advanced disease were considered eligible for this analysis, provided that the disease was evaluable for objective response according to the criteria of the UICC [2].

ER analyses were carried out by the method of King et al. [6] on either primary or metastatic tumours before patients had received any form of endocrine treatment. Receptor-negative patients were defined as having less than 5 fmol receptor/mg cytosol protein. All patients had had prior endocrine therapy, but not cytotoxic chemotherapy, for advanced disease. The cytotoxic regimens used were in accordance with protocol requirements current for this Unit at the time and have been described in detail previously [12, 13]. They included cyclophosphamide alone; cyclophosphamide + methotrexate + 5-fluorouracil + vinblastine; adriamycin ± vincristine; and cyclophosphamide + methotrexate + 5-fluorouracil.

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

The response to cytotoxic chemotherapy was assessed according to the criteria recommended by the UICC, the records of all patients being reviewed by two extramural assessors without knowledge of the ER values [2].

Objective Regression

Complete Response. Disappearance of all known disease. In the case of lytic bone metastases, these must be shown radiologically to have calcified.

Partial Response. A ≥ 50% decrease in the sum of the products of the perpendicular axes of measurable lesions and objective improvement in evaluable, but nonmeasurable lesions; no new lesions. It was not necessary for every lesion to have regressed for partial response to be recorded, but no lesion should have progressed.

No Change

Lesions unchanged (i.e., less than 50% decrease or less than 25% increase in the size of measurable lesions).

Progressive Disease

Mixed. Some lesions regressed while others progressed or new lesions appeared.

Failure. Progression of some or all lesions and/or appearance of new lesions; no lesions regressed.

Reprint requests should be addressed to: R. D. Rubens

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Results

There were 54 patients eligible for this study, 37 of whom had ER+ tumours and 17 ER− tumours. The characteristics of these patients are detailed in Table 1, from which it is seen that the ages, stage of disease at diagnosis, and sites of involvement are generally similar in the two receptor groups. The preponderance of soft-tissue disease reflects the ready accessibility of such sites for receptor assays. Patients with ER+ tumours had longer postoperative disease-free intervals, but the difference is not statistically significant. The time from diagnosis to the start of chemotherapy for advanced disease is also longer in patients with ER+ tumours, and this difference is significant ($P < 0.05$, Student's t-test). Treatments received by the patients are summarized in Table 2.

The response to cytotoxic chemotherapy according to ER status is shown in Table 3, there being no difference in the objective regression rate between the two groups. The median duration of response tended to be longer in ER+ patients, but this difference is not statistically significant when analysed by the log rank method [10] (Fig. 1); $\chi^2 = 0.72$.

To compare the relative speeds of response in the two receptor groups, the responses obtaining after 2 months

Table 1. Patient characteristics

	ER+ ($n = 37$)	ER− ($n = 17$)
Age at diagnosis (years)		
Mean	51.2	50.6
Range	26–74	32–73
Stage at diagnosis (no. patients)		
Operable (I, II)	24 (65%)	11 (65%)
Inoperable (III, IV)	13 (35%)	6 (35%)
Postoperative disease-free interval (months)		
Mean	17.1	10.7
Range	0–54	0–36
Time from diagnosis to start of chemotherapy (months)		
Mean	41.5	23.7
Range	3–135	3–54
Sites of involvement at start of chemotherapy (no. of patients)		
Breast	18 (49%)	7 (41%)
Lymph nodes	27 (73%)	10 (59%)
Skin	24 (65%)	10 (59%)
Skeleton	21 (57%)	4 (23%)
Pleura	10 (27%)	1 (6%)
Lungs	7 (19%)	4 (23%)
Pericardium	0 (0%)	1 (6%)
Liver	5 (13%)	5 (29%)
Ascites	4 (11%)	1 (6%)

Table 2. Previous and current treatments

	No. of patients (%)	
	ER+ ($n = 37$)	ER− ($n = 17$)
Previous postoperative adjuvant chemotherapy	1	1
Prior endocrine therapy for advanced disease		
Ovarian ablation	14 (38%)	8 (47%)
Androgens	11 (30%)	5 (29%)
Oestrogens	9 (24%)	2 (12%)
Antioestrogens	5 (14%)	3 (18%)
Corticosteroids	6 (16%)	2 (12%)
Hypophysectomy	5 (14%)	3 (18%)
No. of patients with an objective response to one or more previous endocrine treatments	8/27 (22%)	1/17 (6%)
Current chemotherapy		
Regimens including adriamycin	26 (70%)	14 (82%)
Regimens excluding adriamycin	11 (30%)	3 (18%)

Table 3. Response to cytotoxic chemotherapy

	ER+ ($n = 37$)	ER− ($n = 17$)
Response category (no. of patients)		
Objective regression		
Complete response	5	5
Partial response	16 } 21 (57%)	6 } 11 (65%)
No change	0	0
Progressive disease	16 (43%)	6 (35%)
Duration of objective regression (weeks)		
Median	103	28
Range	6 to 156+	13+ to 113+

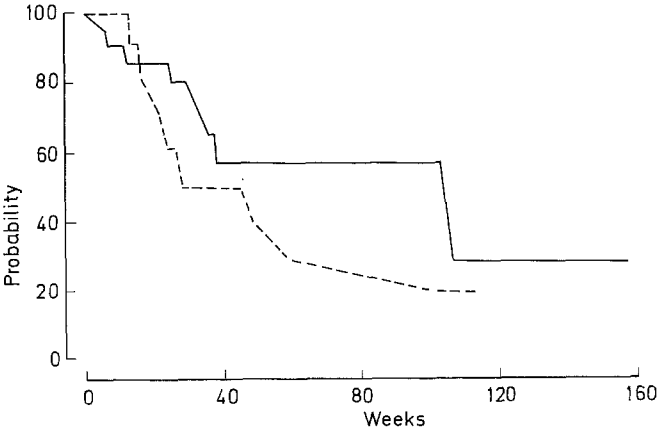

Fig. 1. Percent probability of duration of response to cytotoxic chemotherapy. ——, ER+ ($n = 21$); – – –, ER− ($n = 11$)

of treatment in the responders were studied. Of the 21 responders with ER+ tumours, 18 (86%) had achieved an objective response at 2 months, as against 8/11 (73%) with ER− disease. Complete responses were present in 1 out of 5 ER+ and in 3 out of 5 ER− patients at this time. Hence there is no apparent difference in the speed of response between the two receptor categories.

Discussion

Lippman et al. have reported that 35/45 (76%) patients with ER− tumours respond to cytotoxic chemotherapy, while only 3/25 (12%) of ER+ patients do so. The converse was observed by Kiang et al., who found that 86% of patients with ER+ tumours responded to chemotherapy, as against only 36% with ER−. The data reported here confirm neither of these reports, but suggest that the response to cytotoxic chemotherapy is similar for ER+ and ER− tumours, although it is conceded that a slight difference would be obscured in a small series. The regressions achieved tended to be longer in ER+ patients, but not significantly so. Other reports similarly have not supported the concept that there is a relationship between ERs and cytotoxic chemotherapy (Table 4).

The longer duration of responses, longer mean postoperative disease-free intervals, and longer mean times from diagnosis to start of chemotherapy indicate that ER+ tumours seem to grow more slowly than ER− ones, but receptor status does not appear to be a determinant of response to chemotherapy. The rapidity of response was similar in the two receptor groups.

It is possible that the receptor status of tumours could have been changed by prior endocrine therapy before chemotherapy was started. The occurrence of such a phenomenon could account for the disparity between results so far reported. To clarify whether or not this is the case, a prospective study, in which receptors will be measured immediately before cytotoxic drugs are given, is now being planned.

Table 4. Published results on the association between oestrogen receptor status and response to cytotoxic chemotherapy in advanced breast cancer

Authors	No. of patients responding/ total treated	
	ER+	ER−
Bonnadonna et al [1]	14/28 (50%)	7/16 (44%)
Hilf et al [3]	15/26 (58%)	20/33 (61%)
Kiang et al [5]	24/28 (86%)	13/36 (36%
Lippman et al [7]	3/25 (12%)	34/45 (76%)
Jonat and Maas [4]	6/14 (43%)	20/28 (71%)
Marsland et al [8]	15/18 (78%)	7/15 (46%)
Rosner and Nemoto [11]	5/15 (33%)	9/19 (47%)
	82/154 (53%)	110/192 (57%)

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