The Definition of the 'No Change' Category in Patients Treated with Endocrine Therapy and Chemotherapy for Advanced Carcinoma of the Breast

A. HOWELL,* J. MACKINTOSH,* MARY JONES,† JUDITH REDFORD,‡ J. WAGSTAFF* and R.A. SELLWOOD‡

*CRC Department of Medical Oncology and †Department of Statistics, Christie Hospital and Holt Radium Institute, Wilmslow Road, Manchester and ‡Department of Surgery, Withington Hospital, Nell Lane, Withington, Manchester M20 9BX, U.K.

Abstract—*In the criteria used for assessment of response to treatment for advanced breast cancer the definition of no change (NC) is clear; however, there is no indication of the duration of stabilization required for patients to qualify for this category of response. We have made the assumption that NC is a worthwhile category of response if the overall time to progression (TTP) and survival of this group is not significantly different from patients with partial remissions (PR). Two hundred and sixty-three evaluable patients treated with endocrine therapy and 302 evaluable chemotherapy-treated patients were studied and the TTP and survival curves for PR and periods of NC from 1 to 6 months compared. For the endocrine-treated patients the TTP and survival curves for NC became non-significantly different from the PR curves after 4 and 5 months respectively. For chemotherapy-treated patients the TTP curves became non-significantly different from PR at 4 months and for survival the period was 3 months. In order to define NC as a useful category of response and to eliminate the possibility that NC taken for a shorter period could simply represent a slowly progressive tumour, we suggest that the minimum period of disease stabilization be taken as 5 months for both endocrine- and chemotherapy-treated patients.*

INTRODUCTION

THE CRITERIA for evaluating the response to treatment in patients with advanced cancer of the breast are well established and generally acceptable. This standardization has made the comparison of results from centre to centre and between different treatments more reliable.

The no change (NC) category of response is defined in all international criteria as the maintenance of a <50% decrease or a <25% increase in size of measurable lesions. In the most widely utilized criteria for cancer of the breast published for the International Union Against Cancer (UICC) by Hayward *et al.* [1] there is no mention of the duration of stabilization required for patients to qualify for the NC category; in other published criteria the period is taken as 1 month for non-osseous metastases and 2 or 3 months for osseous metastases [2, 3].

Advanced breast cancer patients achieving a partial remission (PR) with either endocrine therapy or chemotherapy usually survive longer than those with progressive disease. We recognize that this may not be related to the treatment or indeed to a direct effect of response on survival but rather that response may identify a group of patients with pretreatment characteristics favouring longer survival. The problems of analysing survival by tumour response have recently been reviewed [4]. Given these limitations, a comparison of survival curves by response category may still be clinically useful in predicting the subsequent course of a patient's disease, PR being associated with longer survival [5–17]. There is less certainty concerning the value of NC. In some reports patients with NC have similar durations of response and survival as patients with PR [5–11, 18, 19]; in others the NC group fare less well [12–17]. This may be due to

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Address for correspondence: Dr A. Howell, Senior Lecturer and Consultant, Department of Medical Oncology, Christie Hospital, Manchester, U.K.

the variability of response criteria, in particular the minimum required duration of NC. Tonkin *et al.* [20] have shown how even subtle differences in 'standard' response criteria may cause marked variability in reported response rates.

In this study of patients with advanced breast cancer we compared the TTP and survival of partial responders and patients with NC. We have made the assumption that NC is of 'value' if these patients fare as well as those with a PR. We have therefore taken various time periods for the definition of NC (1, 2, 3, 4, 5 and 6 months) and compared the overall time to progression (TTP) and survival so produced with those in patients who have a definite PR. The data suggest that periods of NC from 4 to 5 months indicate subsequent response duration and survival times equivalent to those for advanced patients with PR.

MATERIALS AND METHODS

Patients: endocrine therapy

Two hundred and sixty-three patients treated with tamoxifen (post-menopausal) or ovarian ablation (pre-menopausal) were studied. One had previous systemic treatment for advanced disease although 34 were treated with adjuvant chemotherapy. All patients had progressive disease at the time of entry to the study and were evaluable for response according to UICC criteria [1].

Chemotherapy

Three hundred and two patients were treated with several regimens of combination chemotherapy most of which have been previously described: CMFP [21]; AC [22]; vincristine, adriamycin, cyclophosphamide and prednisolone (VAP cyclo) [23]; dibromodulcitol, mitomycin C and vinblastine (DMV) [24]; and an oral regimen of CMF (CMFo) consisting of cyclophosphamide 250 mg/m^2, methotrexate 16 mg/m^2 and fluorouracil 500 mg given on the 1st, 3rd and 5th days of each week respectively. The majority of patients were treated as part of a randomized trial comparing CMFP (n = 100) and AC (n = 105), 20 were treated with VAPcyclo, six with DMV and 45 with CMFo. A further seven patients were given CMFP and 19 AC, but these patients were not in the trial.

Methods

Criteria for tumour response were as defined by Hayward *et al.* for the UICC [1]. In particular, survival was dated from the time of first treatment to death; duration of response was dated from the start of treatment to the date of tumour progression. Chemotherapy-treated patients were assessed at 3–4 week intervals and endocrine-treated patients at 4–8 week intervals. TTP and survival were calculated according to the method of Kaplan and Meier [25] and compared using the log-rank test [26]. The chi-squared test was used to compare tumour response categories and pretreatment patient characteristics. Mann–Whitney comparisons [27] of Karnofsky performance status were also made. Curves were plotted for durations of NC of 1, 2, 3, 4, 5 and 6 months. TTP and survival curves for patients with each period of NC were compared with the appropriate curves of patients with PR in order to determine the least period of stabilization where there was no statistical difference between NC and PR. Estrogen (ER) and progesterone receptor (PR) status was measured as previously described [28, 29].

RESULTS

Patient characteristics

Response according to the regimen used in patients treated with endocrine therapy and chemotherapy is shown in Table 1. For this analysis a minimum of 5 months of disease stabilization was taken for the definition of NC, as discussed below. For patients treated with endocrine therapy there were no significant differences in response to ovarian ablation (30 oophorectomy and two radiation-induced menopause) compared with tamoxifen (P = 0.48). For patients treated with chemotherapy there were no significant differences in response rates between regimens (P = 0.72).

The TTP for the tamoxifen-treated patients was significantly longer than for those treated with ovarian ablation (Fig. 1A) but there was no difference in survival between the two groups (Fig. 1B). There were no significant differences in either the TTP or the survival for any of the chemotherapy regimens (Fig. 1C and 1D). For the purposes of this analysis it was felt justifiable to combine all chemotherapy-treated patients into one group and all endocrine-treated patients into another group. The characteristics of the patients in these two groups is shown in Table 2.

Comparison of no change and partial response

Duration of NC was taken to be 1, 2, 3, 4, 5 and 6 months and a comparison of TTP and survival curves so produced made with those for patients with PR. Representative curves are shown in Figs. 2 and 3. Patients who progressed within the particular time periods taken for NC were placed in the progressive disease category. Clearly, as the period of NC was increased, less patients qualified for this category and more for the progressive disease category.

For endocrine-treated patients TTP and survival duration for NC were not significantly different from PR at 4 and 5 months respectively (Figs. 2 and 3). For chemotherapy-treated patients these

Table 1. Response according to the type of endocrine therapy and regimen of chemotherapy given

	Endocrine therapy			
	Ovx*	(%)	TAM	(%)
Number	32		231	
Complete response	1	(3)	22	(10)
Partial response	9	(28)	48	(21)
No change	7	(22)	55	(24)
Progressive disease	15	(47)	106	(46)

	Chemotherapy regimen									
	CMFP†		AC		VAPc		DMV		CMFo	
Number	107		124		20		6		45	
Complete response	12	(11)	11	(9)	2	(10)	0	(0)	5	(11)
Partial response	38	(36)	54	(43)	10	(50)	3	(50)	12	(27)
No change	17	(16)	18	(15)	2	(10)	2	(33)	8	(18)
Progressive disease	40	(37)	41	(33)	6	(30)	1	(17)	20	(44)

*Ovx = ovarian ablation; TAM = tamoxifen.
†See text for details of chemotherapy regimens.

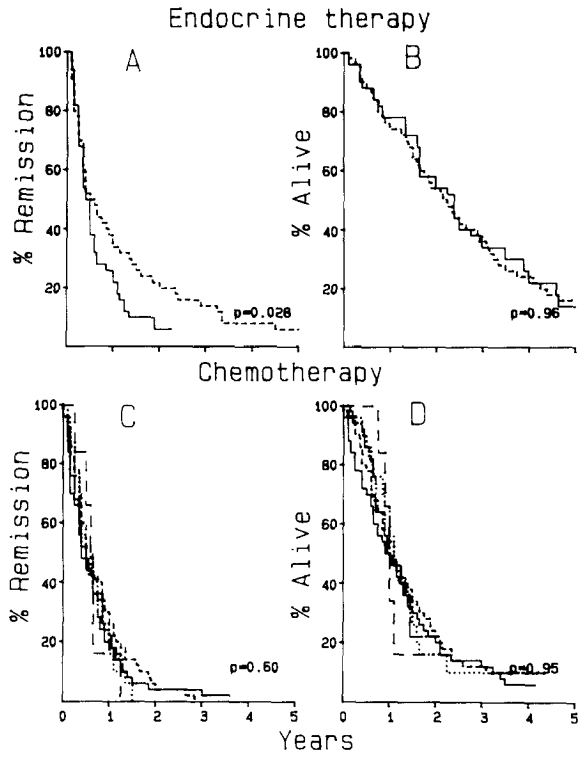

Fig. 1. Times to progression (TTP) and survival by treatment. (A) TTP and (B) survival duration for tamoxifen-treated patients (---) and those treated with ovarian ablation (——). (C) TTP and (D) survival duration for chemotherapy treated patients (---DMV, ———CMFP, ...RC, --- CMFo).

periods were 4 and 3 months respectively (Figs. 2 and 3).

DISCUSSION

The aim of the study was to find a period of NC which defined a group of patients with the same prognosis as those with PR. When this period of NC was defined as 1, 2, 3 or 4 months in patients treated with endocrine therapy the NC category clearly included some patients destined to relapse and die early, and the TTP and survival curves were intermediate between those of PR and progressive disease. However, when the minimum period of NC was taken as 5 months, durations of response and survival were equivalent to PR.

For chemotherapy-treated patients both TTP and survival curves became superimposable when NC was taken at 4 months, suggesting that a shorter period of stabilization is of some prognostic significance. However, we believe a minimum period of 5 months free from disease progression should be taken as standard for all categories of treatment, particularly with the widespread use of combined chemo-endocrine regimes. This period has the advantage that it should exclude from NC those patients with very slowly progressive disease who are unresponsive to systemic treatment.

The chemotherapy group had a much poorer prognosis than the endocrine therapy group with median survivals from the start of treatment of 13 and 27 months respectively. More of the chemotherapy patients had received previous systemic therapy and they formed a more advanced group as reflected by their poorer pretreatment Karnofsky performance status (Table 2). Paradoxically they did not have more sites of tumour involvement but a tendency to have more sites of visceral disease than the endocrine therapy group (Table 2). It is possible that the NC category fared well because this group had particularly favourable prognostic features. However, when the clinical features of the equivalent NC and PR patients were compared there were only minor differences for both the endocrine and chemotherapy-treated patients.

Table 2. Patient characteristics at the start of treatment

	Endocrine therapy	(%)	Chemotherapy	(%)
Number of patients	263		302	
Mean age	63		55	
<50	50	(19)	93	(31)
50+	213	(81)	209	(69)
Premenopausal	43	(16)	30	(10)
Perimenopausal	2	(5)	80	(26)
Postmenopausal	192	(73)	190	(63)
Not known	16	(6)	2	(1)
Previous systemic treatment				
Endocrine:				
adjuvant	—	—	36	(12)
advanced	—	—	183	(61)
Chemotherapy:				
adjuvant	34	(13)	—	—
Median RFI (months)	12		15	
Median time from 1st relapse to systemic treatment (months)	1		6	
Dominant site				
Soft tissue	84	(32)	86	(28)
Bone	77	(29)	62	(21)
Lung	58	(22)	100	(33)
Liver	17	(6)	34	(11)
Number of sites of disease				
1	114	(43)	133	(44)
2	83	(32)	95	(31)
3+	66	(25)	74	(25)
Karnofsky performance status				
90	123	(52)	41	(18)
80	61	(26)	74	(33)
70	39	(16)	52	(23)
≤60	14	(6)	59	(26)
Not known	26	—	76	—

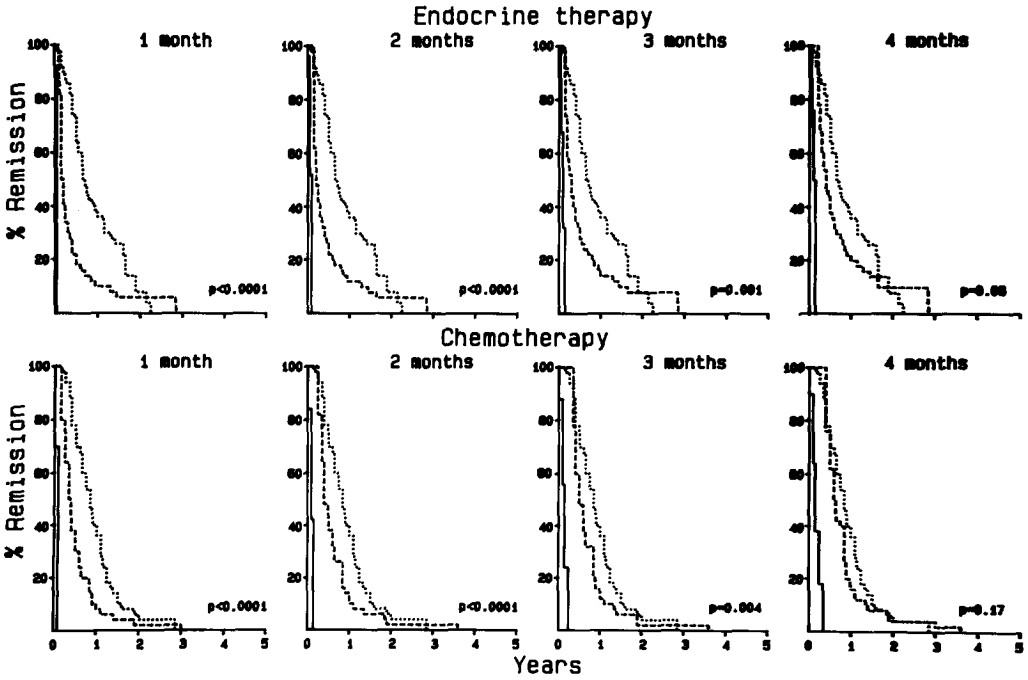

Fig. 2. Comparison of the times to progression between patients with a partial response (PR), no change (NC) between 1 and 4 months, and progressive disease (PD). P values refer to differences between PR and NC only (...PR, ---NC, ———PD).

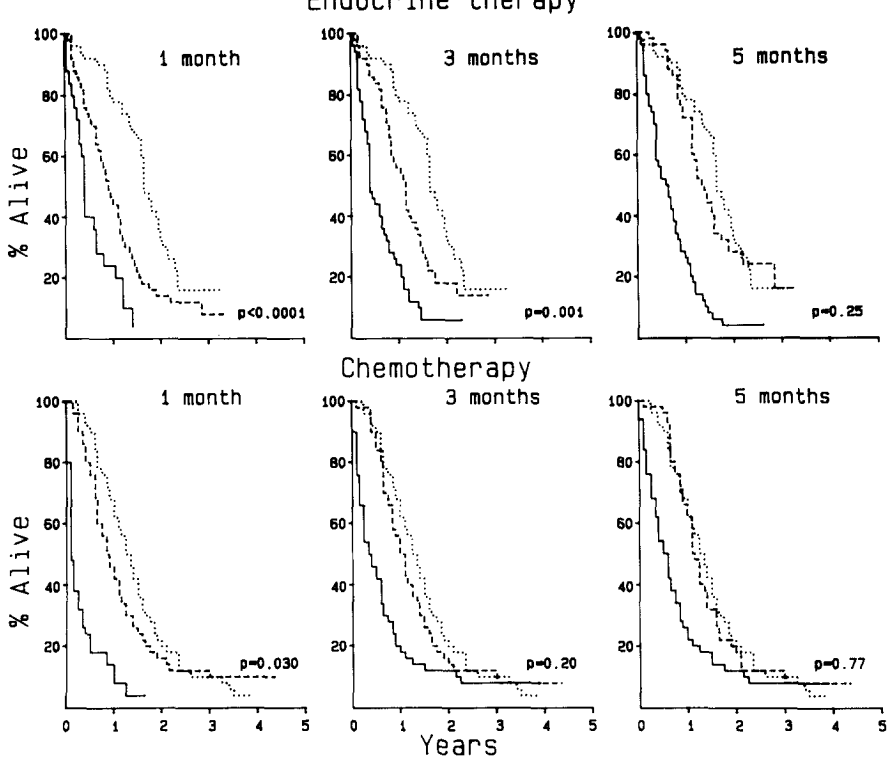

Fig. 3. Comparison of survival duration between patients with a partial response (PR), no change (NC) between 1 and 5 months, and progressive disease (PD). P values refer to differences between PR and NC only (...PR, ---NC, ———PD).

In phase three studies which compare different chemotherapy regimens, it is rare for one to have a significant survival advantage over the other even if the response rates of the two regimens are markedly different. For example, in the study of Nemoto *et al.* [5], four chemotherapy regimens were evaluated in patients with advanced breast cancer and whereas the response rates ranged from 18 to 63% (CR + PR) there were no differences in survival between any of the regimens. When NC (duration not defined) was added, the 'response' rates had a narrow range between 71 and 85%. The least effective regimen in conventional terms had the highest NC category; this may have contributed to the equivalent survival. Failure to define NC appropriately may lead to erroneous conclusions concerning the effectiveness of chemotherapy regimens and a more rigorous definition of this group of patients is required for this supposition to be tested.

We consider that in advanced breast cancer the NC category is valid provided a minimum duration of 5 months is taken. This will allow more meaningful comparisons of response rates between published clinical trials. In addition this NC category gives useful prognostic information and indicates that a treatment regimen should not be prematurely discontinued even if there is no objective tumour regression.

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