Eur J Cancer Clin Oncol, Vol. 19, No. 11, pp. 1615–1624, 1983.
Printed in Great Britain.

0277-5379/83$3.00+0.00

Randomized Trial of 3 Different Regimens of Combination Chemotherapy in Patients Receiving Simultaneously a Hormonal Treatment for Advanced Breast Cancer*

F. CAVALLI,† A. PEDRAZZINI,† G. MARTZ,‡ W. F. JUNGI,§ K. W. BRUNNER,‖ A. GOLDHIRSCH,‖ B. MERMILLOD¶ and P. ALBERTO**††

†*Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland,* ‡*Division of Oncology, University Hospital, 8091 Zürich, Switzerland,* §*Division of Oncology, Kantonsspital, 9007 St. Gallen, Switzerland,* ‖*Institute for Medical Oncology, Inselspital, 3010 Bern, Switzerland,* ¶*Statistical Center, Operations Office SAKK, 1205 Geneva, Switzerland and* **Division of Oncology, Hôpital Cantonal, 1205 Geneva, Switzerland*

Abstract—*We report the results of a randomized trial carried out by the Swiss Group for Clinical Cancer Research (SAKK) and in which 230 patients with advanced breast cancer receiving concurrently a hormonal treatment (oophorectomy for pre- and tamoxifen for postmenopausal women) were randomly allocated to three different regimens of combination chemotherapy. The therapeutic results registered with the two more intensive combinations (LMP/FVP and LMFP/ADM) were similar with regard to response rates, time to progression and survival. The patients receiving the low-dose chemotherapy lmfp showed a statistically significant lower response rate (32%, $P < 0.001$) and a shorter survival ($P = 0.03$) than the results observed in patients treated with the two other regimens. This difference was particularly pronounced, at least regarding survival, in the following subgroups: postmenopausal women, patients with a poor performance status, dominant visceral lesions, two sites of disease and a disease-free interval longer than* 12 months. *Patients with bony metastases as dominant lesion fared similarly with all three regimens of chemotherapy. This latter subset of advanced breast cancer patients should probably be spared too intensive cytotoxic treatment. This is, to our knowledge, the first report of a randomized trial showing an evident correlation between response rate and survival in various subgroups of patients with advanced breast cancer treated with different chemotherapeutic regimens.*

INTRODUCTION

BREAST cancer is believed to be composed of at least two different cellular types: one more responsive to hormonal treatment, and the other more sensitive to cytotoxic drugs [1]. Combination of both therapies should therefore present a possibility of improved results in the treatment of this disease. So far, however, a survival advantage for the combined treatment could not be demonstrated in most of the studies testing this hypothesis [2–5].

We have recently published the results of a randomized trial comparing the simultaneous to the sequential combination of chemotherapy and endocrine treatment in the management of advanced breast cancer [6]. At the time of the randomization the patients were also randomly allocated to three different chemotherapy regimens, representing a low-dose, a more conventional, and a somewhat intensive cytotoxic treatment. In this paper we report the results of the comparison of these three regimens in the patients receiving a simultaneous chemo-hormonotherapy, since these data may be relevant in the ongoing debate concerning the impact of

Accepted 17 May 1983.
*Presented in part at the UICC–ESMO Conference on Clinical Oncology, Lausanne, 28–30 October 1981.
††This study was conducted for the Swiss Group for Clinical Cancer Research (SAKK).

treatment upon survival of patients with advanced breast cancer.

MATERIALS

Patients

Between September 1975 and December 1980, 464 patients with measurable advanced breast cancer and without previous chemo- or hormonotherapy were entered into the study. Patients with brain metastases, creatinine $\geq$1.5 mg/dl or bilirubin $\geq$3 mg/dl were excluded. Osteoblastic bony metastases and malignant effusions were not accepted as measurable lesions. The patients were stratified according to menopausal status and risk-group, based on retrospective analysis of two of our previous studies [7]. Patients with the following features were considered to be 'low-risk': contralateral nodal metastases only, with a free interval (FI) between mastectomy and diagnosis of the first metastasis of at least 2 yr; bony metastases only, irrespective of the FI; and no more than two of the following: (a) lung or liver metastases (not both) with an FI of at least 4 yr, (b) an isolated bony metastasis with an FI of at least 2 yr, (c) skin metastases and/or an ipsilateral malignant pleural effusion with an FI of at least 2 yr or (d) ipsilateral nodal metastases and an FI of at least 2 yr.

All other patients were classified as 'high-risk'. Hormone receptors were not considered, since their determination became generally possible only towards the end of the accrual period. After stratification patients were randomized to treatment groups A or B. Premenopausal women underwent oophorectomy, while postmenopausal patients received 20 mg daily of tamoxifen. The 230 patients randomized in group A received chemotherapy concurrently. In group B (not considered in this paper) cytotoxic drugs were started only after 6–8 weeks of endocrine treatment, except in the presence of documented tumor regression, in which case chemotherapy was begun later and only upon a new progression of the tumor parameters.

Fourteen of the patients receiving a simultaneous chemo-hormonotherapy had to be excluded from the analysis: in 10 there was a major protocol violation, in 2 the tumor parameters were poorly evaluable and 2 women died within 4 weeks of starting treatment. In this report we therefore consider 216 patients, who were randomly allocated to the three different chemotherapy regimens. The drug programs are illustrated in Table 1. These schedules were employed for 6 months. Afterwards the treatment-free periods in lmfp (I) and LMFP/ADM (III) were prolonged for a further 2 weeks, whereas in patients treated with LMP/FVP (II) a therapy-free interval of 2 weeks was introduced between the two blocks of treatment (LMP and FVP). When the doxorubicin dose reached 450 mg/m^2, this drug was discontinued and the patients were treated only with LMFP. The treatment was stopped in patients who have been in complete remission for 2 yr. In patients who had extensive bone involvement or who were more than 65 yr of age the first dosage of adriamycin was decreased to 40 mg/m^2, of 5-fluorouracil to 400 mg/m^2 and of methotrexate to 30 mg/m^2. Doxorubicin and vincristine doses were appropriately modified in the presence of liver dysfunction.

The full dosage of chemotherapy was given provided the leukocyte count was greater than 4000/mm^3 and platelets higher than 100,000/mm^3. Half-dosages of medication were given when the leukocyte count was between 2500 and 4000/mm^3 and the platelets between 75,000 and 100,000/mm^3. Chemotherapy was withheld and the blood

Table 1. *Regimens of combination chemotherapy*

	CLB	5 mg/m$_2$/day,	days 1–14	p.o.	
I 'Minimal'	MTX	10 mg/m$_2$/week,	days 1 + 8	p.o. (1 dose!)	q 4 weeks
(lmfp)	5-FU	500 mg/m$_2$/week,	days 1 + 8	p.o.	= intermittent
	PDN	30 mg/m$_2$/day,	days 1–14	then↓	
	CLB	as in I			
	MTX	15 mg/m$_2$/week,	subdivided in 3 daily doses, days 1–3 and 8–10	p.o.	
II 'Medium'	PDN	30 mg/m$_2$/day,	days 1–14		q 4 weeks
(LMP/FVP)	5-FU	500 mg/m$_2$/week,	days 15 + 22	i.v.	= continuous
	VCR	1.2 mg/m$_2$/week,	days 15 + 22	i.v.	
	PDN	30 mg/m$_2$/day,	days 5–28	then↓	
	CLB	as in I			
	MTX	40 mg/m$_2$/week,	days 1 + 8	i.v.	
III 'Maximal'	5-FU	600 mg/m$_2$/week,	days 1 + 8	i.v.	q 8 weeks
(LMFP/ADM)	PDN	30 mg/m$_2$/day,	days 1–14	then↓	= intermittent
	ADM	60 mg/m$_2$,	day 28		

counts checked weekly if the leukocyte count was below 2500/mm^3 or the platelets were less than 75,000/mm^3.

Table 2 summarizes the pretreatment characteristics of the 216 evaluable patients: all the major prognostic factors are well balanced among the cases randomly allocated to the three different regimens of chemotherapy.

The criteria for response correspond to those defined by the UICC [8], with the exception of the category 'minor response' (MR): in 1975 we were still using the latter to define a clear-cut tumor shrinkage which did not reach the limits of a partial response (PR).

Survival and time to progression of the disease were calculated from entrance into the study. Actuarial curves were based on the method described by Kaplan and Meier [9]. The statistical comparison among actuarial curves was carried out using the following methods: the log-rank test, the Mantel–Cox test and the generalized Wilcoxon test [10]. In case of differences among the statistical tests, the least significant result was considered. These results were based on a cut-off carried out on 15 May 1982, which represents a median observation time well beyond 5 yr.

Table 2. Characteristics of the 216 evaluable patients

	Treatment group I	II	III
Median age (yr)	57.9	57.2	57.6
Median free interval (months)	28	21	29
No. of premenopausal patients	20	18	20
No. of postmenopausal patients	54	52	52
No. of high-risk patients	21	17	17
No. of low-risk patients	53	53	55
No. of metastatic lesions:			
patients with 1	20	21	24
patients with 2	31	27	24
patients with ⩾3	23	22	24
Performance status:			
patients with 0–1	51	47	48
patients with 2–4	23	23	24
Site of metastases			
local	4	7	4
skeletal	13	10	13
local + pleura	3	2	1
* local + skeletal	12	10	11
visceral + local	11	8	8
visceral + skeletal	21	27	26
visceral only	10	6	9
liver	12	17	11
lung	31	24	31
* local + soft tissue	4	7	6
bone	26	21	24
others	1	1	0

*All patients are accounted for.

RESULTS

Of the 216 evaluable patients, 74 were randomized to lmfp (I), 70 received LMP/FVP (II) and 72 LMFP/ADM (III). The 58 premenopausal women underwent oophorectomy immediately prior to the start (8–10 days later) of cytotoxic drugs. The 158 postmenopausal patients received concurrently tamoxifen. The response rate is summarized in Table 3. Among the patients receiving the low-dose chemotherapy lmfp, 24/70 (32%) showed a response (CR + PR). The response rates were 52% (36/70) and 54% (38/72) for the women treated with the two more intensive regimens of chemotherapy. The distribution of responses shows a statistically significant difference among the three regimens ($P = 0.005$), while the therapeutic results are very similar in II and III. The comparison of the responses observed in I with the global results of the two other regimens (II + III) shows a highly significant statistical difference ($P < 0.001$). Complete responses were distributed as follows: 7/74 (10%) in I, 14/70 (20%) in II and 15/72 (21%) in III (I vs II + III: $P < 0.05$).

Table 3. Therapeutic results according to treatment

Treatment	CR (%)	PR (%)	MR (%)	NC (%)	PD (%)
I = lmfp	10	22	13	24	31
II = LMP/FVP	20	32	22	16	10
III = LMFP/ADM	21	33	19	19	8

Distribution of results among the 3 treatments: $P = 0.005$ ($\chi^2 = 21.8$); distribution of results II vs III: P = n.s. ($\chi^2 = 0.3$); distribution of results I vs (II + III): $P < 0.001$ ($\chi^2 = 21.6$).

The therapeutic results registered with LMP/FVP and LMFP/ADM are essentially similar with regard to response rates, time to progression and survival, not only globally but also considering each prognostic subtype. The analysis of the influence of the different prognostic factors upon response rate and survival (Tables 4 and 5) will therefore always compare lmfp (I) to the two other regimens (II + III). Table 4 summarizes the impact of the prognostic parameters upon the reponse rate. LMP/FVP and the alternating regimen LMFP/ADM show a statistically significant higher response rate in the following subgroups: postmenopausal patients (and here, chiefly, those beyond 60 yr), high-risk cases, women with a poor performance status (⩾2) or visceral lesions. As regards the number of sites and the disease-free interval (FI), the difference is statistically significant only in the 'intermediate' category (2 diseased sites, FI 12–60 months), whereas the results vary less in the other subgroups (FI 0–12, ⩾60 months and 1 or ⩾3 sites

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

	Repsonse rate (% CR + PR)		
	Treatment I	Treatment (II + III)	*P*
Premenopausal	40	58	0.054
Postmenopausal	30	50	<0.05
Low-risk	24	47	n.s.
High-risk	36	54	<0.05
No. of sites:			
1	30	49	n.s.
2	16	55	<0.01
⩾3	57	52	n.s.
Performance status:			
0–1	39	51	n.s.
2–4	17	56	<0.01
Age (yr):			
⩽50	33	62	0.058
50–60	37	40	n.s.
⩾60	28	57	<0.01
Free interval (months):			
0–12	33	46	n.s.
12–60	31	57	<0.01
⩾60	36	50	n.s.
Site of metastases:*			
osseous only	31	39	n.s.
visceral + local	18	69	<0.05
visceral only	20	73	<0.05
lung (dominant)	26	55	<0.05

*Patients broken down according to 2 different systems (see Table 2).

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

	Median survival (months)		
	Treatment I	Treatment (II + III)	*P*
Premenopausal	26	25	n.s.
Postmenopausal	17	28.5	0.018
Low-risk	26	31	0.043
High-risk	19.5	27	n.s.
No. of sites:			
1	28.5	33	n.s.
2	13.5	25	0.22
⩾3	15	26	n.s.
Performance status:			
0–1	27.5	33.5	n.s.
2–4	13	22.5	0.002
Age (yr):			
⩽50	25	26	n.s.
50–60	18	19	n.s.
⩾60	19	33	0.03
Free interval (months):			
0–12	16.5	19	n.s.
12–60	25	33.5	0.05
⩾60	17.5	32.5	0.04
Site of metastases:†			
osseous only	28	31	n.s.
osseous + local	26.5	30.5	n.s.
visceral + local	8	21.5	0.05
osseous + visceral	12	22	n.s.
liver (dominant)	7	20.5	0.004
lung (dominant)	16	32.5	0.03

*Besides degree of response (see Fig. 3).
†Patients broken down according to 2 different systems (see Table 2).

of metastases). This finding may be related to an observation correlating the number of lesions to specific sites of disease. In fact we found the following correlations: osseous lesions only and 1 site of disease, liver metastases and 2 sites, lung metastases (mostly with pleural effusion and soft-tissue disease) and the presence of lesions in 3 organs [Pedrazzini *et al.*, in preparation].

The median time to disease progression was 19.6 months for all patients achieving an objective response (CR + PR). This result was similar in all three regimens: 20.5 months for I, 18.5 for II and 19.5 for III.

Table 6 summarizes the myelosuppression elicited by the three combinations of chemotherapy. The distribution of the toxicity grades is statistically different between lmfp and the two other regimens. A similar difference was previously reported in non-hematologic toxicities [11].

Figure 1 represents the survival curves for all patients and Fig. 2 for the postmenopausal women only, according to the three regimens of chemotherapy. Among the 216 evaluable patients the median survival time is 23.5 months for lmfp, 27 months for LMP/FVP and 30 months for LMFP/ADM ($P = 0.1$). The difference is, however, statistically significant ($P = 0.03$) if the survival curve of the patients receiving lmfp (I) is compared to the survival time of the patients who receive the two other regimens. The survival curve is very similar for the 58 pre- and the 158 postmenopausal patients: 26 months median survival time for premenopausal and 25.5 months for postmenopausal patients. Among the premenopausal patients there is no difference according to the therapeutic regimens, whereas among postmenopausal patients those receiving the two more intensive combinations of cytotoxic drugs show a longer survival (Fig. 2).

Table 5 summarizes, in addition to menopausal status, the influence of other prognostic factors upon survival, comparing the results registered with lmfp (I) to those observed with the two other regimens (LMP/FVP and LMFP/ADM). The following subgroups show a statistically significant survival advantage for the patients treated with a more intensive chemotherapy: postmenopausal patients (particularly those older than 60 yr), women with a bad performance status, visceral lesions, 2 sites of disease and a disease-free interval longer than 12 months. A survival disadvantage for lmfp is seen in both risk-groups, even if statistical significance is reached ($P = 0.04$) only among low-risk patients.

Figure 3 represents survival correlated with overall therapeutic results: the median survival time is almost 4.5 yr (51.5 months) for patients

Table 6. Hematologic toxicity according to chemotherapy

Chemotherapy	Grade of hematologic toxicity (%)* 0	1	2
lmfp (I)	29	51	20
LMP/FVP	13	48	39
LMFP/ADM	8	47	45
	I vs (II + III), $P < 0.001$		

*Grade 0: WBC $>4 \times 10^3/mm^3$, platelets $>100 \times 10^3/mm^3$; grade 1: WBC $1.5–4 \times 10^3/mm^3$, platelets $75–100 \times 10^3/mm^3$; grade 2: WBC $<2.5 \times 10^3/mm^3$, platelets $<75 \times 10^3/mm^3$.

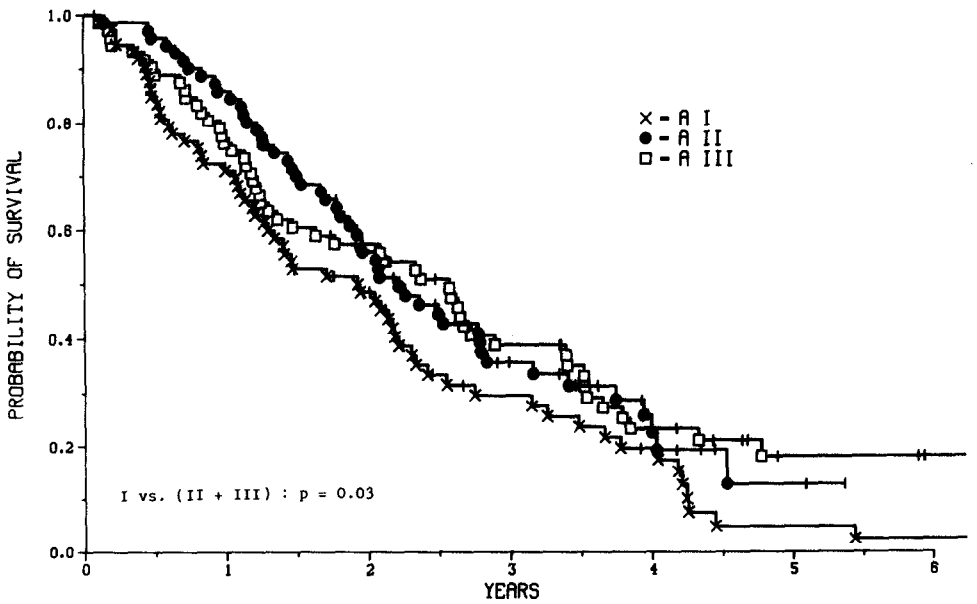

Fig. 1. Survival of all 216 patients according to the regimen of chemotherapy: AI = lmfp, AII = LMP/FVP, AIII = LMFP/ADM.

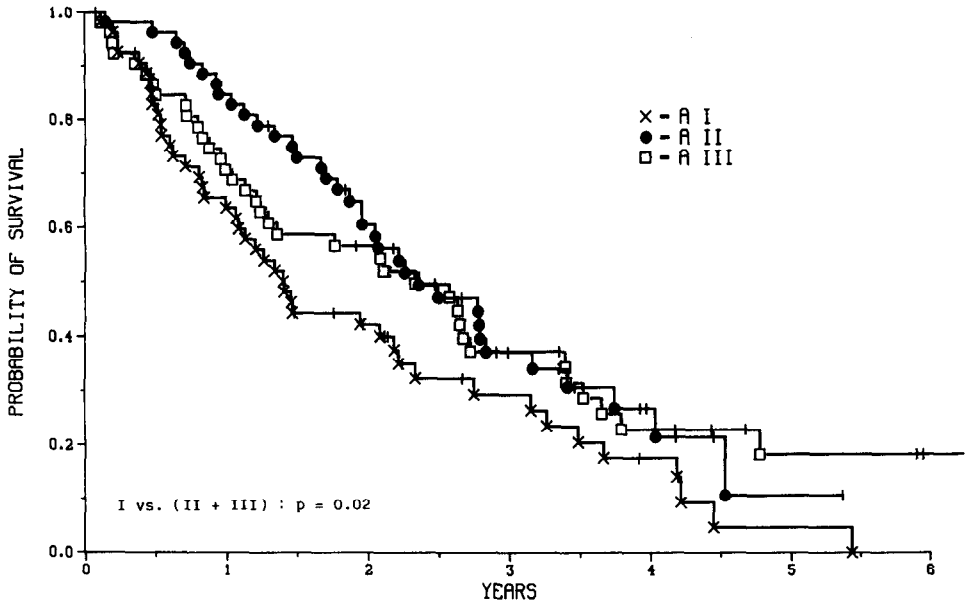

Fig. 2. Survival for postmenopausal patients only according to regimen of chemotherapy: AI = lmfp, AII = LMP/FVP, AIII = LMFP/ADM.

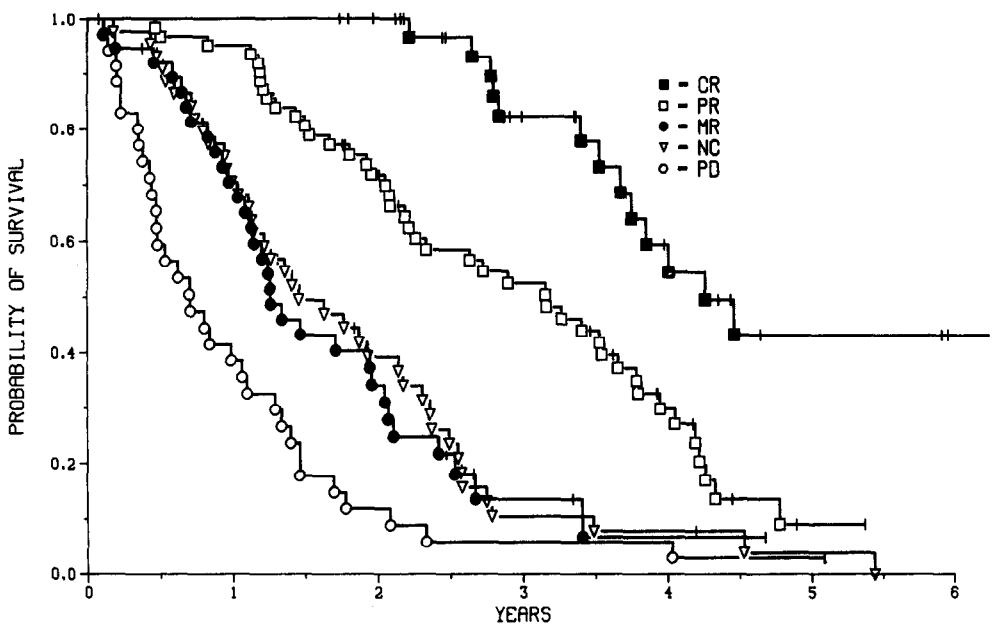

Fig. 3. Survival of all 216 patients related to therapeutic result.

with a CR, more than 3 yr (38 months) in case of a PR, less than 8 months for progressing cases and, with 18 and 17 months respectively, very similar ones for MR and NC. This similarity demonstrates once more the futility of using two different categories (MR and NC), since they are biologically indistinguishable.

Figure 4 depicts survival among the 216 evaluable cases according to the age of the patients and irrespective of the randomized treatment. The longest survival (median: 30.5 months) is registered among patients older than 60 yr and the shortest (18 months) in women between 50 and 60 yr. Overall the difference is not quite statistically significant ($P = 0.07$); this limit is reached, however, if only those patients older or younger than 60 yr are compared ($P < 0.05$) in favor of older patients.

DISCUSSION

The best therapeutic approach to patients with metastatic breast cancer remains a matter of debate. Recently, the overall impact of combination chemotherapy upon the survival of most patients with advanced breast cancer has even been questioned [12]. The following approaches are currently being evaluated for their potential to improve upon the present therapeutic results:

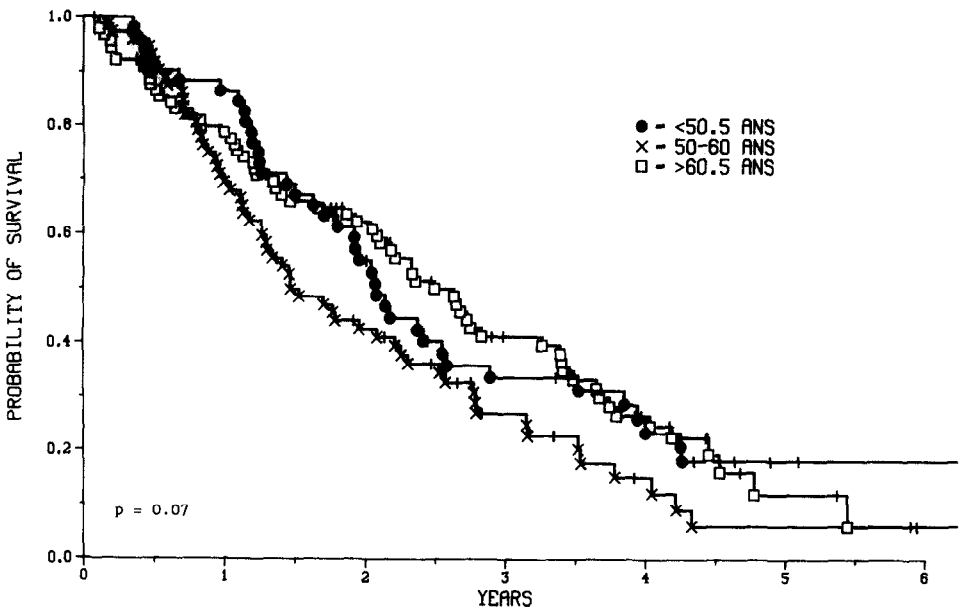

Fig. 4. Survival of all 216 patients related to age.

very intensive chemotherapy [13, 14], consolidation with radiotherapy [15, 16] and various combinations of chemotherapy and endocrine manipulations [1, 17].

We have recently reported the results of our trials comparing simultaneous and sequential combinations of chemo-hormonotherapy [6]. Overall the results were similar for the two therapeutic strategies, except in postmenopausal low-risk patients, who survived longer if they received chemotherapy only after the failure of tamoxifen to achieve or maintain a tumor regression. In the same study the patients were also randomly allocated to three different regimens of chemotherapy (lmfp, LMP/FVP, LMFP/ADM). Considering all 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 [11].

In this paper we have limited the analysis of the correlation between response rate and survival to only the patients of our trial who received chemotherapy *concurrently* with an endocrine treatment. This restriction permits us to analyze 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 [6, 18, 19].

In the 216 evaluable patients concurrently receiving hormono-chemotherapy, the low-dose, peroral combination of cytotoxic drugs (lmfp) elicited a lower response rate ($P < 0.01$) and a shorter survival ($P = 0.03$) than the results registered in all patients receiving the other two more intensive chemotherapies. This is, to our knowledge, the first report showing a stringent correlation between response rate and survival in patients with advanced breast cancer treated with different chemotherapeutic regimens. A recently published study of the ECOG reported that CMFP was superior to CMF and AV both in terms of time to treatment failure ($P = 0.04$) and survival ($P = 0.03$), but response rates were very similar (63, 56 and 57%) [20]. In another study comparing low-dose intravenous CMF to VAC the pronounced difference in the response rate (16% with low-dose CMF, 47% with VAC, $P < 0.05$) was not translated into any difference as regards survival [21]. We must, however, admit that the fact that all our patients received hormonotherapy concurrently may have influenced the therapeutic outcome. The same observation also applies to some extent to the ECOG trial, in which after 6 months of induction therapy the responding patients were randomized to either maintenance with CMF or to CMF plus fluoxymesterone 20 mg daily.

Considering that most studies comparing chemotherapy to the combination of hormonal and cytotoxic treatment show a higher remission rate for the combined approach [3, 5, 6], the percentages of response in our trial (32% in I, 52% in II, 54% in III) must be considered as rather low. In particular, we were unable to confirm some of the striking results observed by other authors in a non-randomized trial evaluating low-dose CMF [22]. Our low response rate cannot be explained by the use of chlorambucil instead of the more

conventional cyclophosphamide, since we have demonstrated in a previous study that both alkylating agents are equivalent in the treatment of advanced breast cancer [23]. Moreover, our results are basically consistent with the finding of the already mentioned randomized study comparing low-dose CMF to VAC [21]. The fact that in our study only patients without any previous systemic treatment were eligible may partially account for the low response rates. In most other studies evaluating cytotoxic drugs patients with prior endocrine treatment are accepted: they represent most probably a positive selection [18, 19].

After having observed a therapeutic advantage for the two more intensive regimens of chemotherapy, we analyzed various subsets of patients in order to evaluate the impact of the treatment upon different prognostic groups (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 artefacts 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. Future studies exploring a further intensification of the cytotoxic treatment should probably be restricted primarily to this subset of cases.

It has recently been shown that patients with only bony metastases are quite responsive to cytotoxic drugs [24]. In our analysis we found that in this subset neither the response rate nor the median survival (approximately 2.5 yr) are influenced by the intensity of the chemotherapy given concurrently with an endocrine manipulation. About one-quarter of all women presenting with advanced breast cancer have their metastases initially confined to bone [24, 25]. In our trial these represent the vast majority of the low-risk postmenopausal patients, who fared statistically better with the sequentially delayed chemotherapy. This subset of advanced breast cancer patients should probably be spared too intensive cytotoxic treatment.

But some of our findings were quite unexpected. Particularly striking are the essentially similar survival curves in all premenopausal patients, notwithstanding the different intensities of the chemotherapy. It can, however, be argued that the groups here are very small and that various factors may therefore have biased the results. 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 yr. This finding cannot be considered an artefact, 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 2 sites of metastases or those with a disease-free interval between 12 and 60 months. The differences were less pronounced in patients presenting 1 or $\geqslant 3$ diseased sites and with a free interval <12 or >60 months. These results are somewhat parallel to another surprising observation: the risk-group, the free interval, the localization and the number of metastatic sites produced a statistically significant impact on the survival of the 430 evaluable patients of the study as a whole [11]. Analyzing only the 216 women receiving concurrently chemo-hormonotherapy, we registered a decreased influence of the free interval ($P = 0.07$) and of the number of sites ($P = 0.075$) upon the survival. This somewhat puzzling data may be at least partially related to the different impact of chemotherapy and endocrine treatment upon some of the prognostic factors. For instance, for combination chemotherapy the likelihood of response is generally unrelated to the recurrence-free interval and more closely related to tumor burden than to the site of involvement [26, 27]. Results with hormonotherapy are, on the contrary, closely related to the recurrence-free interval and the site of involvement [27]. In our study as well as in other reports [28], there is, moreover, a correlation between the number of sites and certain localizations of the disease.

It has long been speculated that, because of their different and somewhat antagonistic mechanisms of action, cytotoxic drugs and endocrine treatment combined may even have a detrimental effect [4, 17]. So far, only the results of one trial lend a measure of support to this speculation [4]. But, as shown by some of our findings, we do not completely comprehend the manner of interaction of these two types of treatment. In the hope of contributing to an understanding of the differences in the therapeutic impact of these two treatment modalities, we are presently evaluating the prognostic importance of the clinical parameters in a retrospective multivariate analysis encompassing about 800 patients with advanced breast cancer who have been entered in our last three randomized trials [Pedrazzini *et al.*, in preparation].

Acknowledgement—We are grateful to Mrs. S. Kistler for her careful preparation of the manuscript.

REFERENCES

1. HENDERSON IC, CANELLOS GP. Cancer of the breast. The past decade. *N Engl J Med* 1980, **302**, 17–30, 78–90.
2. BRUNNER KW, SONNTAG RW, ALBERTO P *et al.* Combined chemo- and hormonal therapy in advanced breast cancer. *Cancer* 1977, **39**, 2923–2933.
3. CARTER SK. The interpretation of trials: combined hormonal therapy and chemotherapy in disseminated breast cancer. *Breast Cancer Res Treat* 1981, **1**, 43–52.
4. RUBENS RD, BEGENT RHJ, KNIGHT RK, SEXTON SA, HAYWARD JL. Combined cytotoxic and progeston therapy for advanced breast cancer. *Cancer* 1978, **42**, 1680–1686.
5. COCCONI G, DE LISI V, BONI C, MORI P. CMF vs. CMF plus tamoxifen (T) in postmenopausal metastatic breast cancer. A prospective randomized study. *Proc Am Soc Clin Oncol* 1982, **1**, 75.
6. CAVALLI F, BEER M, MARTZ G, JUNGI WF *et al.* Concurrent or sequential use of cytotoxic chemotherapy and hormone treatment in advanced breast cancer: report of the Swiss Group for Clinical Research. *Br Med J* 1983, **286**, 5–8.
7. FEY MF, BRUNNER KW, SONNTAG RW. Prognastic factor in metastatic breast cancer. *Am J Clin Oncol* 1981, **4**, 237–248.
8. HAYWARD JL, CARBONE PP, HENSON JC, KUMAOKA S, SEGALOFF A, RUBENS RD. Assessment of response to therapy in advanced breast cancer. *Cancer* 1977, **39**, 1289–1293.
9. KAPLAN EL, MEIER P. Nonparametric estimation from incomplete observations. *J Am Statist Assoc* 1958, **53**, 457–481.
10. PETO R, PIKE MC, ARMITAGE P *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 1977, **35**, 1–39.
11. CAVALLI F, BEER M, MARTZ G *et al.* Gleichzeitige oder sequentielle Hormono/Chemotherapie sowie Vergleich verschiedener Polychemotherapien in der Behandlung des metastasierenden Mammakarzinoms. *Schweiz Med Wochenchr* 1982, **112**, 774–783.
12. POWLES TJ, COOMBES RC, SMITH IE, JONES JM, GAZET JC. Failure of chemotherapy to prolong survival in a group of patients with metastatic breast cancer. *Lancet* 1980, **i**, 580–581.
13. TORMEY DC, KLINE J, DAVIS TE, LOVE RR, CARBONE PP. Short term intensive chemo-hormonotherapy in metastatic breast cancer. *Proc Am Soc Clin Oncol* 1981, **22**, 445.
14. VOGEL C, LEFANTE J, EAST D, ROGERS B, SMALLEY R. Cyclophosphamide, adriamycin and 5-fluorouracil alternating with a cycle-active regimen in metastatic breast cancer. A randomized Southeastern Cancer Study Group trial. *Proc Am Soc Clin Oncol* 1981, **22**, 439.
15. NERVI C, ARCONGELI G, CONCOLINO F, CORTESE M. Prolonged survival with post-irradiation adjuvant chemotherapy in stage IV breast cancer. In: JONES SE, SALMON SE, eds. *Adjuvant Therapy of Cancer.* New York, Grune & Stratton, 1979, Vol. II, 311–318.
16. BUZDAR A, BLUMENSCHEIN G, MONTAGNE E, POWELL K, HORTOBAGYI G, YAP H. Retional consolidative therapy following systemic chemotherapy in metastatic breast cancer. *Proc Am Soc Clin Oncol* 1982, **1**, 74.
17. BRUNNER KW, CAVALLI F. Combination endocrine/cytotoxic therapy in breast cancer. In: STOLL BA, ed. *Hormonal Management in Endocrine-related Cancer.* London, Lloyd-Luke Medical Books, 1981.
18. LEGHA SS, BUZDAR AU, SMITH TL, SWENERTON KD, HORTOBAGYI GN, BLUMENSCHEIN GR. Response to hormonal therapy as a prognostic factor for metastatic breast cancer treated with combination chemotherapy. *Cancer* 1980, **46**, 438–445.
19. MANNI A, TRUJILLO JE, PEARSON OH. Sequential use of endocrine therapy and chemotherapy for metastatic breast cancer: effects on survival. *Cancer Treat Rep* 1980, **64**, 111–116.
20. TORNEY DC, GELMAN R, BAND PR *et al.* Comparison of induction chemotherapies for metastatic breast cancer. An Eastern Cooperative Oncology Group Trial. *Cancer* 1982, **50**, 1235–1244.
21. MUSS HB, RICHARDS F, JACKSON DV *et al.* Vincristine, doxorubicin and cyclophosphamide versus low-dose intravenous cyclophosphamide, methotrexate and 5-fluorouracil in advanced breast cancer. *Cancer* 1982, **50**, 2269–2274.

22. CREECH RH, CATALANO RB, MASTRANGELO MD, ENGSTROM PF. An effective low-dose intermittent cyclophosphamide, methotrexate and 5-fluorouracil treatment regimen for metastatic breast cancer. *Cancer* 1975, **35**, 1101–1107.
23. BRUNNER KW, SONNTAG RW, MARTZ G, SENN HJ, OBRECHT P, ALBERTO P. A controlled study in the use of combined drug therapy for metastatic breast cancer. *Cancer* 1975, **36**, 1208–1219.
24. SMALLEY RV, SCOGNA DM, MALMUD LS. Advanced breast cancer with bone-only metastases. A chemotherapeutically responsive pattern of metastases. *Am J Clin Oncol* 1982, **5**, 161–166.
25. VALAGUSSA P, BONADONNA G, VERONESI U. Patterns of relapse and survival following radical mastectomy. Analysis of 716 consecutive patients. *Cancer* 1978, **41**, 1170–1178.
26. SWENERTON KD, LEGHA SS, SMITH T, BLUMENSCHEIN GR, FREIREICH ED. Prognostic factors in metastatic breast cancer treatment with combination chemotherapy. *Cancer Res* 1979, **39**, 1552–1560.
27. STOLL BA. Prolonged survival in breast cancer. In: STOLL BA, ed. *Prolonged Arrest of Cancer*. New York, Wiley, 1982, 59–86.
28. CUTLER SJ. ASIRE AJ, TAYLOR SG. Classification of patients with disseminated cancer of the breast. *Cancer* 1969, **24**, 861–869.