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Sequential Combination Chemotherapy in Advanced Breast Cancer

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Summary. *The results of a prospective controlled study with alternating cycles of two effective non-cross resistant combinations in advanced breast cancer are reported. The two combinations consisted of adriamycin plus vincristine (AV) and cyclophosphamide, methotrexate and fluorouracil (CMF). The study was carried out with the main intent to obtain a higher incidence and a longer duration of response compared to that obtained with either combination alone. A total of 110 evaluable patients (55 for each treatment group) not previously treated with chemotherapy were randomly allocated to receive either Therapy A (2 AV followed by 2 CMF) or Therapy B (2 CMF followed by 2 AV). Complete plus partial response (53% vs 60%) as well as duration of remission (11 vs 12 months) were similar in both treatment groups. At the time of present analysis, 20 patients died from cancer (Therapy A: 9; Therapy B: 11) and in 9 of them death occurred during the first 12 months. The administration of sequential combinations was no more toxic than the administration of either combination alone.*

Introduction

Disseminated breast cancer is responsive to many therapeutic modalities. However, major advances have been recently achieved using multiple drug regimens. From 50–75% of patients respond to combination chemotherapy and this high response rate has made a favorable impact upon survival. However, different combinations when given alone have reached a plateau in their capacity to control advanced breast cancer [5, 8]. Therefore, new approaches must be considered, namely the use of new drugs, the addition of hormone or immunotherapy as well as the administration of non-cross resistant combinations.

The present study was undertaken with the intent to increase both the incidence and the duration of response by alternating two non cross resistant combinations. In fact, it is theoretically conceivable that improved results could be obtained by exposing an heterogeneous population of neoplastic cells to various agents having different mechanisms of action. The combinations selected were AV (adriamycin and vincristine) and CMF (cyclophosphamide, methotrexate and fluorouracil) which were shown in a previous controlled study to be equally effective and non-cross resistant upon primary chemotherapy failure [7]. Since the initial tumor regression could affect the duration of remission, we have decided to randomize our series to investigate, on a controlled basis, the optimal sequence schedule. In fact, we have observed in our previous trial [7] that the tumor regression was more rapidly induced by AV compared to CMF. In particular, at the level of soft tissue lesions, after 2 cycles of treatment, 58% of women started on AV were already in good partial remission compared to 38% of those given CMF.

Patients and Methods

Drug Treatment

Patients not previously treated with chemotherapy and with measurable lesions were randomly allocated to receive either Therapy A: 2 cycles of AV followed by 2 cycles of CMF, or Therapy B: 2 cycles of CMF followed by 2 cycles of AV. The alternating treatment was continued until progression of disease or for 6 additional cycles after the achievement of complete remission. If patients remained in complete remission after additional chemotherapy, no further treatment was given. In patients still responding to treatment and who had reached a total dose of 550 mg/m² of adriamycin, therapy was con-

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Table 1. AV and CMF regimens

AV		
Adriamycin (ADM) 60 mg/m²	i.v. on day 1	recycle: day 22
Vincristine (VCR) 1.4 mg/m²	i.v. on day 1 and 8	
CMF		
Cyclophosphamide (CTX) 100 mg/m²	p.o. from day 1–14	recycle: day 29
Methotrexate[a] (MTX) 40 mg/m²	i.v. on day 1 and 8	
Fluorouracil[b] (FU) 600 mg/m²	i.v. on day 1 and 8	

[a] MTX 30 mg/m²
[b] FU 400 mg/m²
for age > 65 years or widespread bone lesions

Table 2. Characteristics of evaluable patients

	Therapy A	Therapy B
Total evaluable	55	55
Median age (years)	53 (32–74)	53 (30–74)
Still menstruating	11 (20%)	10 (18%)
Prior treatment	29 (53%)	32 (58%)
R. Mastectomy	26	25
Primary radiotherapy	1	1
Postoperative radiotherapy	21	13
Palliative radiotherapy	13	9
Castration	14	11
Adrenalectomy	–	–
Androgens	5	6
Estrogens	1	2
Progestins	1	2
Corticosteroids	1	1
No prior treatment	26 (47%)	23 (42%)
Not older than 65 years	6 (11%)	4 (7%)

tinued only with CMF, to avoid the risk of cardiomyopathy. Patients failing to chemotherapy were given additive endocrine therapy. Stratification included menopausal status (0–1 year from menopause, or > 1 year), disease-free interval (simultaneous, 1–5 years, and > 5 years) and site of dominant lesion (viscera, skeleton, soft tissues). AV and CMF were given at the same doses employed in our previous study except for adriamycin which was administered at the dose of 60 mg/m² rather than 75 mg/m² (Table 1). An initial dose reduction was utilized for MTX and FU in women either older than 65 years or with widespread bone lesions. During treatment, a dose attenuation schedule was utilized in the presence of myelosuppression. As in all our previous studies [7, 11], we have categorized the hematologic toxicity according to grade 0, 1 and 2. Half dose of all drugs was given for grade 1 toxicity (leukocytes ranging from 2500–3999/mm³ and/or platelets from 75,000–129,000/mm³). No therapy was administered for grade 2 toxicity (leukocytes < 2500/mm³ and/or platelets < 75,000/mm³) and treatment was resumed as soon as grade 1 toxicity was reached. CTX was reduced or discontinued in the presence of chemical cystitis and VCR in the presence of severe paresthesia. In all women treatment was administered in the out patient clinic.

Patient Sample

From January 1975 to March 1, 1977, a total of 119 women were entered into the study. Patients were selected in fairly good conditions (performance status ≥ 50 according to the Karnofsky scale) and with a life expectancy longer than 2 months at the start of therapy. According to the protocol requirements, all patients had measurable disease. Therefore, a patient was not found suitable for this trial if the only manifestation of disease was either pleural effusion or osteoblastic or mixed-osteoblastic lesions. Patients with brain metastases, with hepatic failure due to massive liver involvement, with extensive previous irradiation to the spine, as well as those with electrocardiographic abnormalities were also excluded from the study. Patients have had no previous chemotherapy. Prior hormonal manipulation was not a necessary pre-requisite for inclusion in the study, but a period of 4–8 weeks should have elapsed since hormonal treatment was discontinued. The main features of patient population are presented in Table 2. At the time of present analysis, 55 patients in both treatment groups were considered evaluable. In the present series, a patient was considered evaluable if a minimum of four cycles of either treatment were administered. For this reason, nine patients are presently non evaluable. As can be seen, both groups were comparable in terms of median age, menstrual status and prior therapy. In the two groups, 20% and 18% of patients, respectively, were still menstruating at the start of chemotherapy. In these women, combination chemotherapy was given instead of castration because they presented with rapidly progressive disease (in particular inflammatory carcinoma) or their age was below 35 years. Nine percent of patients were older than 65 years and therefore, they were started on a lower dose of CMF. Estrogen binding protein was tested in only few patients, because the routine use of this test was started only at the end of 1975 in women undergoing mastectomy. In the two treatment groups, viscera represented the dominant site of disease in 14 and 18 patients; osseous lytic metastases represented the site of major involvement in 10 and 7 cases, respectively. Soft tissue dominant lesions were equally distributed in the two groups (31 vs 30). In about half of these patients soft tissue involvement was the only site of disease as they presented with inflammatory carcinoma (17 vs 16). For this reason, in our present series a large fraction of patients was categorized as having no free interval (Therapy A: 60%, Therapy B: 69%).

Assessment of Results

Besides measurements in centimeters of all palpable lesions, baseline studies have included chest X-ray, roentgenogram of the skull, entire spine and pelvis, hemogram with differential and platelets, liver and renal function tests. Only if clinically indicated, bone scan, liver scan, laparoscopy, bone marrow biopsy, serial EKG (before and during treatment) were performed. The hemogram was repeated before each drug administration, and measurement of palpable lesions at the start of each cycle. Chest roentgenograms and biochemistry were repeated at 1–2 month intervals, and bone X-rays every 3 months. In 5 patients laparoscopy was performed to confirm clinical or radioisotopic findings of liver involvement. The criteria for treatment response are those utilized during all our previous controlled studies on

advanced breast cancer [6, 7, 11, 12], and are practically identical to the international criteria recently proposed by Hayward et al. [15]. In particular, the categories of response were as follows: *Complete remission* (CR): disappearance of all known disease for a minimum of 1 month. In the presence of osteolytic metastases, they must be shown radiologically to have recalcified. *Partial remission* (PR): decrease of 50% or greater in the product of 2 largest perpendicular diameters of measurable lesions, and/or partial recalcification of lytic metastases for a minimum of 1 month. Partial remission was also defined as a CR or PR at the level of all soft tissue and/or visceral metastases associated with unchanged osteolytic lesions. It was not necessary for every lesion to have regressed to qualify for partial reponse, but no lesion should have progressed and no new lesions appeared. *Objective improvement* or *no change:* a 25–50% decrease in the size of measurable lesions or stady state which included a lesser than 25% increase of initial tumor mass. In the presence of concomitant non-measurable, but evaluable lesions which represented the bulk of disease and which clearly did not respond, even though measurable lesions have improved, then this was considered as "no change", unless the site of no change was bone. *Mixed response:* some lesions regressed while others progressed or new lesions appeared. *Failure:* progression of some or all lesions and/or appearance of new lesions, while no lesions showed regression. *Relapse:* appearance of new lesions and/or increase in the product of the two largest perpendicular diameters of measurable lesions by 50% over the size recorded at the initiation of the therapy, following a period of initial response.

Besides the above mentioned criteria, we also have analyzed the various types of response in different organs irrespective of other sites of involvement, or dominant lesion. Furthermore, we have considered complete plus partial response in relation to stratification parameters.

Results

Table 3 presents the comparison of results. No difference was observed between the two treatment groups. If the two series are considered as a whole, CR plus PR was obtained in 56% of patients (62 of 110). The analysis performed at two, four, six and eight cycles failed to confirm that by starting treatment with AV rather than with CMF an earlier and a higher response rate could be induced. Only in the subgroup with inflammatory carcinoma the response after the first two cycles was higher after AV (35%) than after CMF (12%). No difference was also detected by breaking down complete plus partial responders according to the stratification parameters. Menopausal status and free interval did not significantly affect the response rate in both groups (Table 4). The analysis of response related to sites of metastases showed a difference in favor of treatment B at the level of visceral involvement. This was primarily due to the difference in the response rate observed in women with lung metastases (treatment A: 38%, treatment B: 67%). It is noteworthy that partial and even complete recalcification of lytic metastases was documented in a total of 8 out of 31 patients (26%) (Table 5).

Median duration of complete plus partial response calculated from the start of chemotherapy (Fig. 1), was similar for both treatment groups (11 vs 12 months). At the time of present analysis (26 months from the beginning of study), the median survival was not yet reached. Twenty patients died of progressive cancer (9 for Therapy A and 11 for Therapy B) and in 9 of them death occurred during the first 12 months from start of treatment. Three of 9 patients had showed response to combination chemotherapy.

Toxic manifestations are listed in Table 6. The administration of sequential combination chemotherapy

Table 3. Comparison of response

Type of response	Therapy A	Therapy B
Progression	7	4
No change	2	4
Objective improvement	17	14
Partial remission (≥ 50%)	18 (33%)	23 (42%)
Complete remission	11 (20%)	10 (18%)
Complete + partial	29 (53%)	33 (60%)
Total No. with response	46 (84%)	47 (85%)

Table 4. Complete plus partial response related to stratification parameters

	No.	Therapy A	No.	Therapy B
Dominant lesion				
Viscera	14	7 (50%)	18	10 (56%)
Osseous	10	4 (40%)	7	6 (86%)
Soft tissue	31	18 (58%)	30	17 (57%)
Menopausal status				
0–1 year	19	9 (47%)	19	12 (63%)
>1 year	36	20 (56%)	36	21 (58%)
Free interval				
0–1 year	33	17 (52%)	38	23 (61%)
1–5 years	13	8 (62%)	11	7 (64%)
>5 years	9	4 (44%)	6	3 (50%)

Table 5. Complete plus partial response related to sites of metastases

Metastatic site	Therapy A		Therapy B	
	No.	%	No.	%
Soft tissue	55/84	65	52/81	64
Breast	18/34	53	21/32	66
Skin	16/22	73	11/20	55
Nodes	21/28	75	20/29	69
Viscera	6/16	37.5	10/18	56
Lung	5/13	38	6/9	67
Liver	0/1	–	2/5	40
Pleura	1/1	100	1/3	33
Others	0/1	–	1/1	100
Bone (lytic)	3/15	20	5/16	31

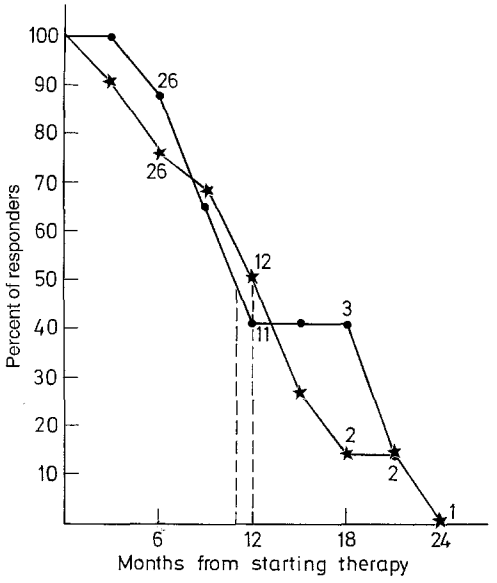

Fig. 1. Remission duration according to treatment group. ●—● Therapy A; ★—★ Therapy B

Table 6. Percent of observed toxic manifestations

	Therapy A	Therapy B
Anemia	56	62
Leukopenia	60	60
Grade 1 (3999–2500)	56	54
Grade 2 (< 2500)	4	6
Thrombocytopenia	60	64
Grade 1 (129,000–75,000)	51	59
Grade 2 (< 75,000)	9	5
Loss of hair	96	88
Mucositis	22	30
Neurotoxicity	75	68
Cystitis	7	20
Amenorrhea	55	80
Cardiac toxicity	1.8	–

was no more toxic than the administration of either combination alone [7]. Temporary bone marrow suppression was the dose limiting factor in both groups. Loss of hair and neurotoxicity were the most frequent toxic signs observed. However, in only few patients was the reduction or discontinuation of VCR required because of severe peripheral neuropathy or adynamic ileus. One patient developed a reversible congestive heart failure after a total dose of 210 mg/m^2 of adriamycin.

Discussion

The results of this prospective study failed to show that in advanced breast cancer treatment with two sequential non-cross resistant combinations such as AV and CMF was superior to the therapeutic effect of either combination alone. In particular, the incidence of various types of response, median duration of response and median survival after sequential chemotherapy were practically superimposable to the findings observed in a similar series of patients treated with AV or CMF alone followed by crossover treatment upon failure or progression [7]. Therefore, although toxicity was not increased by alternating two combinations, there is no documented reason to utilize in clinical practice such a treatment instead of a single effective multiple drug regimen. Similar results were recently observed by Ahmann et al. [1] who noticed little therapeutic advantage to fixed alternative crossover treatment compared to alternative treatment after initial drug program failure.

As stated in the introduction, present drug combinations have definitely improved the treatment of disseminated breast cancer. However, although the response rate is considerably high, few patients achieve complete remission and the median duration of response does not exceed 10–12 months. To our knowledge, only Muss et al. [17] have reported a median duration of remission of 16 months utilizing a combination of cyclophosphamide, vincristine, methotrexate, prednisone and adriamycin. Other recent studies [2, 10, 13] provided results which are similar to those reported in our present series.

In conclusion, available multiple drug treatments do not seem to produce in responding patients a long-term disease-free status as observed, for instance, in embryonal rhabdomyosarcoma, testicular cancer, Hodgkin's disease and histiocytic lymphoma. To increase the median duration of response and survival, hormone therapy and immunotherapy should be tried in conjunction with combination chemotherapy. Some early reports [3, 9, 16] would indicate that this type of approach is worth of further trials. The main strategic approach for the treatment of breast cancer probably lies in the combined treatment modality for women with resectable disease but at high risk of early relapse when the axillary nodes are involved [4, 14]. Cure can be expected only in a fraction of patients with minimal residual disease. In the presence of overt disseminated breast cancer and with the available tools, only good palliation can be achieved. Therefore, future studies should be directed in the search of new simple treatments which can achieve a prolonged control of the disease at the expense of minimal toxicity.

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