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HORMONO-CHEMOTHERAPY IN THE TREATMENT OF ADVANCED BREAST CANCER

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Summary—The current situation in the treatment of metastatic breast cancer is reviewed. Overall the concurrent use of endocrine treatment and chemotherapy does not improve the therapeutic results as compared to a treatment encompassing only one modality. However, results diverge widely in different subgroups. Data emerging from various randomized trials are beginning to define subgroups of patients, who should be treated differently. Such data are discussed and their importance for future trials in the field of advanced breast cancer reviewed.

INTRODUCTION

The best treatment for advanced breast cancer remains a matter of debate. Historically hormonotherapy was the first modality, which was applied in the therapy of this disease. In an unselected population the results of endocrine treatment have remained stable in the last three decades: about 30% of the patients will achieve a partial remission, which will last between 10–20 months. In the last 10 years combination chemotherapy became the most important treatment modality for advanced breast cancer. However, nowadays it has been realized, that combination chemotherapy can only be palliative, whereas a few years ago it was hoped that with this treatment at least some patients could be cured. With an optimal combination chemotherapy 50–70% of the patients will achieve a partial remission, which generally lasts 10–15 months. Because it is at present widely felt that combination chemotherapy has reached a plateau in its effectiveness and because of the discovery of hormone receptors, hormonotherapy is presently experiencing an unexpected and important revival.

This paper will briefly review the current situation in the treatment of advanced breast cancer: major emphasis will be put on combined hormono-chemotherapy and on some methodological problems which, at least in our opinion, are of utmost importance in the future design of clinical trials in the treatment of advanced breast cancer.

CURRENT RESULTS OF CHEMOTHERAPY

The era of combination chemotherapy started with the first publication of Greenspan in 1966 [1], but mainly after Cooper reported in 1969 a remission rate of 90% in 60 patients treated with a five-drug combination (CMFVP) [2]. Table 1 summarizes the results of some of the trials, which were prompted by this report of Cooper. These data can be briefly summarized as follows: none of the different modifications of the original five-drug combination proved to be significantly superior [3]; CMF is globally as active as the five-drug combination [4–7]; however, the addition of prednisone to CMF improves the global results, most probably through avoidance of excessive dose reductions [5, 8]; CMFVP is probably more active if given continuously than when an intermittent schedule is used [9]; however, long-term analyses of studies comparing the concurrent administration to the sequential use of the five cytotoxic drugs failed to demonstrate a significant superiority of the concurrent approach [10].

The introduction of adriamycin opened new avenues for clinical trials in advanced breast cancer. The next step in the evolution of the chemotherapeutic management of advanced breast cancer was the comparison of CMF (VP) and various adriamycin-containing regimens. Table 2 summarizes the most important comparative studies [11–15]. As can be seen, no significant advantage for an adriamycin-containing regimen over CMF (VP) could be *globally* demonstrated. We shall address this question later on in this paper. We will then particularly address the

Table 1. Combinations of cyclophosphamide (C), methotrexate (M), 5-fluorouracil (F), vincristin (V) and prednisone (P)

Combination	Number of studies or institution	Number of patients	Remission rate (%)
CMFVP	Nine studies	503	51
CMFV	Three studies	118	53
CMFP	ECOG	88	59
CMF	Three studies	366	50
CFP	Three studies	113	39
FVP	CALGB	82	36
CFV	Michigan Univ.	46	43
CMV	SAKK	46	32
CMP	SAKK	67	44

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Table 2. Comparisons of CMF(V) and CAF(VP) in breast cancer

Reference	Treatment	Number of patients	Response		Time to response		Median survival (months)
			CR + PR	CR	P (months)	Duration (months)	
Bull *et al.*[12]	CMF	40	62	8	6	8	17
	CAF	38	82	18	10	10	27
Muss *et al.*[13]	CMFVP	72	57	11	—	14	20
	CAFVP	76	58	13	—	16	33
Smalley and Bartolucci[27]	CMFVP	107	42	8	4.3	5.5	14.0 Good risk
	CAF	106	60	19	8.0	8.0	16.7 Good risk
							11.0 Poor risk
							13.0 Poor risk
Carmo-Pereira *et al.*[15]	CMFP	26	65	19	—	12	22
	CAF	25	56	16	—	12	18
Tormey *et al.*[21]	CMFP	76	53	5	5.7	6.3	15.8
	CAF	79	53	17	7.8	11.0	18.6

methodological question as to whether possible differences were simply nullified by the fact that the trials were probably confusing the issue by including *all* prognostic subsets of patients with advanced breast cancer.

Historically the next step can be seen in the development of so-called "non-cross-resistant regimens". Since CMF (P) and AV were felt to be not cross-resistant, their sequential use was evaluated in two studies [16, 17]. So far, an advantage for the sequential use of two different non-cross-resistant regimes has not been demonstrated.

COMBINED HORMONO-CHEMOTHERAPY

Breast cancer tissue is thought to be composed of at least two different cellular types, one which is responsive to hormone treatment and one which is sensitive to cytotoxic drugs [18]. A combination of both treatments should therefore improve the results of treatment of advanced breast cancer. The first trials of the efficacy of combining endocrine and cytotoxic drug treatment yielded conflicting results [19–21]. In particular, in the trial of the Swiss Group for Clinical Cancer Research (SAKK) oophorectomy + chemotherapy elicited a higher response rate than chemotherapy alone, but the difference in survival was not statistically significant [19]. In the same trial, postmenopausal women without a previous endocrine treatment received either chemotherapy combined with oestrogens or chemotherpay alone: the survival curves were statistically not different for both treatment groups, even if a subset of postmenopausal patients seemed to profit from the combined approach. In postmenopausal women previously treated with hormonotherapy the two treatment arms were as follows: chemotherapy + MPA weekly or chemotherapy alone. In this subset of patients the combination of hormono-chemotherapy elicited inferior results as compared to chemotherapy alone [19]. Nevertheless there is a widespread tendency to treat many patients with a combination of both treatments simultaneously. The SAKK performed, therefore, a trial comparing the concurrent to the sequential use of cytotoxic chemotherapy and hormone treatment in the management of 464 patients with advanced breast cancer. In the treatment arm with the sequential use of both modalities, cytotoxic drugs were given only if the antitumour activity of the hormone treatment was inadequate. Hormone treatment consisted of oophorectomy for premenopausal and tamoxifen administration for postmenopausal patients. The results of this trial have already been reported in detail [22]. Length of survival was better, though not significantly, in premenopausal patients ($P = 0.29$) treated concurrently and in postmenopausal women ($P = 0.17$) treated sequentially. The difference in survival was, however, highly significant ($P = 0.003$) for postmenopausal women in the low-risk category (indolent disease), who received chemotherapy only after primary or secondary failure of the endocrine treatment. In all other subsets the differences in survival between the two treatment strategies were not statistically significant, even if generally there was a tendency for longer survival in patients with a more aggressive disease when they were treated with a combined approach. On the contrary, patients with a rather indolent disease seemed generally to profit from a treatment plan, encompassing hormonotherapy alone at first and the delayed use of chemotherapy [23]. These findings suggest that postmenopausal women with metastatic breast cancer should probably be treated primarily by carefully monitored hormone treatment, while most prognostic subsets among premenopausal women should probably receive a combined chemo-hormonotherapy. In this trial we were also able to confirm among the patients receiving a delayed chemotherapy, that endocrine treatment is able to influence the response rate and the duration of remission of the following chemotherapy. Patients responding to hormonotherapy also showed statistically longer survival as compared to patients showing only a no-change or a progressive disease with the endocrine treatment ($P < 0.05$).

Table 3. Regimens of combination chemotherapy

I.	"Minimal" (lmfp)	CLB	5 mg/m²/day days 1–14	p.o.	for 4 weeks = Intermittent
		MTX	10 mg/m²/week days 1 + 8	p.o. (1 dose!)	
		5-FU	500 mg/m²/week days 1 + 8	p.o.	
		PDN	30 mg/m²/day days 1–14	then ↓	
II.	"Medium" (LMP/FVP)	CLB	as in I		for 4 weeks = Continuous
		MTX	15 mg/m²/week subdivided into 3 daily doses days 1–3, days 8–10	p.o.	
		PDN	30 mg/m²/day days 1–14		
		5-FU	500 mg/m²/week days 15 + 22	i.v.	
		VCR	1, 2 mg/m²/week days 15 + 22	i.v.	
		PDN	30 mg/m²/day days 5–28	then ↓	
III.	"Maximal" (LMFP/ADM)	CLB	as in I		for 8 weeks = Intermittent
		MTX	40 mg/m²/week days 1 + 8	i.v.	
		5-FU	600 mg/m²/week days 1 + 8	i.v.	
		PDN	30 mg/m²/day days 1–14	then ↓	
		ADM	60 mg/m² days 28		

A RANDOMIZED TRIAL OF THREE DIFFERENT REGIMENS OF COMBINATION CHEMOTHERAPY

In the SAKK trial described above (concurrent vs sequential chemo-hormonotherapy), at the time of the randomization, the patients were also randomly allocated to three different chemotherapy regimens, representing a low-dose (lmfp = I), a more conventional (LMP/FVP = II) and a somewhat intensive cytotoxic treatment (LMFP/ADM = III). The drug programmes are illustrated in Table 3. Considering all 397 patients who received chemotherapy either concurrently with or sequentially to the endocrine treatment, we observed that statistically significant differences in the response rate elicited by the three chemotherapeutic regimens were only marginally translated into different survival curves [22]. We decided therefore in a subsequent analysis of this study to limit our evaluation to the patients who received chemotherapy concurrently with an endocrine treatment. This restriction permits us to analyse a more homogeneously-treated patient population and also eliminates the influence of a possible hormone-induced remission upon the therapeutic result of a subsequent cytotoxic treatment [22, 24, 25]. We have recently reported this new analysis in more detail [26].

Among the 216 evaluable patients treated concurrently with hormono-chemotherapy, the patients receiving the low-dose regimen (mfp showed a response rate (CR + PR) of 32% (24/70). The response rates were 52% (36/70) and 54% (38/72) for the women treated with the two more intensive regimens of chemotherapy. The low-dose, peroral combination of cytotoxic drugs (lmfp) elicited a lower response rate ($P < 0.01$) and shorter survival ($P = 0.03$) as compared to the results registered in all patients receiving the two more intensive chemotherapies, which showed very similar therapeutic results as regards response rate, time to progression and survival.

After having observed a therapeutic advantage for the two more intensive regimens of chemotherapy, we analysed various subsets of patients in order to evaluate the impact of the treatment upon different prognostic groups. The results of this analysis are summarized in Tables 4 and 5. Some of the inconsistencies registered comparing the impact of therapy upon either the objective response or the survival may in fact be due rather to statistical artifacts generated by the multiplicity of statistical analyses in small groups. Some of our findings can, however, be considered as rather obvious, e.g. the superiority of a more intensive chemotherapy in patients with a poor performance status or with visceral lesions. Furthermore, we found that in patients with only bony metastases neither the response rate nor the median survival (approx. 2.5 years) are influenced by the intensity of the chemotherapy given concurrently with an endocrine manipulation.

However, some of our findings were quite unexpected. Particularly striking are the essentially similar survival courses in all premenopausal patients, notwithstanding the different intensities of the chemotherapy. On the contrary, we observed a statistically significant advantage for the more intensive chemotherapies in postmenopausal women and, even more surprisingly, in this group the difference was almost completely confined to the patients older than 60 years. This finding cannot be considered an artifact, since postmenopausal patients represent more than three-quarters of the evaluable cases and since all prognostic factors were extremely well-balanced among the three different regimens of chemotherapy.

Also, somewhat surprising was the fact that the therapeutic advantage for the more intensive chemotherapies was statistically significant only in patients with two sites of metastases or those with a disease-free interval of between 12–60 months. The differences were less pronounced in patients presenting 1 or ≥ 3 diseased sites and with a disease-free interval of less than 12 or more than 60 months. These results are somewhat parallel to another surprising observation: the risk-group, the disease-free interval, the localization as well as the number of metastatic sites produced a statistically significant impact on the survival of the 430 evaluable patients of the study as a whole [22]. Analysing only the

Table 4. Influence of prognostic factors upon response rate in different regimens of chemotherapy

	Response rate (% CR + PR)		
	Treatment I	Treatment (II + III)	*P*
Premenopausal	40	58	0.054
Postmenopausal	30	50	<0.05
Low-risk	24	47	NS
High-risk	36	54	<0.05
Number of sites:			
1	30	49	NS
2	16	55	<0.01
⩾3	57	52	NS
Performance status			
0–1	39	51	NS
2–4	17	56	<0.01
Age (years)			
⩽50	33	62	0.058
50–60	37	40	NS
⩾60	28	57	<0.01
Disease-free interval (months)			
0–12	33	46	NS
12–60	31	57	<0.01
⩾60	36	50	NS
Site of metastases[a]			
Osseous only	31	39	NS
Visceral + local	18	69	<0.05
Visceral only	20	73	<0.05
Lung (dominant)	26	55	<0.05

[a]Patients broken down according to two different systems (see Table 2).

216 women receiving concurrently chemo-hormonotherapy we registered a decreased influence of the disease-free interval ($P = 0.07$) and of the number of sites ($P = 0.075$) upon survival. These somewhat puzzling data may be at least partially related to the different impact of chemotherapy and endocrine treatment upon some of the prognostic factors.

Table 5. Influence of prognostic factors upon survival in patients treated with different regimens of chemotherapy[a]

	Median survival (months)		
	Treatment I	Treatment (II + III)	*P*
Premenopausal	26	25	NS
Postmenopausal	17	28.5	0.018
Low-risk	26	31	0.043
High-risk	19.5	27	NS
Number of sites:			
1	28.5	33	NS
2	13.5	25	0.02
⩾3	15	26	NS
Performance status:			
0–1	27.5	33.5	NS
2–4	13	22.5	0.002
Age (years):			
⩽50	25	26	NS
50–60	18	19	NS
⩾60	19	33	0.03
Disease-free interval (months):			
0–12	16.5	19	NS
12–60	25	33.5	0.05
⩾60	17.5	32.5	0.04
Site of metastases[b]			
Osseous only	28	31	NS
Osseous + local	26.5	30.5	NS
Visceral + local	8	21.5	0.05
Osseous + visceral	12	22	NS
Liver (dominant)	7	20.5	0.004
Lung (dominant)	16	32.5	0.03

[a]Besides degree of response (see Table 3).
[b]Patients broken down according to two different systems (see Table 2).

Table 6. Results of SWOG and ECOG with CMFP(V) vs CAF in different survival risk categories of breast cancer

Category of metastases	SWOG	ECOG
0 Bone only	Too few cases	Survival ↑ with CMFP
1 Loco-regional (± bone)	CAF better:	Survival ↑ with CMFP
2 Nodular lung	—Removal rate	No significant differences
3 Soft tissue progr. to liver	—TTP	
4 Untreated primaries	—Survival	
5 Ipsilateral pleural ± bone	No significant differences	
6 Lymphangitic pulmonary		
7 Liver ± other metastases		Survival ↑ with CAF; Time to P ↑ with CAF

ARE THE CURRENT TRIALS IN ADVANCED BREAST CANCER CONFUSING THE ISSUE?

In order to reach the methodological conclusion, which seems to us to be currently the main issue in the design of trials carried out in advanced breast cancer, we have to compare the results we have reported with the three different regimens of chemotherapy with some recent indication in the literature.

If one analyses the two most important studies among the five comparing an adriamycin-containing regimen to CMF (P)—that of SWOG [27] and that of ECOG [28]—then some interesting features appear (Table 6). As regards the site of metastases, in the SWOG study CAF produced a higher remission rate, a longer time to progression and survival in patients with loco-regional metastases ± bony metastases, nodular secondaries in the lung as well as soft tissue metastases. No difference whatsoever was seen among patients presenting ipsilateral pleural metastases, lymphangiatic lung involvement or liver metastases. In the ECOG study the median survival was significantly longer where patients with bony metastases or loco-regional disease received CMFP instead of CAF. On the contrary, women with liver ± other sites lived longer if they were treated with CAF. The other sites did not show any difference in the ECOG trial.

Globally the findings related to the site of metastases can be summarized as follows: even if CMFP (V) and CAF did not show a difference in survival in the two studies, these differences became apparent as soon as different subsets were analysed.

The ECOG study was then further analysed taking into consideration further prognostic factors such as: oestrogen receptors, age, number of sites, performance status. This analysis has still to be published in detail. We restrict our consideration therefore only to the overall findings. The ECOG study demonstrates that the more intensive therapy with CAF tends to elicit better results as compared to CMFP in patients showing a more aggressive disease (ER −, visceral metastases, poor performance status, $\geqslant 4$ sites of disease). Concerning the age of the patients the findings of the ECOG are quite similar to those of the SAKK study: CAF tends to be superior to CMFP in women below 50 or above 60 years, while in patients between 50 and 59 years CMFP seems to be superior.

In advanced breast cancer the only hard parameter is survival. Looking only at survival, at least in the ECOG and SWOG studies, the more intensive chemotherapy does not produce statistically longer survival. However, in subsets statistically significant differences are observed: in fact, in some subsets they are in favour of CAF, in some others of CMFP(V). Similar trends were observed in the detailed analysis of the SAKK study.

However, if one merges all the patients in one sole trial, then the differential response of the various subsets tends to nullify the overall difference as regards the impact of treatment upon survival.

Therefore, the general current tendency to merge all patients with advanced breast cancer in the same trial is probably hampering the solution of the therapeutic problems by further confusing the issue.

This may be particularly true for trials evaluating the impact of chemo-hormonotherapy. In some of the studies presented here, the overall survival is not different between patients receiving chemotherapy alone or the combination of chemo-hormonotherapy. However, there is a survival difference, if only patients *responding* to the treatment are analysed. This may hint to a possible detrimental effect of hormono-chemotherapy in non-responding patients as has already been suggested by the adjuvant trial of the NSABP (PF ± TAM) for some subsets. Since the receptor status may be the most important discriminator in that respect, we feel that future trials evaluating the combination of chemotherapy and endocrine treatment should include only patients with positive receptors or at least "hormonally favourable" prognostic factors.

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