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The efficacy of two different dosages of epirubicin in neoadjuvant setting: FEC50 v.s. FEC100. Preliminary report

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ABSTRACT

Neoadjuvant chemotherapy is increasingly used in the treatment of patients with large tumor and locally advanced breast cancer. We evaluated the efficacy of FEC50 (5-fluorouracil 500 mg/m^2, epirubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2) and FEC100 (same regimen except with epirubicin 100 mg/m^2) chemotherapy regimen in neoadjuvant setting. Fifty-one eligible patients with stage II-III invasive breast carcinoma were retrospectively analyzed. FEC50 group included 25, FEC100 group included 26 patients. Mammographic and ultrasonographic determination of tumor size and nodal status at the initial and preoperative stages were considered to evaluate the efficacy of chemotherapy. Both groups were to receive median 4 (3-4) cycle chemotherapy. Pretreatment features of the patients and tumors were similar in both groups. The response rate was 48% (95% CI, 28.4-67.5) in FEC50, and 57.6% (95% CI, 38.4-76.5) in FEC100 group. Clinical and pathological complete response rate was 4% (95% CI, 0.0-11.6) in FEC50, and 15.3% (95% CI, 1.4-29.1), 7.6% (95% CI, 0.0-17.7) in FEC100. In this retrospective analysis of our own experience, the response rates observed in FEC50 and FEC100 groups are similar after 4 cycles of neoadjuvant chemotherapy. [Turk J Cancer 2005;35(1):19-25].

KEY WORDS:

Breast cancer, epirubicin, neoadjuvant chemotherapy

INTRODUCTION

The addition of systemic chemotherapy to local therapy in primary operable breast cancer demonstrated significant improvements in progression-free and overall survival (1). In animal models the survival was found to be improved when mice were treated with chemotherapy and tamoxifen before surgical resection (2,3). These preclinical observations promoted several clinical trials that have compared preoperative and postoperative chemotherapy in operable breast cancer, but no significant advantage in terms of long-term survival has been demonstrated especially in large randomized trials (4,5). However, it has been observed that the response of the breast cancer to neoadjuvant chemotherapy is the most important predictive factor for survival (4,6).

For this reason, we retrospectively evaluated the two different dosages of epirubicin in FEC (FEC50 and FEC100) on patients who received neoadjuvant chemotherapy.

MATERIALS AND METHODS

Fifty-one eligible patients with stage II-III invasive breast carcinoma who applied to our department and received neoadjuvant FEC regimen were retrospectively analyzed. Patients with inflammatory carcinoma were excluded. Pathologic diagnosis was performed in all patients

by core needle and/or fine needle aspiration biopsy. At the time of referral, a staging work-up consisted complete history and physical examination, complete blood count, chemistry profile, chest radiography, liver ultrasonography or computed tomography scan of the liver, and bone scan. Twenty-five patients were treated with 5-fluorouracil 500 mg/m², epirubicin 50 mg/m², cyclophosphamide 500 mg/m² (FEC50), 26 patients were treated with 5-fluorouracil 500 mg/m², epirubicin 100 mg/m², cyclophosphamide 500 mg/m² (FEC100). Both chemotherapy regimens were repeated at 21 day-intervals. FEC50 and FEC100 patients were to receive median 4 (3-4) cycles of chemotherapy before local therapy. Neoadjuvant median epirubicin dosage was 200 mg/m² in group FEC50 and 400 mg/m² in group FEC100.

Tumor size and axillary assessment for lymph nodes were conducted by ultrasonography, mammography and physical examination. The tumor size was calculated as the product of the two greatest perpendicular diameters assessed ultrasonographically before chemotherapy and surgery. Radiological response was recorded according to the UICC criteria: a) Complete response (CR), disappearance of the primary tumor; b) Partial response (PR), a tumor reduction of ≥50%; c) stable disease (SD), a tumor reduction <50% or an increase in tumor size of <25%; and d) progressive disease (PD), an increase in tumor size of ≥25% (7). Pathologic complete response (pCR) was evaluated in the dissected mammary and axillary specimens and this was defined if no residual invasive tumor was found.

The pretreatment and posttreatment tissue specimens had been fixed in 10% buffered formalin and embedded in paraffin. 5 μm thick sections were cut and stained with hematoxylin and eosin. The primary tumor characteristics studied included tumor size, histologic type according to the World Health Organization recommendations, histologic grade using the Scarff, Bloom and Richardson (SBR) method. Estrogen (ER) and progesteron (PgR) receptor status were assessed by immunohistochemistry. The proportion of ER and PgR positive cells was determined as the percentage of invasive tumor cells. The threshold of 10% positivity was chosen as the cut-off value. All specimens were re-examined by an experienced pathologist who was unaware of the clinical data.

Toxicity was assessed through clinical examination at baseline and before each drug administration. Laboratory tests, including a complete biochemical routine and blood count, were performed at baseline and at the end of each cycle. Blood cell counts were also repeated on days 7 and 10 of each cycle to catch the presumably worst hematologic side effects. A baseline cardiac assessment included an electrocardiogram and evaluation of left ventricular function with echocardiogram. Electrocardiogram was repeated at the end of treatment. Toxicity was evaluated according to World Health Organization (WHO) criteria.

RESULTS

Pretreatment patient and tumor characteristics were similar in both groups, and are listed in table 1. Overall response rate (PR+cCR+pCR) was 52.9% (27 patients), with 9.8% (5 patients) clinical and 5.8% (3 patients) pathologic complete response. Progressive disease was not observed. The response rate was 48% (12 of 25 patients) in FEC50, and 57.6% (15 of 26 patients) in FEC100 group. Four of five cases with cCR and 2 of 3 cases with pCR were in FEC100 group (Table 2). The clinical and pathological features such as age, clinical nodal status, tumor size, SBR grade, ER and PR status, as well as the relation of menopausal status with response were listed in table 3. The response rate was 86.6% (95% CI, 69.3-100) in ER-negative group and 38.8% (95% CI, 22.8-54.7) in ER-positive group. High response rate was observed in ER negative group.

Chemotherapy was administered as programmed for both groups. Both regimens were well tolerated. Cardiac toxicity and infection were not seen in both groups. Neutropenic toxicity was observed 20% (95% CI, 4.3-35.6) of FEC50 and 61.5% (95% CI, 42.7-80.7) of FEC100 group. Grade 3-4 neutropenia was found to be 4% (95% CI, 0.0-11.6) and 23% (95% CI, 6.8-39.1) in FEC50 and FEC100 groups respectively. Neutropenic toxicity rate was highest in FEC100 group. The frequency of other toxicities are similar both groups and are listed in table 4.

DISCUSSION

In our retrospective analysis, we evaluated the response rates to two different dosages of epirubicin containing FEC regimens in neoadjuvant chemotherapy. The response rates were 48% and 57.6% in FEC50 and FEC100 groups, respectively. The response rates in other studies using different dosages of FEC and EC regimens were reported to vary

Table 1

Pretreatment characteristics of patients and tumors

	FEC50	FEC100
No of patients	25	26
Mean age (years)	49.6±9.5	45.6±11.7
Mean tumor size (mm)	35.0±10.2	32.0±12.1
Clinically positive axillary nodes (%)	72.0 (18/25)	69.2 (18/26)
SBR grade (median)	G II	G II
G1 (%)	16 (4/25)	11.5 (3/26)
G2 (%)	56 (14/25)	50.0 (13/26)
G3 (%)	28 (7/25)	38.4 (10/26)
ER Positivity (%)	76.00 (19/25)	65.38 (17/26)
PR Positivity (%)	52.00 (13/25)	46.15 (12/26)
Hormonal receptor negativity (%)	24.00 (6/25)	30.76 (8/26)
Menopausal status		
Premenopausal (%)	44 (11)	56 (14)
Postmenopausal (%)	65.3 (17)	34.6 (9)

Table 2

The response rate and comparison of two different regimens

	FEC50 % (n)	CI 95% (%)	FEC100 % (n)	CI 95% (%)
Response Rate (RR)	48.00 (12/25)	28.4-67.5	57.69 (15/26)	0.38.6-76.5
Clinical Complete Response (cCR)	4.00 (1/25)	0.0-11.6	15.38 (4/26)	1.4-29.1
Pathologic Complete Response (pCR)	4.00 (1/25)	0.0-11.6	7.69 (2/26)	0.0-17.7
Stable Disease	52.00(13/25)	32.4-71.5	42.30(11/26)	23.3-61.2
Progressive Disease	-		-	

Table 3
Response rates according to patient and tumor characteristics

	FEC50	FEC100
	% (n)	% (n)
Age (year)		
<50	46.1 (6/13)	41.1 (7/17)
≥50	50.0 (6/12)	88.8 (8/9)
Tumor size (mm)		
<30	75.0 (6/8)	46.1 (6/13)
≥30	35.2 (6/17)	69.2 (9/13)
Clinical nodal status		
Positive	44.4 (8/18)	50.0 (9/18)
Negative	57.1 (4/7)	75.0 (6/8)
SBR grade		
I	50.0 (2/4)	0.0 (0/3)
II	64.2 (9/14)	61.5 (8/13)
III	14.2 (1/7)	70.0 (7/10)
ER		
Positive	36.8 (7/19)	41.1 (7/17)
Negative	83.3 (5/6)	88.8 (8/9)
PR		
Positive	46.6 (7/15)	45.4 (5/11)
Negative	50.0 (5/10)	66.6 (10/15)
Menopausal status		
Premenopausal	45.4 (5/11)	41.1 (7/17)
Postmenopausal	50.0 (7/14)	88.8 (8/9)

Table 4

Chemotherapy-related adverse effect

	FEC50 (n=25)		FEC100 (n=26)	
	No	**%**	**No**	**%**
Neutropenia				
Grade 0	20	80.0	10	38.4
Grade 1-2	4	16.0	10	38.4
Grade 3-4	1	4.0	6	23.0
Anemia				
Grade 0	23	92.0	23	88.4
Grade 1-2	2	8.0	3	11.5
Grade 3-4	0	0	0	0
Thrombocytopenia				
Grade 0	22	88.0	22	84.6
Grade 1-2	3	12.0	4	15.3
Grade 3-4	0	0.0	0	0
Nausea/vomiting				
Grade 0	11	44.0	7	26.9
Grade 1-2	11	44.0	14	53.8
Grade 3-4	3	12.0	5	19.2
Stomatitis				
Grade 0	23	92.0	22	86.6
Grade 1-2	2	8.0	4	15.3
Grade 3-4	0	0	0	0
Infection				
Grade 0	25	100	26	100
Grade 1-2	0	0	0	0
Grade 3-4	0	0	0	0
Cardiac				
Grade 0	25	100	26	100
Grade 1-2	0	0	0	0
Grade 3-4	0	0	0	0

Table 5

EC and FEC regimens' response rate in neoadjuvant setting

Author (Ref.)	Year	Patient (n)	Neoadjuvant Chemotherapy	Response (%)
van der Hage (5)	2001	350	4 FEC ([600 mg/m^2], [60 mg/m^2], [600 mg/m^2])	49
Pelissier (9)	2002	84	6 FEC ([500 mg/m^2], [60 mg/m^2], [500 mg/m^2])	36
			6 FEC ([1000 mg/m^2], [100 mg/m^2], [1000 mg/m^2])	38
Petit (10)	2001	39	6 FEC ([500 mg/m^2], [50 mg/m^2], [500 mg/m^2])	61.5
		40	6 FEC ([500 mg/m^2], [100 mg/m^2], [500 mg/m^2])	82.5
Therasse (11)	2003	224	6 CEF([75 mg/m^2/d 1-14], [60 mg/m^2 d 1,8], [500 mg/m^2 d 1,8])	79.9
			6 EC ([120 mg/m^2], [830 mg/m^2])	85.7
Wilt (12)	2002	100	6 FEC ([500 mg/m^2], [100 mg/m^2], [500 mg/m^2])	72

between 36-85% (Table-5) (5, 8-11). In one of the previous studies comparing the two different FEC regimens, Pelissier et al. (8) observed the response rate as 36% in low dose FEC and 38% in high dose FEC, the difference was not statistically significant. In their study comparing FEC50 and FEC100, Petit et al. (9) found the response rates as 61.5% and 82.5%, respectively with a significant difference. Due to the low response rates (%49) in their study, van der Hage et al. (5) emphasized that epirubicin dosages below 300 mg/m² should be considered as suboptimal. However, it's not possible to determine the duration and dosaging of epirubicin to achieve higher response rates in neoadjuvant chemotherapy.

Previous studies on metastatic patients revealed an increase in response rates as the epirubicin dosage is increased. Three trials were conducted by The French Epirubicin Study Group in metastatic breast cancer. Each trial comparing FEC50 versus FEC75, FEC50 versus FEC100, FEC75 versus FEC100 demonstrated a better response in the high epirubicin dosage group (12-14).

High response rate was observed in ER negative group. In the neoadjuvant setting, it has been reported that ER-negative tumors were more likely associated with higher response rates than ER-positive tumors (15). This data could be explained by the the statement that tumors most often have an associated poorly differentiated nuclear grade and nuclear grade is correlated with high cell-cycle proliferative activity (16,17). Thus, high dose epirubicin application to the tumors with these features might increase the response rate but the hypothesis that proliferative activity, negativity of steroid receptors and poor differentiation increases response rate is debatable (18-20).

In this retrospective analysis of our own experience, the response rates observed in FEC50 and FEC100 groups seemed to be similar after 4 cycles of neoadjuvant chemotherapy. Only well-designed, randomized, and prospective clinical trials could contribute to establish the optimum dosage and duration of anthracyclines in neoadjuvant therapy.

References

1. Early Breast Cancer Trialists' Collaborative Group: Polychemotherapy for early breast cancer: An overview of the randomized trials. Lancet 1998;352:930-42.
2. Fisher B, Saffer E, Gunduz N, et al. Serum growth factor following primary tumor removal and the inhibition of its production by preoperative therapy. Prog Clin Biol Res 1990;354A:47-60.
3. Fisher B, Saffer E, Rudock C, et al. Effect of local or systemic treatment prior to primary tumor removal on the production and response to a serum growth stimulating factor in mice. Cancer Res 1989;49:2002-4.
4. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998;16:2672-85.
5. van der Hage JA, van de Velde CJ, Julien JP, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001;19:4224-37.
6. Bonadonna G, Valagussa P, Brambilla C, et al. Primary chemotherapy in operable breast cancer: eight-year experience at the Milan Cancer Institute. J Clin Oncol 1998;16:93-100.
7. Miller AB, Hoogstraten B, Staquet M, et al. Reporting results of cancer treatment. Cancer 1981;47:207-14.
8. Pelissier P, Delaloge S, Mathieu MC, et al. Intensified anthracyclin doses do not improve clinical and pathological responses to neoadjuvant FEC for operable breast cancer: results of a multicenter randomized trial. Proc Am Soc Clin Oncol 2002;21:254 (Abstr).
9. Petit T, Borel C, Ghnassia JP, et al. Chemotherapy response of breast cancer depends on HER-2 status and anthracycline dose intensity in the neoadjuvant setting. Clin Cancer Res 2001;7:1577-81.
10. Therasse P, Mauriac L, Welnicka-Jaskiewicz M, et al. Final results of a randomized phase III trial comparing cyclophosphamide, epirubicin, and fluorouracil with a dose-intensified epirubicin and cyclophosphamide + filgrastim as neoadjuvant treatment in locally advanced breast cancer: an EORTC-NCIC-SAKK multicenter study. J Clin Oncol 2003;21:843-50.
11. Wilt M, Millon R, Velten M, et al. Comparative value of SBR grade, hormonal receptors, KI 67, HER-2 and topoisomerase II alpha (topo II alpha) status as predictive markers in breast cancer patients treated with neoadjuvant anthracycline-based chemotherapy. Proc Am Soc Clin Oncol 2002;21:123 (Abstr).
12. French Epirubicin Study Group: A prospective trial comparing epirubicin monochemotherapy to two fluorouracil, cyclophosphamide and epirubicin regimens differing in epirubicin dose in advanced breast cancer patients. J Clin Oncol 1991;9:305-12.
13. Focan C, Andrien JM, Closon MT, et al. Dose-response relationship of epirubicin based first-line chemotherapy for advanced breast cancer: A prospective randomized trial. J Clin Oncol 1993;11:1253-63.
14. Bastit P, Roche H, Namer M, et al. Final results of a randomized trial comparing three epirubicin based regimens as first line chemotherapy in metastatic breast cancer (MBC) patients (PTS). Proc Am Soc Clin Oncol 1999;18:487 (Abstr).
15. Bonadonna G, Veronesi U, Brambilla C, et al. Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters or more. J Natl Cancer Inst 1990;82:1539-45.
16. Fisher ER, Sass R, Fisher B. Pathologic findings from the national surgical adjuvant breast project. Correlations with concordant and discordant estrogen and progesterone receptors. Cancer 1987;59:1554-9.
17. Dabbs DJ. Ductal carcinoma of breast: nuclear grade as a predictor of S-phase fraction. Hum Pathol 1993;24:652-6.
18. Aas T, Geisler S, Eide GE, et al. Predictive value of tumor cell proliferation in locally advanced breast cancer treated with neoadjuvant chemotherapy. Eur J Cancer 2003;39:438-46.
19. Collecchi P, Baldini E, Giannessi P, et al. Primary chemotherapy in locally advanced breast cancer (LABC): effects on tumor proliferative activity, bcl-2 expression and the relationship between tumor regression and biological markers. Eur J Cancer 1998;34:1701-4.
20. Colleoni M, Orvieto E, Nole F, et al. Prediction of response to primary chemotherapy for operable breast cancer. Eur J Cancer 1999;35:574-9.