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II. Antiestrogens in Combination with Chemotherapy in Advanced Breast Cancer

CHEMOTHERAPY WITH OR WITHOUT TAMOXIFEN IN POSTMENOPAUSAL PATIENTS WITH LATE BREAST CANCER. A RANDOMIZED STUDY

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Summary—Eighty-one patients with advanced measurable breast cancer were randomized to receive only chemotherapy (Group C) or the same chemotherapy + tamoxifen (Group CH). The chemotherapeutic regimen was based on the cyclic administration of two noncross-resistant cytotoxic combinations: CMFV (cyclophosphamide 300 mg/m² i.v., days 1 and 5; methotrexate, 20 mg/m² i.v., days 1 and 4; 5-fluorouracil 325 mg/m² i.v., days 1–5; vincristine 0.75 mg/m² i.v., days 2 and 5) and AC (adriamycin 40 mg/m² i.v., day 1; cyclophosphamide 200 mg/m² i.v., days 3–5) every 4–5 weeks. Tamoxifen (10 mg) was given twice daily continuously. The treatment results were as follows in Groups C and CH, respectively: PD 19.4 and 6.3%, SD 38.9 and 18.7%, PR 27.8 and 56.2% and CR 13.9 and 18.7%. The difference in response (CR + PR) rate observed between the two treatment groups was highly significant ($P < 0.025$). Median time to progression was 10.6 months in Group C and 17.2 months in Group CH (NS). Median duration of survival was 20 and 34 months, respectively (NS). In conclusion: the addition of tamoxifen to chemotherapy significantly improved the results in terms of response rate and duration of responses. A significant benefit to short-term survival was also evident.

INTRODUCTION

The simultaneous administration of chemotherapy and hormone therapy appears to be one of the most promising ways for achieving control of early as well as disseminated breast carcinoma.

Hormonal agents and cytotoxic drugs have different mechanisms of action and their toxicities do not usually overlap. In addition, there is increasing evidence that breast cancer results from different cell clones which may not be inhibited by a single type of treatment. These basic considerations provide the rational for investigating the therapeutic possibilities deriving from the combination of endocrine and cytotoxic modalities [1].

In January 1978 a prospective, controlled randomized trial was undertaken at the National Cancer Institute in Genoa, Italy, to investigate whether the addition of tamoxifen to chemotherapy would produce better results than chemotherapy alone in terms of remission rate, duration of response and survival. The study was closed in July 1982 and the results obtained in these 6 years form the basis of the present analysis.

EXPERIMENTAL

Patient sample

Postmenopausal patients for at least 2 years (natural menopause) with advanced biopsy-proven breast cancer who had not received any prior chemotherapy and/or hormonal therapy were entered in the study. Other requirements included: age $\leqslant 75$ years; performance status (PS) $\leqslant 3$ (ECOG score); objectively evaluable or measurable disease; adequate bone marrow reserve (WBC $\geqslant 4000$ and platelets $\geqslant 120{,}000$); and absence of major electrocardiographic abnormalities. The main characteristics of the study patients are summarized in Table 1.

Drug treatment

Patients were randomly allocated to receive either chemotherapy (group C) or chemotherapy + hormonal therapy (Group CH). Patients in Group C received a treatment based on two noncross-resistant cytotoxic combinations, CMFV and AC, administered in 5-day courses every 4–5 weeks. Patients in Group CH received the same chemotherapy described above plus tamoxifen, at a daily dosage of 20 mg. Doses and schedules of cytotoxic drugs were as follows: regimen CMFV (cyclophosphamide 300 mg/m² i.v., days 1 and 5; methotrexate 20 mg/m² i.v., days 1 and 4; 5-fluorouracil 325 mg/m² i.v., days 1–5; vincristine 0.75 mg/m² i.v., days 2 and 5); regimen AC (adriamycin 40 mg/m² i.v., day 1; cyclophosphamide 200 mg/m² i.v., days 3–5). Two different alternating noncross-resistant regimens were employed in an attempt to prolong the duration of response and to decrease the total dose of adriamycin.

Tamoxifen was used because of its proven efficacy in postmenopausal breast cancer patients and its

Table 1. Main characteristics of evaluable patients

	Treatment	
	Chemotherapy	Chemohormone therapy
No. patients	36	32
Age: median (range)	60 years (48–74)	61 years (45–72)
Median duration of menopause	12 years	10 years
Median PS (ECOG score)	1	1
Disease-free interval (median)	26 months	34 months
Site of metastasis/total sites:		
Viscera	15/62 (24.2%)	17/53 (32.0%)
Bone	18/62 (29.0%)	15.53 (28.3%)
Soft tissues	29/62 (46.8%)	21/53 (39.7%)
No. sites/patient:		
1	22/36 (61.0%)	20/32 (62.5%)
2	9/36 (25.8%)	8/32 (25.0%)
>3	5/36 (14.0%)	4/32 (12.5%)
Dominant sites of metastasis:		
Viscera	12/36 (33.3%)	15/32 (49.6%)
Bone	14/36 (38.9%)	12/32 (37.5%)
Soft tissues	10/36 (27.8%)	5/32 (15.6%)

negligible side effects [2]. In both groups treatment was continued until progression of disease or for a total of 14 cycles. In the presence of myelosuppression, cytotoxic but not hormonal therapy was suspended until bone marrow was restored.

Assessment of response

Besides measurement in centimeters and photographs of all palpable lesions, baseline studies include chest X-ray, bone survey and/or scan, hemogram, liver and renal function tests. Liver scan and/or ecography were performed if needed.

Patients receiving at least three cycles of therapy were considered suitable for assessment of response, unless progression of disease had occurred previously. Assessment of response was then performed every 3 months. The criteria for assessment of response were those proposed by Hayward *et al.* for UICC [3]. In summary, the categories of response were as follows: *complete remission (CR)*—disappearance of all known sites of disease, with recalcification of osteolytic metastases, for at least 1 month; *partial remission (PR)*—at least a 50% decrease in the sum of the products of the largest perpendicular diameters of measurable lesions with partial recalcification of osteolytic metastases, associated with improvement in evaluable but nonmeasurable lesions, for at least 1 month; *stationary disease (SD)*—lesions unchanged, or a decrease of less than 50% or an increase less than 25% in the sum of the products of the two largest perpendicular diameters of measurable mesions (patients in whom nonmeasurable but evaluable lesions representing the bulk of disease did not respond were also categorized as SD); *progressive disease (PD)*—greater than 25% increase in the sum of the products of the two largest perpendicular diameters of any measurable lesion and/or appearance of new lesions. In the case of a different response to treatment in the same patient without evidence of progressive disease, the category of response shown by the dominant site of metastasis was considered for analysis.

Table 2. Overall response rate

	Treatment		
Response	Chemotherapy	Chemohormone therapy	*P*
No. evaluable patients	36	32	
CR	5/36 (13.9%)	6/32 (18.8%)	<0.85
PR	10/36 (27.8%)	18/32 (56.2%)	<0.05
Total response (CR + PR)	15/36 (41.7%)	24/32 (75.0%)	<0.025
SD	14/36 (38.9%)	6/32 (18.7%)	<0.13
PD	7/36 (19.4%)	2/32 (6.3%)	<0.22

Statistical comparisons of the response rates in the two treatment arms has been performed by means of the χ^2-test. Actuarial progression-free survival (PFS), median time to progression (MTP) and actuarial survival (S) have been calculated from the beginning of treatment according to the Kaplan–Meier product limit procedure and compared by means of the log–rank test and the Cox–Mantel test [4, 5].

RESULTS

Overall, 81 patients were entered in the study. Eight patients were not considered for evaluation because they did not fulfill entry requirements. Therefore 73 patients, 39 in Group C and 34 in group CH, remained available for comparative analysis of S and PFS. Among these patients, 3 were lost to follow-up and 2 died of progressive disease before the completion of the third therapeutic cycle (early deaths). Thus, a total of 68 patients, 36 in Group C and 32 in Group CH, were fully assessable for response to therapy.

Table 2 shows the overall response rate to therapy in both treatment groups: 15 out of 36 patients in Group C (42%) and 24 out of 32 patients in Group CH (75%) achieved a complete or a partial response. This difference is statistically significant ($P < 0.025$) and is mainly due to the difference in partial response rates. It is noteworthy that patients receiving the combined treatment also showed a lower PD rate.

The response by metastatic sites is shown in Tables 3 and 4. The addition of tamoxifen to chemotherapy achieved a higher response rate for every metastatic site, the therapeutic advantage approaching and reaching significance for soft tissue and viscera lesions, respectively. To date 34 patients have progressed in Group C as compared to 27 in Group CH. Progestins alone (medroxiprogesterone acetate

Table 3. Response by metastatic sites

	Treatment		
Metastatic site	Chemotherapy	Chemohormone therapy	*P*
Viscera	7/15 (46.7%)	15/17 (88.2%)	<0.05
Bone	4/18 (22.2%)	7/15 (46.6%)	<0.27
Soft tissues	15/29 (51.7%)	17/21 (80.9%)	<0.072
Total	26/62 (41.9%)	39/53 (73.6%)	<0.001

Table 4. Response by dominant site of metastasis

	Treatment	
Dominant site	Chemotherapy	Chemohormone therapy
Viscera	6/12 (50.8%)	13/15 (86.7%)
Bone	4/14 (28.6%)	6/12 (50.0%)
Soft tissues	5/10 (50.8%)	4/5 (80.0%)

1 g p.o. daily) or in combination with mitomycin C (10 mg/m^2 i.v. every 6 weeks) have been the salvage treatment for most cases in both groups.

Figure 1 shows the curves representing actuarial PFS. The difference between the two treatment arms is statistically significant up to 36 months following the beginning of treatment (C = 10%; CH = 19.3% $P < 0.005$) but loses significance in the long run, the figures at 60 months being 5 and 6.73%, respectively ($P > 0.05$).

Median time to progression was 10.6 months in Group C as compared to 17.2 months in Group CH.

Actuarial S plots are shown in Fig. 2. Again patients receiving chemohormonal treatment appeared to do significantly better during the first 2 years after the start of treatment (C = 40.90%; CH = 69.73%; $P < 0.05$). In the long run the difference approaches significance up to 60 months (C = 5%; CH = 11%; $Z = 3{,}76$; $P = 0.05$). Median survival time was 20 and 34 months, respectively. Loss of significance in both cases at the end of the curves may probably be due to the small number of patients still in the study.

Side effects related to treatment were comparatively mild. Most patients experienced gastrointestinal complaints and hair loss. A few patients showed minor electrocardiographic changes related to adriamycin. Myelotoxicity was moderate and only in some cases was the prolongation of the interval between chemotherapy cycles required. However no case required the suspension of treatment. Tamoxifen did not appear to substantially increase the myelotoxicity from chemotherapy in group CH.

DISCUSSION

A few randomized studies have been performed with the aim of assessing the superiority of the combination of tamoxifen with cytotoxic chemotherapy over chemotherapy alone in advanced breast carcinoma.

Cocconi *et al.*[6] randomized postmenopausal patients to receive either CMF or CMF + tamoxifen (CMFT). Patients with prior endocrine therapy were permitted to enter the study. Overall, 145 patients were entered into the trial and final analysis showed that patients receiving combined chemohormonal treatment achieved a significantly higher response rate than patients receiving CMF alone (74 vs 51%; $P < 0.001$). Duration of response in the former group was also longer but not significantly so (51 vs 47 weeks). In contrast while no difference in overall survival was evident between the two treatment arms, patients treated with CMF alone appeared to benefit from a slightly longer survival. While a clear-cut effect upon response rate of combined regimen is evident in this trial, it is difficult to argue whether and to what extent the difference in treatment on progression (CMFT for patients failing CMF; the treatment was not specified for patients failing first

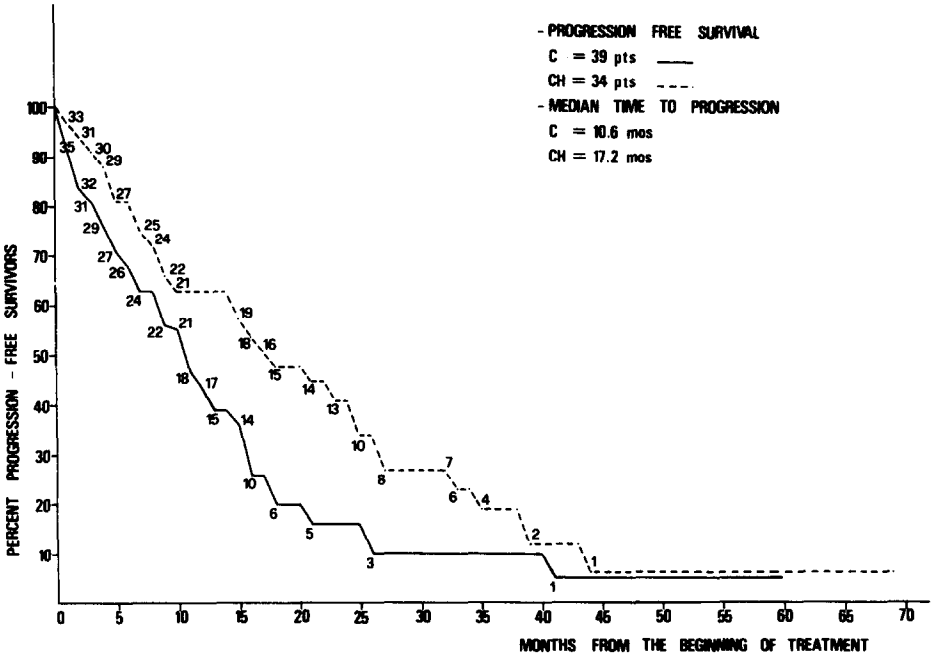

Fig. 1. Actuarial PFS of 39 patients receiving CMF and 34 patients receiving CMFT.

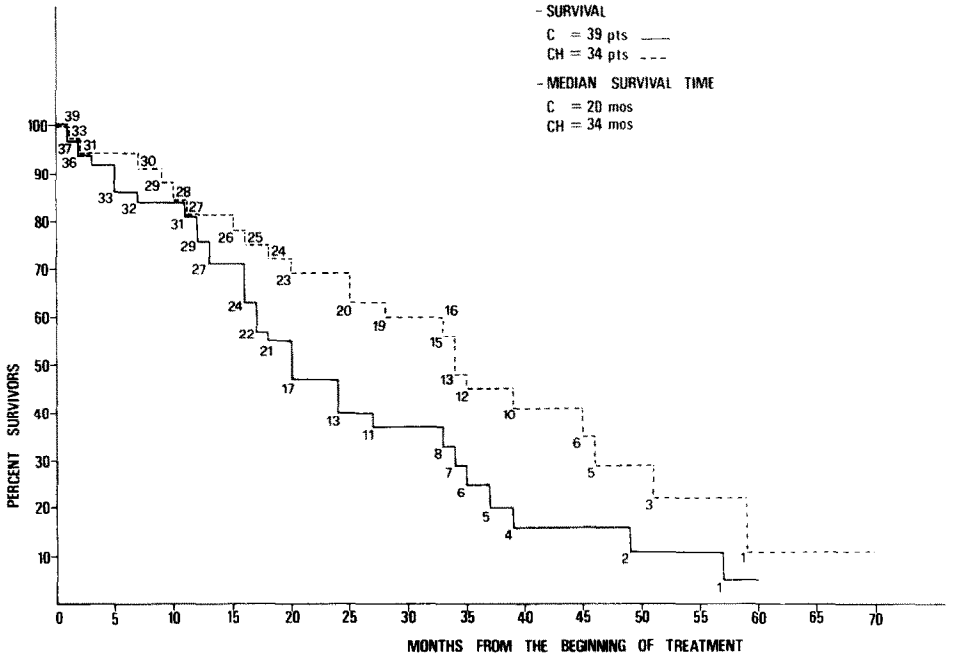

Fig. 2. Acturial S of 39 patients receiving CMF and 34 patients receiving CMFT.

line CMFT) might have influenced the behavior of survival in the two treatment arms.

Very close to Cocconi's trial is the design of a study carried out by the EORTC breast cancer cooperative group. Here again postmenopausal patients were randomized to receive either CMF alone or CMF in combination with tamoxifen (CMFT). Overall 263 patients were entered into the study, a small proportion of whom had been previously treated with hormonal therapy. Overall, 45% of patients receiving CMF alone showed a partial or a complete remission of their disease as compared to 72% of patients receiving in addition tamoxifen ($P < 0.0001$). Patients in the CMFT arm showed also a significantly longer time to progression and a consistently longer survival [7].

Tormey *et al.*[8] reported on 135 patients failing prior chemotherapy and hormonal manipulations, who had been randomly allocated to receive either a combination regimen including dibromodulcitol and adriamycin (DA) or the same cytotoxic regime plus tamoxifen (DAT). Patients in this study were both in pre- and postmenopause. Again patients receiving the DAT regimen showed a higher response rate (50 vs 29%; $P < 0.004$) and a longer duration of responses (280 vs 160 days; $P < 0.03$). Survival of patients receiving the DAT regimen was increased although not significantly so.

Results from our study are consistent with those previously reported as far as the effect of combined chemohormonal treatment upon response rate, duration of response and survival are concerned. It is worthwhile to note that neither in our study nor in others has Tamoxifen increased at any time the toxicity from cytotoxic treatment.

The effect of combined chemohormonal therapy upon survival still remains a matter for debate. In fact, while there is little doubt that the simultaneous administration of chemotherapy and endocrine therapy is able to achieve a higher response rate, it is still questionable whether the advantage observed in response rate can also affect survival and whether the sequential use of chemotherapy on endocrine therapy failure, would achieve similar or even better results.

The only study which has investigated this point is a large controlled one carried out by the Swiss Group for Clinical Cancer Research (SAAK), the interim results of which have been recently updated by Varini *et al.*[19]. Previously untreated postmenopausal patients with advanced breast cancer were randomized to receive either tamoxifen in combination with chemotherapy or tamoxifen alone initially, with chemotherapy added upon disease progression. A further randomization among three different cytotoxic regimens was also carried out in both groups. Overall, 42% remission rate was achieved in the group receiving tamoxifen + chemotherapy simultaneously while only 18% of patients responded to tamoxifen alone. However, 16% of patients in the latter group achieved a remission after subsequent addition of chemotherapy for an overall response rate of 34%. Median survival time was 23.5 months in the group receiving the two therapeutic modalities concurrently, as compared to 32.2 months in the group receiving chemotherapy on tamoxifen failure. Thus, no substantial difference both in response rate

and survival was evident between the two groups. In our opinion, however, any of the studies reported in the literature may give the correct solution to the question.

Survival of patients with disseminated breast carcinoma depends upon variables such as site of involvement, number of sites involved, prior treatment and response to prior treatment. Most studies have entered patients previously selected on the basis of response or failure after hormonal and/or cytotoxic treatment, thus with different life expectancies. Lack of standardization of treatment on progression may probably have enhanced this bias in some instances. Despite this, all studies but one showed a survival trend in favor of patients receiving chemotherapy and tamoxifen simultaneously. In our present study, patients who received combined chemohormonal therapy showed a longer survival than patients receiving chemotherapy alone.

Accordingly, a significant difference in the time to progression was found. In both cases however significance was lost in the long run probably due to the small number of patients still on study at the longest follow-up time. It is noteworthy to consider that all patients have probably been enrolled at the same time of relapse, thus with comparable expected survival, and that treatment on progression was also comparable, allowing all patients in our series to receive hormonal treatment at least once in the course of their disease.

In conclusion, our results and those of the literature indicate that the combination of tamoxifen with cytotoxic chemotherapy is additive and is more effective than tamoxifen or chemotherapy alone in inducing improved response rates and longer duration of response. These advantages are likely to be also reflected by a longer survival.

In view of these preliminary findings, larger trials, allowing proper stratification of patients according to basic risk factors such as menopausal status, dominant site of metastasis, hormonal receptor status and life expectancy, are warranted in order to provide a basis to select *a priori* those patients who are likely to derive major benefits from a combined approach.

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