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Reintroducing FAC regimen as Neoadjuvant Chemotherapy in Clinically Node Positive Locally Advanced Breast Cancer

Oncology

KEYWORDS: locally advanced, Breast cancer, neoadjuvant chemotherapy, preoperative systemic therapy, clinical response, toxicity

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ABSTRACT

The aim of our study was to compare the relative efficacy of Fluorouracil based versus Taxol based regimens, in combination with doxorubicin and cyclophosphamide (FAC Vs TAC) as neoadjuvant chemotherapy for clinically node positive locally advanced breast cancer (LABC). Over a period of two years, 100 women evaluated at a tertiary care center with clinically node positive locally advanced breast cancer were randomized to either receive FAC (500/50/500 mg/m2) every 3 weeks for 3 cycles or TAC (75/50/500 mg/m2) every 3 weeks for 3 cycles. Our primary end point was tumor downsizing after 3 cycles of either regimen. We adjusted data for potential interactions (number of positive nodes, tumor size, and treatment center) and found that tumor downsizing with FAC was very similar to TAC regimen. But more side effects were reported with TAC regimen. There was no toxicity related deaths in either group. Fluorouracil in combination with doxorubicin and cyclophosphamide is equally efficacious in comparison with docetaxel and doxorubicin, cyclophosphamide as neoadjuvant chemotherapy in clinically node positive locally advanced breast cancer. Considering the higher toxicity and cost of TAC as compared to FAC, we recommend FAC as first line regimen for LABC and reserving taxol based therapy for patients with recurrent or resistant breast cancer in developing countries like India.

I. INTRODUCTION

Breast cancer is the most frequently diagnosed cancer worldwide and it is the leading cause of cancer related deaths [1]. Early detection with appropriate management can improve survival [2]. Management strategies involve a multimodal approach. There are 5 standard treatment options: Surgery, Chemotherapy, Radiotherapy, Hormonal therapy and Targeted therapy [3]. Neoadjuvant Chemotherapy (NAC) was initially used in treatment of advanced non-operable breast cancers. With time, use of neoadjuvant chemotherapy was extended to early stage breast disease to downstage tumors. The goal of such use was to make inoperable tumors operable and to allow performing breast conservation surgery in place of mastectomy [4]. Neoadjuvant chemotherapy can also help detect tumor sensitivity to particular chemotherapeutic regimen. Pathologic complete response (pCR) with NAC is associated with excellent prognosis and disease free survival [5, 6].

II. MATERIALS AND METHODS

We conducted the study in a multispecialty hospital in Madurai, Tamil nadu, India. Our inclusion criteria were woman aged 18 to75 years, with a diagnosis of clinically node positive locally advanced breast cancer. Locally advanced breast carcinoma was defined as T3 tumors (>5cm) and T4 tumors with N2/N3 disease [11]. Written informed consent was obtained from all the patients. Patients with metastatic/recurrent cancer, prior documented cardiac, renal or liver dysfunction, inadequate bone marrow function, pregnant, life expectancy less than one year and inflammatory carcinomas were excluded. All included patients underwent complete history and physical examination, followed by FNA or core biopsy to determine histopathology. Basic laboratory investigations, mammography, staging workup with Chest X-ray, abdominal ultrasound were obtained. Spiral CT chest was obtained in all patients prior to receiving preoperative chemotherapy. All the patients were randomized to receive FAC (fluorouracil, doxorubicin, cyclophosphamide-500/50/500 mg/m2) or TAC (docetaxel, doxorubicin, cyclophosphamide- 75/50/500 mg/m2) every 21 days for 3 cycles. After each cycle of NAC, patients were evaluated clinically for size of tumor and regional lymph node status. After completion of 3 cycles of NAC, a repeat spiral CT was obtained to assess tumor size. One radiologist reviewed pre and post chemotherapy images in the same window. RECIST criterion was used to determine response [12]. It involves 4 categories: Complete response (CR) indicates disappearance of all lesions. Partial response (PR) means a 30% decrease in sum of longest diameter of target lesions in reference to baseline sum longest diameter. Progressive disease (PD) denotes 20% increase in longest diameter, in reference to baseline sum of smallest diameter of target lesions recorded when the treatment started or the appearance of one or more new lesions. Stable disease (SD) denotes neither sufficient shrinkage to qualify as PR nor sufficient increase to qualify as PD, taking as reference the smallest sum longest diameter since treatment began [12].

We recorded toxicity profiles in all patients. Clinical symptoms such as nausea, vomiting, paresthesia and bone marrow toxicity evidenced by complete blood count were recorded.

III. RESULTS

We included 100 patients. 51 were in the FAC group, 49 in the TAC group. Patient characteristics are reported in TABLE 1. Most patients were in the above 45 age group and postmenopausal. Most of the tumors were in Right breast, upper and outer quadrant, Stage T3N2. TABLE 2 denotes the clinical response after preoperative systemic therapy. The FAC and TAC groups were compared using RECIST criteria. TABLE 3 reveals toxicity profiles of patients treated with FAC vs TAC.

Statistical significance was determined by Fischer's exact test using software R. There was no statistically significant difference between FAC Vs TAC groups in terms of clinical response. Chemotherapy toxicity such as bone marrow dyscrasias, nausea, vomiting, paresthesia and alopecia were higher in TAC group

IV. DISCUSSION

As per the International expert panel on use of Preoperative systemic therapy for operable breast cancer, Primary systemic therapy (PST) is the standard of care in patients with locally advanced breast cancer. The aim of the expert panel was to consolidate evidence in regard to use of PST in patients with LABC (inflammatory carcinoma, cancer with skin, chest wall or extensive regional lymph node involvement). Experts from the United States, United Kingdom, France, Germany, Italy gathered and recommended anthracycline based chemotherapy regimens as the first line of treatment for LABC [7]. After introduction of taxanes, newer regimens have been formulated with improved survival, clinical and histopathological response rate [8]. But the higher efficacy with taxanes was associated with more side effects [9]. A prospective trial done in 2000, among 129 patients revealed similar efficacy between FAC and taxane [10].

In developing countries like India, the incidence of breast cancer has

been increasing over decades. It was estimated that around 100,000 woman will be diagnosed of breast cancer annually [14]. There are many government hospitals and private organizations providing cancer care in India. Cost is a big consideration at all healthcare sector in India considering the huge population of breast cancer patients [15]. More than 90% patients lack proper health care insurance and pay out of their pockets for health care in developing countries [16]. Approximately half of the women diagnosed with breast cancer in India do not receive treatment because of financial issues [17]. FAC regimen is cheaper in comparison to TAC regimen in India. Thereby considering similar efficacy and lower cost, FAC is clearly superior to TAC regimen in developing countries as preoperative systemic therapy for LABC.

I. FIGURES AND TABLES

Table 1. Patient Characteristics

Patient Characteristics		FAC group (N=51)		TAC group (N=49)	
		Number	Percentage	Number	Percentage
Age in Years	<35	3	6	2	4
	35-<=45	5	10	4	8
	>45	43	84	43	88
Menstrual status	Premenopausal	18	35	21	43
	Postmenopausal	33	65	28	57
Hx of Child birth/Lactation	+ve	45	88	41	88
	-ve	6	12	8	16
Family history	+ve	5	10	3	61
	-ve	46	90	46	94
Laterality	R breast	35	69	37	76
	L breast	16	31	12	24
Primary tumour site	Upper Outer Quad	40	78	32	66
	Upper inner Quad	6	12	8	16
	Lower outer Quad	5	10	3	6
	Lower inner Quad	0	0	5	10
	Retroareolar	0	0	1	2
T stage	T3	35	69	41	84
	T4	16	31	8	16
N stage	N2	47	92	44	90
	N3	4	8	5	10
ER status	+ve	30	59	28	57
	-ve	18	35	15	31
	Unknown	3	6	6	12
PR status	+ve	22	43	18	37
	-ve	25	49	26	53
	Unknown	4	8	5	10
HER 2 Neu	+ve	25	49	26	53
	-ve	19	37	20	40
	Unknown	7	14	3	6

Table 2: Clinical response after neoadjuvant Chemotherapy

RECIST RESPONSE	FAC group (N=51)		TAC group (N=49)		P value (Fischer's exact test)
	Number	Percentage	Number	Percentage	
Complete response (CR)	5	10	8	16	P=0.2512
Partial response (PR)	28	55	27	55	P=0.5718
Stable disease (SD)	15	29	12	25	P=0.7819
Progressive disease (PD)	3	6	2	4	P=0.8062

Table 3: Grade 2 or higher toxicity profile for patients (based on CTC toxicity profile, 1999) [13]

TOXICITY	FAC group (N=51)		TAC group (N=49)	
	Number	Percentage	Number	Percentage
Anaemia	17	33	20	41
Neutropenia	12	24	22	45
Thrombocytopenia	2	4	3	6
Alopecia	36	71	41	84
Nausea	42	82	39	80
Vomiting	23	45	31	63
Paresthesia	17	33	13	27

VI. CONCLUSION

In our small scale clinical trial, there was no difference in efficacy between FAC Vs TAC regimens for clinically node positive locally advanced breast cancer (NP-LABC). Hence we conclude that FAC regimen can be recommended as first line neoadjuvant chemotherapy for NP-LABC patients in developing countries. TAC regimen is to be reserved for resistant or recurrent lesions.

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