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Combined Chemotherapy-Radiotherapy Approach in Locally Advanced (T_{3b}–T_4) Breast Cancer

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Summary. *Combined treatment modality was applied in 110 consecutive women with primary inoperable (T_{3b}–T_4) breast cancer. Treatment was started with four cycles of adriamycin plus vincristine (AV). This was followed in responders by high-energy radiotherapy (RT). At the end of combined therapy, patients in complete remission (CR) were randomized to either no further treatment or six more cycles of chemotherapy. AV induced objective response in 89% of patients (complete 15.5%, partial 54.5%, improvement 19%). At the end of RT, 81 of 98 (82.7%) patients responding to AV were classified in CR. The median duration of CR was 15 months. The median free interval was statistically prolonged by additional chemotherapy. The three-year survival was 52.8%. Altogether, present findings indicate that combined treatment modality has improved the three-year survival compared to the previous series treated with radiotherapy alone. However, to achieve a satisfactory control of T_{3b}–T_4 breast cancer a more aggressive and prolonged treatment is required.*

Introduction

In a previous retrospective evaluation on 454 consecutive patients we have shown that primary radiotherapy (RT) produced satisfactory long-term control only in the minority of women presenting with T_{3b}–T_4 breast cancer [23]. In fact, despite initial effective control of local disease in about 50% of patients, 45% showed relapse within the first 18 months from starting RT. During this period of time, in 158 of 193 women with relapse (82%), new disease manifestations were documented in areas distant from the irradiation fields. The median survival for the whole series was 2.5 years and that of the subset with inflammatory carcinoma 1.2 years. A selected subgroup of 133 patients with good local control or clinical complete remission was subjected to radical mastectomy about 6–8 weeks after completion of RT. Only in 10% of patients was no histological evidence of residual neoplastic disease documented. Thus, also true local control was achieved only in a minority of patients. Similar results were recently reported by Rubens et al. [20] in a series of 184 patients with Stage III carcinoma. The conclusion drawn from both retrospective studies was that the incorporation of systemic therapy into primary management was deemed necessary to improve the prognosis of locally advanced breast cancer.

In this paper we report the three-year results of a combined chemotherapy-radiotherapy approach for women with primary inoperable breast cancer. The drug combination selected for this study consisted of adriamycin plus vincristine (AV). In two previous trials carried out in our institute [4, 5, 8], AV produced complete plus partial remission in 50–60% of patients with advanced breast cancer. In particular, at the level of soft tissue lesions this type of response was achieved in 58% after only two cycles, while the total response rate was 70%. The effects of AV were confirmed by subsequent studies [2]. The rationale for starting treatment with chemotherapy was provided by the observation that relapse in distant sites was documented during the time of irradiation in an appreciable number of patients of the previous series.

Patients and Methods

Study Design and Treatment Schedule. The treatment protocol is outlined in Figure 1. The induction phase consisted of four cycles of

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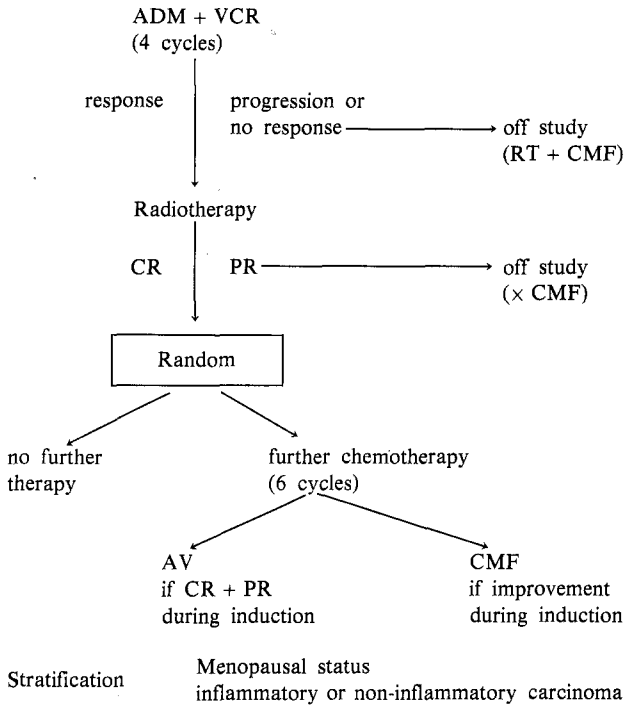

Fig. 1. Outline of treatment study

AV followed after 1 month by RT in patients showing objective response to chemotherapy. Patients achieving clinical complete remission at the end of the irradiation program were then randomized to either no further therapy or to six more cycles of chemotherapy (maintenance phase). During maintenance treatment chemotherapy consisted of AV if the initial response was classified as complete or partial remission. If only objective improvement was obtained, cyclophosphamide, methotrexate, and fluorouracil (CMF) were administered since in previous studies no cross resistance was found between AV and CMF.

During induction and maintenance phases, adriamycin (ADM) was injected intravenously on day 1 at the dose of 75 mg/m^2. Vincristine (VCR) was given intravenously on day 1 and 8 at the dose of 1.4 mg/m^2. Treatment was recycled on day 22. CMF was administered at the classical monthly dose schedule described in previous publications [5, 8]. A low dose schedule was utilized for patients older than 60 years (ADM 60 mg/m^2, MTX 30 mg/m^2, FU 400 mg/m^2).

Radiotherapy was administered using Co^{60} teletherapy. Tangential fields were employed to irradiate the primary tumor while axillary, supraclavicular, and internal mammary lymph nodes were irradiated through direct portals. The tissue dose for breast was calculated at the midplane, 4 cm in depth for axilla, and 3.5 cm for supraclavicular and internal mammary nodes. The breast received 6,000 rad in 6 weeks; one-third of the dose was delivered with plexiglas bolus to increase the dose administered to the skin. Most patients received a boost dose of 1,000 rad with a direct reduced field to the residual tumor. The dose delivered to the axilla was ranging from 5,000–6,000 rad in 6 weeks, that to supraclavicular and internal mammary nodes from 4,000–5,000 rad in 5–7 weeks. In only two patients were the internal mammary nodes not included in the irradiation program. In patients older than 5 years the dose to the internal mammary chain was reduced to 4,000 rad to limit the risk of cardiomyopathy. The irradiation program was completed in 8–9 weeks.

Table 1. Main characteristics of patients sample

	Inflammatory carcinoma	Noninflammatory carcinoma	Total
T_{3b}	–	5	5
T_4	36	69	105
N_0	7	20	27
N_{1-3}	29	54	83
Premenopause	20	37	57
Postmenopause	16	37	53
Median age (year)	52 (22–72)	50 (27–69)	51 (22–72)

In complete responders showing relapse once combined treatment modality was completed, secondary therapy was not uniform. It included either AV or CMF in relation to the treatment assigned after randomization. Endocrine manipulation was also employed in most premenopausal patients (ovariectomy) and in some elderly women (estrogens).

Patients Sample. From April 1973 to September 1975 a total of 110 consecutive patients with clinical and mammographic diagnosis of T_{3b}–T_4 N_xM_0 breast cancer were admitted to the study. Histological confirmation of clinical findings was obtained in 66 patients through needle biopsy of the breast. Table 1 summarizes the main characteristics of patients. All patients were considered evaluable for treatment response. Only five women were classified as having T_{3b} extent (tumor more than 5 cm in its greatest dimension with fixation to underlying pectoral fascia and/or muscle). Of those with T_4 lesions (tumor of any size with direct extension to chest wall or skin), 36 also showed the clinical features of dermal lymphatic carcinomatosis (so-called inflammatory carcinoma). The diagnosis of inflammatory carcinoma was made when clinical findings included erythema, peau d'orange, and wheals or ridges in the skin. Regional adenopathy was clinically detectable in a total of 75% with no particular difference between the groups with (80.6%) and without (73%) inflammatory carcinoma. About half the patients were in either pre- or postmenopausal status.

Study Parameters. Baseline studies included a centimetric measurement of both primary lesion and regional adenopathy, a thorough radiological evaluation (bilateral mammography and thermography, roentgenograms of chest, skull, spine, pelvis, and upper third of femurs, liver scan with ^{99}mTc), blood chemistry (blood urea nitrogen, serum bilirubin, alkaline phosphatase, SGOT, SGPT, total proteins, calcium and phosphorus), complete hemogram with differential and platelet count, and electrocardiogram. In 40 consecutive patients a unilateral needle marrow biopsy was also performed and found to be negative in all cases. During chemotherapy, tumor measurements were repeated on day 1 of each cycle. Radiological studies and blood chemistry were repeated before starting RT and prior to randomization. Once treatment was completed, chest roentgenogram, mammography, and thermography were performed every 2–3 months, while bone X-rays, liver scan, and blood chemistry were repeated every 6 months. In the presence of hepatomegaly and/or positive liver scan, peritoneoscopy with multiple liver biopsies was performed in two patients. In 14 patients with suspicious recurrence in the breast, a single needle biopsy was carried out to confirm or rule out the clinical findings.

Criteria of Response. During inital chemotherapy the criteria for complete (CR) and partial remission $\geq$ 50% (PR) as well as for objective improvement, status quo, and progression were those al-

ready described in detail in our previous publications on chemotherapy for advanced breast cancer [4, 5, 8, 9]. In patients with inflammatory carcinoma the objective response was based on clinical disappearance of skin changes as well as on reduction of bulky tumor mass. In six of 14 patients thermography also showed a marked decrease of inflammatory signs. The status of remission after RT was much more difficult to assess on a clinical-radiological basis. Besides induration of skin and of subcutaneous tissues, a residual area of density of uncertain interpretation was present on mammography in patients classified as complete responders on physical examination. In 67% of patients a good correlation between clinical and mammographic response was observed. In women with clinical-radiological discrepancy the status of CR was arbitrarily assessed on palpation.

Statistical Evaluation. Duration of complete remission curves representing the distribution of the treatment failure time was calculated from the date of completion of radiotherapy. Overall survival curves were calculated from the start of induction chemotherapy. The curves were computed using the life-table method and were statistically compared using the Mantel method of the Wilcoxon test [15].

Results

Table 2 presents the type of response to induction AV, and findings are related to the presence or absence of inflammatory carcinoma. The incidence of complete plus partial remission as well as the overall response was superior to that observed in metastatic breast carcinoma at the level of soft tissue lesions (89 vs 70%) [5]. It is noteworthy that the presence of inflammatory carcinoma failed to unfavorably affect the response to chemotherapy.

One month after the end of RT, 81 of 98 (82.7%) patients showing response to AV were classified as complete responders. Table 3 shows that there was a direct correlation between the degree of response achieved after chemotherapy and the incidence of CR at the completion of irradiation. Once more, no statistical difference was observed in the response rate between patients with and without inflammatory carcinoma.

Table 2. Response to induction chemotherapy

	Inflammatory carcinoma		Noninflammatory carcinoma		Total	
	(No.)	(%)	(No.)	(%)	(No.)	(%)
Progression	2	5.5	4	5.5	6	5.5
No response	–	–	6	8	6	5.5
Objective improvement	10	28	11	15	21	19
Partial response ≥ 50%	17	47	43	58	60	54.5
Complete response	7	19.5	10	13.5	17	15.5
Complete + partial	24	67	53	72	77	70
Overall response	34	94	64	86	98	89

Table 3. Response to induction phase (chemotherapy plus radiotherapy)

Response to chemotherapy		Response to radiotherapy		
	No.	CR	PR	Progression
CR	17			
Inflammatory ca.		6 (86%)	0	1
Noninflammartory ca.		10 (100%)	0	0
PR	60			
Inflammatory ca.		13 (76%)	4	0
Noninflammartory ca.		38 (88%)	3	2
Improvement	21			
Inflammatory ca.		6 (60%)	2	2
Noninflammartory ca.		8 (73%)	3	0
Overall	98			
Inflammatory ca.		25 (73%)	6 (18%)	3 (9%)
Noninflammartory ca.		56 (87.5%)	6 (9.5%)	2 (3%)

The duration of CR after combined AV-RT in graphically illustrated in Figure 2. The median duration for the entire series was 15 months. Although the curves show a pattern of continuous relapse during the first 24 months from completion of the induction phase, the median free-interval was statistically prolonged by maintenance chemotherapy (19 vs 11 months, $P = 0.02$).

Table 4 shows the patterns of first relapse in patients classified as complete responders at the end of RT. In the group given maintenance therapy the incidence of local recurrence was inferior compared to the group given no further therapy after randomization. Of patients showing local relapse, one of nine (11%) and seven of 22 (32%), respectively, were classified as complete responders after the first four cycles of AV. Of 14 patients with suspicious local recurrence, needle biopsy of the breast was interpreted as positive for cancer in six and negative in three, while in five patients the specimen was considered inadequate for histologic examination. In patients with negative biopsy, two showed relapse in the breast after 3 and 13 months. In those with inadequate specimen, two had local relapse after 6 months. No difference in the incidence of distant metastases was documented between the two treatment groups.

Table 4. Pattern of first relapse (no. findings)

	Maintenance therapy	No maintenance therapy
Local	9* (24.3%)	22** (50.0%)
Inflammatory ca.	2	8
Noninflammatory ca.	7	14
Distant	13* (35.1%)	13* (29.5%)
Inflammatory ca.	4	6
Noninflammatory ca.	9	7

Concomitant local and distant relapse: 4* and 6**

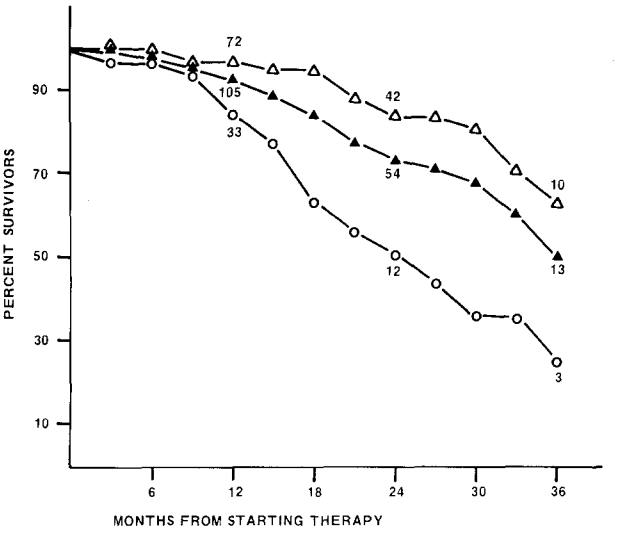

Fig. 3. Survival: inflammatory vs non-inflammatory carcinoma. ▲—▲ whole series (110 patients); △—△ non-inflammatory carcinoma (74 patients); ○—○ inflammatory carcinoma (36 patients) ($P = 0.0001$)

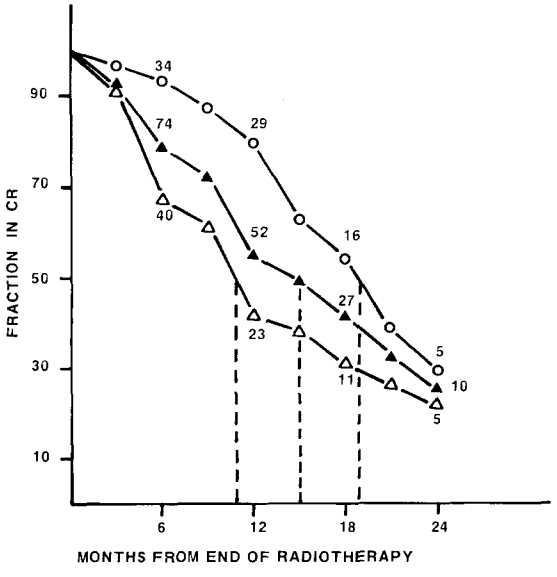

Fig. 2. Remission duration: maintenance vs no maintenance chemotherapy. ▲—▲ whole series (81 patients); ○—○ maintenance (37 patients); △—△ no maintenance (44 patients) ($P = 0.02$)

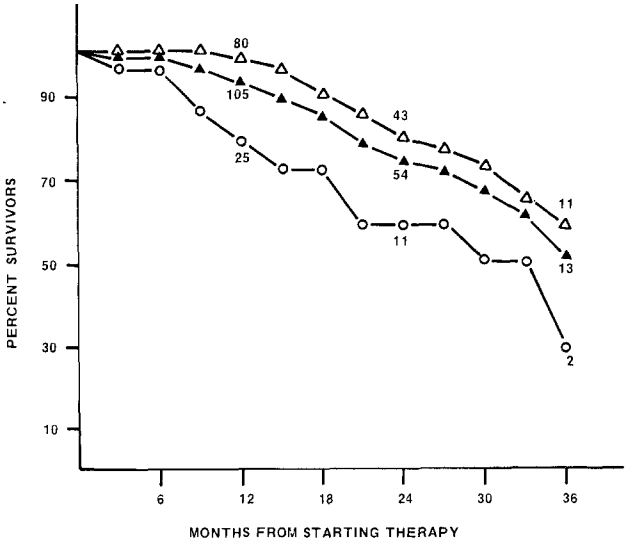

Fig. 4. Survival: complete vs non-complete responders. ▲—▲ whole series (110 patients); △—△ complete responders combined treatment (81 patients); ○—○ non-complete responders (29 patients) ($P < 0.01$)

The three-year survival was 52.8%. Patients with inflammatory carcinoma showed a significant lower survival (median: 25 months) compared to those without inflammatory carcinoma (Fig. 3). The status of clinical CR was statistically correlated to an improved survival compared to that of partial or no responders (Fig. 4). Both disease-free and overall survival were not influenced by menopausal status or by the clinical status of regional nodes.

Myelosuppression represented the most frequent dose-limiting factor observed during chemotherapy. During induction chemotherapy, grade 1 toxicity (leukocytes 3,999 – 2,500 per cu mm and platelets 129,000 –75,000 per cu mm) occurred in 35 and 24% respectively. Grade 2 toxicity (leukocytes < 2,500 per cu mm and platelets < 75,000 per cu mm) was documented in only 1 and 3% respectively. Loss of hair was observed in 94% of patients, peripheral neuropathy in 61% and oral mucositis in 15%. Drug-induced amenorrhea was documented in 40% of premenopausal patients. During the induction phase the average total dose of ADM was 95.5%, that of VCR 86%. During the maintenance phase these findings were 83 and 74.7%, respectively. In patients treated with CMF, the percent of optimal dose administered was as follows: CTX 81.6%, MTX 89%, FU 89%. Severe myelosuppression was never observed during irradiation and treatment was never discontinued because of toxicity. No 'recall' skin reaction was observed. Side effects from RT included a moderate degree of pulmonary fibrosis in six patients (6%) and deficit of brachial nerves in two.

Late sequelae from treatment were documented in two of 30 patients given maintenance therapy with ADM. Both developed nonfatal cardiomyopathy after a total dose of 400 and 600 mg/m^2. The patient who developed cardiac toxicity after 400 mg/m^2 had a left-sided breast cancer, and the irradiation field encompassed most of the cardiac area. The patient who developed cardiac toxicity at 600 mg/m^2 had a right-sided breast cancer. Symptoms occurred 20 days after the conclusion of maintenance treatment in the first patient and after the fifth cycle of AV in the second patient.

Discussion

Our study represents one of the first attempts to treat primary inoperable breast cancer utilizing a combination of local-regional irradiation with systemic chemotherapy. Although most women presenting with T_{3b}–T_4 breast cancer could be technically suitable for mastectomy, primary surgery was recognized a long time ago to represent a useless procedure in this stage of the disease because of frequent, multiple, and early recurrences. For this reason, radiation therapy has gradually replaced radical surgery as primary treatment for locally advanced disease. The technique of irradiation was pionered by Baclesse [1] and subsequently developed by several investigators [7, 10–12, 14, 16, 22, 23]. With optimal external radiotherapy, local control in T_{3b}–T_4 breast cancer can be achieved in about 50% of patients. Since the possibility of achieving satisfactory local control is inversely related to tumor size, the external beam therapy was either preceded by tumorectomy [13, 14, 22] or supplemented by iridium 192 [14, 17, 18, 22], radium and gold grain [3] interstitial implantation.

Despite different efforts to control the overt disease, T_{3b}–T_4 breast cancer most often recurs in distant sites. Besides the findings of Zucali et al. [23] and Rubens et al. [20] which were mentioned in the introduction, Levene et al. [14] have more recently reported that 61 of 86 (71%) patients developed distant metastases with over 90% occurring within the first 3 years of primary radiotherapy. In the series of Ghossein et al. [13] local and distant failure after irradiation occurred in 18 of 22 (82%) patients. A subgroup of locally advanced breast cancer is that with dermal lymphatic infiltration. With the possible exceptions of the series of Rubens et al. [20] and Levene et al. [14], inflammatory carcinoma of the breast carries, in general, a very poor prognosis. Following primary external irradiation, Zucali et al. [23] observed that 38 of 70 (54%) patients showed relapse within the first 18 months and only 28% were alive at 3 years. More recently Barker et al. [3] reported an incidence of distant metastases in 78% of women within 1 year and a mortality rate of 77% within 2 years. Altogether, the above mentioned results confirm that T_{3b}–T_4 breast cancer is, in general, a very aggressive disease and that only a few patients such as those with deep fixation of the primary tumor [20] are running a slow-growing, nonmetastasing course. The high incidence of failures in distant sites indicates that disseminated micrometastases are already present at the time of diagnosis. Therefore, in this stage the application of the strategy of combined local-systemic treatment appears logical.

The combined treatment as applied in the present study failed to make a substantial clinical impact in either the disease-free or the overall survival. However, the addition of chemotherapy to the conventional irradiation program produced a favorable prognostic trend which, in our opinion, should not be neglected. When results are retrospectively compared to our previous series [23], the median overall three-year survival was statistically improved from 40.7–52.8% ($P = 0.02$). Furthermore, radiation therapy preceded by AV chemotherapy induced a clinical complete local-regional remission in more than three-fourths of patients, which is one of

the best rates yet reported. Additional chemotherapy following radiotherapy improved significantly the remission duration and decreased the incidence of local recurrence. However, at present, its usefulness should be considered only as a clinical investigation. The combined treatment apparently failed to influence the course of disease in women with inflammatory carcinoma, and no difference could be found in the three-year survival rate of the present series (24.9%) compared to the previous series (28%) treated only with radiotherapy. Three other reports on combined local-systemic therapy have recently appeared in the literature. Sponzo et al. [21] achieved CR in 11 of 12 patients with high dose radiotherapy (7,000–9,000 rad) plus cyclophosphamide, fluorouracil, and prednisone. The median duration of response was 16 months. Blumenschein et al. [6] treated 13 patients with inflammatory carcinoma utilizing fluorouracil, adriamycin and cyclophosphamide (FAC) plus BCG followed by radical radiotherapy and by further chemoimmunotherapy. An additional five patients received chemotherapy without radiotherapy. The preliminary results showed complete remission in 94% as well as a projected median duration of 13 months and a projected median survival of 28 months. Rojas et al. [19] treated with radiotherapy a series of 43 women with primary inoperable breast cancer. After achieving a clinical disease-free status, patients were allocated alternately to no further treatment or to levamisole for three consecutive days every other week until there was evidence of progressing disease. In the levamisole-treated group, there was a significant prolongation of the median disease-free interval (25 vs 9 months) and survival (90 vs 35% alive at 30 months).

In conclusion, locally advanced (Stage III or T_{3b}–T_4) breast cancer remains a challenging disease for contemporary treatment strategies. There is little doubt that systemic medical treatment should be tried as primary therapy in the attempt to improve the prognosis. Available results, including our own, show that there is early evidence that different forms of systemic treatment are improving both the incidence and the duration of complete remission as well as the median survival. Despite these promising results, a satisfactory combined therapy is not yet available. Medical treatment must be optimized in terms of drug combinations, duration of therapy, addition of either endocrine therapy in women with positive receptors or immunotherapy. Furthermore, if medical treatment can really improve the incidence of complete remission and decrease the incidence of distant recurrence, surgery may be resumed to achieve a better local-regional control especially in the subgroup with non-inflammatory carcinoma and without involvement of supraclavicular lymph nodes. Most probably, prospective controlled clinical trials could solve some of these problems.

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