SURGICAL DJUVANT CHEMOTHERAPY FOR BREAST CANCER: A COMPARISON OF CMF AND CAF REGIMENS

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ABSTRACT

Combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil (CMF) was compared with cyclophosphamide, adriamycin and fluorouracil (CAF) as adjuvant to modified radical mastectomy in primary operable breast cancer with positive axillary lymph nodes. After 18 months of study, treatment failure occurred in 10% patients in each group. The new clinical manifestations occurred locally in 75% and at distant site in 25% of relapsed patients. Long term chemotherapy produced an acceptable toxicity, thus allowing the administration of a high percentage of drug dosage. This study suggests that CMF and OAF regimens have comparable efficacy and toxicity in surgical adjuvant chemotherapy for breast cancer (JPMA 41: 293, 1991).

INTRODUCTION

The ideal treatment for primary operable breast cancer has been the subject of controversy for decades. Despite different approaches of surgical and radio-therapeutic treatments, the overall cure rate has remained essentially unchanged. Differences among case series probably reflect patient selection rather than actual therapeutic improvement. To overcome the plateau reached by curative operations, new approaches were attempted. The first of there was postoperative oophorectomy. However, results showed that prophylactic endocrine therapy prolonged the disease-free period in some series but failed to improve the overall survival[1-3]. The favourable effects of chemotherapeutic agents in advanced malignancies[4] as well as reports of the frequent presence of cancer cells in the circulating blood of patients during operative manipulations[5] provided the rationale for undertaking systemic adjuvant treatments. The results of early controlled studies were conflicting[6-11]. In retrospect the short-term single agent therapy used in practically all series was thought to represent the major cause of treatment failure. In the last two decades many clinical findings affected the design of new adjuvant trials. The high correlation between positive axillary nodes and relapse rate[12], as well as the observation that postoperative radiotherapy was unable to influence the prognosis significantly[13], led to the conclusion that in most patients with regional nodes involved, the disease was already disseminated at the time of mastectomy. Consequently there was a conceptual change in emphasis from destruction of free cells in the circulation at the time of surgery to the need to destroy the micro-metastases[14]. From this emerged the concept of prolonged adjuvant chemotherapy for high risk patients. Many controlled trials were performed using single agent chemotherapy, but with conflicting results[15-21]. Based upon the fact that combination chemotherapy is superior to single agents in advanced breast cancer[22-24] and CMF is the active component[25], a controlled trial was conducted by the Instituto Nazionale Tumori, Milan, using CMF. The results were superior to those with single agent chemotherapy[26]. Many other trials of adjuvant chemotherapy with CMF or one of its variant have shown encouraging results[27-29]. Adriamycin is one of the most active single agent used in advanced carcinoma of the breast. It is also being used in various combination regimens[30,31]. Recently some studies have been reported on the use of adriamycin containing regimens in adjuvant chemotherapy for breast cancer. The initial results are

very encouraging[32,33]. During the last decade adjuvant antioestrogens have also been tried either alone or in conjunction with chemotherapy[34,35]. This study consists of a comparison of efficacy and toxicity of CMF & CAF regimens in surgical adjuvant chemotherapy for primary operable breast cancer.

PATIENTS AND METHODS

The study was carried out on patients admitted to the East Surgical and Radiotherapy-Oncology Units, Mayo Hospital, Lahore.

Selection of patients

All female patients who had undergone modified radical mastectomy for potentially curable breast carcinoma and who had one or more axillary lymphnodes positive on histologic study were eligible for inclusion in the study provided they satisfied the following protocol requirements: tumour confined to the breast or breast and axilla, extent of primary tumour and axillary lymph node metasta.sis - T1, T2, T3 N0, N1, negative radiologic studies (chest and skeletal x-rays and liver scan) and adequate bone marrow reserve (WBC count more than 4000/mm^3 and platelet count more than 130,000/mm3). The following conditions made patients ineligible: age over 75 years, pregnancy or lactation, previous treatment for current neoplasms, previous or concomitant neo plasms, bilateral breast cancer, malignant breast tumour other than carcinoma and poor risk patients having non-malignant systemic disease.

Treatment

The modified radical mastectomy consisted of removal of the breast and axillary contents enbioc. The primary neoplasm and all lymphnodes removed at operation were histologically examined. Chemotherapy was started two to four weeks after mastectomy and continued for 6 cycles. CMF consisted of cyclophosphamide (100 mg/m^2, p.o., days 1-14), methotrexate (40 mg/m^2, i.v., days 1,8) and fluorouracil (600 mg/m^2, i.v., days 1,8). CAP consisted of adriarnycin (30 mg/m^2, i.v., days 1,8) and cyclophospharnide and fluorouracil (doses similar to that in CMF regimen). The next cycle was started after a two week rest (days 15-28). The total dose of cyclophosphamide was adjusted to the nearest 50 mg since fractions of tablets cannot be. administered. In patients over 65 years of age the initial dose of methotrexate was reduced to 30 mg/rn2 and that of fluorouracil to 400 mg/m^2. A reduced schedule was used in the presence of myelosuppression, determined on the first day of each cycle. If no toxicity was evident or Grade 0 (leukocyte count more than 4000/mm3 and platelet count more than 130,000/mm3), 100% of each drugwas administered. For Grade 1 toxicity (leukocyte count of 3999 to 2500/mm^3 or platelet count of 129,000 to 75,000/mm^3 or both), 50% of the calculated dose was given. In the presence of Grade 2 toxicity (leukocyte count less than 2500/mm^3 or platelet count less than 75,000/mm^3 or both) no drug was administered unless grades I toxicity was reached.

Follow-up study

Radiograph of the chest was performed every three months and a skeletal survey and liver scan every six months. Bone scan was performed only in the presence of either suspicious osseous lesions on x-rays or persisting bone pain. Blood chemical studies (urea, sugar, transaminases, alkaline phosphatase, bilirubin and calcium) were carried out every three months.

RESULTS

TABLE 1. Characteristics of 30 patients treated with CMF and 10 patients treated with CAF with observed failure proportions.

Characteristic		Evaluable Patients			
		CMF		CAF	
		No.	%	No.	%
1. Total with recurrences		3/30	10	1/10	10
2. Age:					
	Less than 50 yrs.	2/23	8.7	1/9	11.1
	More than 50 yrs.	1/7	14.3	0/1	-
3. Menopause:					
	Pre	2/21	9.5	1/8	12.5
	Post	1/9	11.1	0/2	-
4. Stage:					
	T1	-	-	-	-
	T2	0/11	-	0/3	-
	T3	3/19	15.8	1/7	14.3
5. Histology:					
	Ductal	3/26	11.5	0/8	-
	Lobular	0/1	-	1/1	100
	Other	0/3	-	0/1	-

Table I presents the characteristics of patients with treatment failure. There was no difference in total rate of treatment failure in each group (10%). There was no significant difference in the incidence of relapse between pre-menopausal and post- menopausal patients. The rate of recurrence increased as the size of primary tumour increased (T3 > T2). The histologic characteristics of the tumour showed no relationship to the rate of recur rence. In both the groups the most frequent site of recurrence was chest wall (2 cases in CMF group and one case in CAP group). The only other site of recurrence was the skeletal metastasis in one case of CMF group. There was no case of second primary breast carcinoma. As various degrees of nausea and vomiting were expected, all patients were given metocloperamide 10mg intravenously before the start of intravenous drug administration. Inspite of that a good proportion of patients had nausea and vomiting. The frequency of vomiting showed a tendency to decrease after the initial cycles. About 10% of the patients did not complain of nausea and vomiting. The most important abdominal disturbance was prolonged nausea and anorexia produced by the Continuous administration of oral cyclophosphamide. The toxic manifestations are listed in Table II.

TABLE II. Toxic manifestations.

	Manifestation	CMF		CAF	
		No.	%	No.	%
1.	Leukopenia:				
	3,999-2,500/mm^3	17	56.6	6	60
	Less than 2,500/mm^3	1	3.3	0	-
2.	Thrombocytopenia:				
	129,000-75,000/mm^3	15	50	4	40
	Less than 75,000/mm^3	1	3.3	0	-
3.	Oral mucositis	2	6.6	0	-
4.	Conjunctivitis	3	10	1	10
5.	Alopecia	14	46.6	4	40
6.	Cystitis	5	16.6	1	10
7.	Cardiotoxicity	0	-	1	10
8.	Hepatotoxicity	1	3.3	0	-
9.	Amenorrhoea (Premenopausal pts.)	13	61.9	5	62.5
10.	No toxicity	2	6.6	1	10

Leukopenia and thrombocytopenia, as detected on the first and eighth day of each treatment cycle, represented the most frequent sign of toxicity in each group. Prolonged haematosuppression was rare. No increased rate of infections was observed. Different degrees of loss of hair occurred in about half the patients in each group. The loss of hair usually started after the first cycle and in most cases stopped after cessation of chemotherapy. In most cases regrowth of hair was observed at the end of therapy. Mild oral mucositis occurred in CMF group (6.6%). Conjunctivities occurred in 10% of cases in each group. Chemical cystitis produced by cyclophosphamide occurred in one sixth and one fifth of the patients in CMF and CAF groups respectively. Haemorrhagic cystitis was not seen in any patient. One patient in CAF group developed cardiomyopathy during the follow-up period. One case in CMF group developed impairment of biochemical liver function tests; she however did not develop any clinical manifestation and liver functions returned to normal after cessation of therapy. In more than half the premenopausal patients in each group, amenorrhoea occurred; it was reversible in some patients.

DISCUSSION

Surgical adjuvant chemotherapy is being increasingly used in potentially curable breast cancer with positive axillary lymphnodes, as it reduces chances of recurrence[36]. This study shows that both CMF and CAF regimens are equally effective in preventing recurrence during first 18 months after mastectomy. New manifestations of disease occurred at distant site in a quarter of the recurred patients. This observation confirms that many patients with involved axillary lymph nodes have microscopic metastatic disease at the time of mastectomy. This finding represents the best indicator that systemic approach is necessary in the subgroup of high risk patients in the attempt to eradicate subclinical or minimal residual disease. Prolonged chemotherapy produced an acceptable rate and type of toxic manifestations, thus allowing the administration of a high percentage of drug dosage. Among the agents

employed cyclophosphamide was responsible for some unpleasant sequelae such as prolonged gastric disturbances, cystitis and amenorrhoea. Furthermore, this drug was probably the major cause for loss of hair. All side effects were reversible in most patients. The prolonged cessation of menses in some patients may represent premature ovarian failure[37]. My results support and extend the Fisher and Bonadonna studies[21,26]. This study may be helpful in devising a more practical approach to the treatment of early breast cancer.

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