Effect of different neoadjuvant chemotherapy regimens on locally advanced breast cancer

U. Coskun[1], N. Gunel[1], E. Onuk[2], E. Yilmaz[2], O. Bayram[2], D. Yamac[1], A. Cihan[3], B. Ucan[3], Y. Yildirim[1], G. Celenkoglu[1], S. Ozkan[4]

Departments of [1]Medical Oncology, e-mail: ugurcos@hotmail.com, [2]Surgery, [4]Public Health, Gazi University Medical School, 06500 Ankara, Turkey, [3]Department of Surgery, Karaelmas University Medical School, Zonguldak, Turkey

Received November 11, 2002

In this retrospective study, we evaluated the results of 91 locally advanced breast cancer (LABC) patients (30 patients in stage IIIA – 33.0%, 61 patients in stage IIIB – 67.0%) who had been treated with different neoadjuvant chemotherapy regimens. Forty-three (47.3%) patients treated with FAC (5-Fluorouracil, doxorubicin, cyclophosphamide) or CA (cyclophosphamide, doxorubicin), 33 (36.3%) with FEC (5-Fluorouracil, epirubicin, cyclophosphamide) or CE (cyclophosphamide, epirubicin) and 15 (16.5%) with CMF (cyclophosphamide, methotrexate, 5-Fluorouracil) combination as neoadjuvant setting. Median follow-up duration was 33 (6–116) months in 91 patients. There was no significant difference in the pretreatment characteristics of patients receiving FAC/CA, FEC/CE and CMF including age, disease stage, menopausal and estrogen/progesteron receptor (ER/PR) status ($p>0.05$). In CMF group, no patient was treated with taxan as adjuvant setting. However, ten patients (30.3%) in FEC/CE group and 21 patients (48.8%) in FAC/CA group were treated with taxans. Overall response rate was lower in CMF group (60.0%), when compared to FEC/CE (81.9%) and FAC/CA (91.0%) groups ($p<0.05$). Median overall survival (OS) and diseases free survival (DFS) were similar in three groups; 28.0 months (range: 14.8–41.1) and 12.0 months (range: 5.3–18.6) in CMF, 45.0 months (range: 16.8–73.1) and 23.0 months (range: 0.0–48.6) in FEC/CE, 46.0 months (range: 41.1–50.8) and 22.0 months (range: 11.1–32.8) months in FAC/CA groups, respectively ($p>0.05$). In conclusion, overall response rates were found to be higher in anthracycline-based combinations than CMF, but these regimens had no additional survival advantage over CMF regimen. Long-term effects of these regimens should be investigated in further randomized trials.

Key words: Breast cancer, neoadjuvant chemotherapy, locally advanced disease.

At the present time, it is accepted that neoadjuvant chemotherapy is the standard approach for locally advanced breast cancer (LABC) patients. Neoadjuvant chemotherapy induces tumor downstaging in a significant proportion of patients and can convert inoperable disease to operable disease. Moreover, micrometastatic disease can be treated before it develops chemoresistant clones [4, 6, 17]. The most benefical chemotherapy regimen or further adjuvant chemotherapy regimen may be selected by the assesment of primary tumor response to neoadjuvant chemotherapy [19]. Administrating of neoadjuvant chemotherapy and adjuvant chemotherapy following surgery was reported to significantly improve overall survival (OS) and disease free survival (DFS) in LABC patients [7, 32]. In addition, response to neoadjuvant chemotherapy has been demonstrated in many studies to be a prognostic indicator of overall survival in LABC patients [29, 33]. There are a lot of different drug regimens and applications in the literature described as neoadjuvant chemotherapy modality. Doxorubucin has been frequently included in such regimens [11, 29, 32, 33].

In this retrospective study, we analysed 91 locally advanced breast cancer patients treated with different types of neoadjuvant chemotherapy regimen and other sequential modalities.

Patients and methods

In this retrospective analysis, we surveyed 91 locally advanced breast cancer patients treated with neoadjuvant che-

Table 1. Neoadjuvant chemotherapy regimens*

Drugs	Dose (mg/m^2)	Days
F 5-Fluorouracil	600	1
E Epirubicin	60–75	1
C Cyclophosphamide	600	1
C Cyclophosphamide	600	1
E Epirubicin	60–75	1
F 5-Fluorouracil	600	1
A Doxorubicin	60	1
C Cyclophosphamide	600	1
C Cyclophosphamide	600	1
A Doxorubicin	60	1
C Cyclophosphamide	600	1 and 8
M Methotrexate	40	1 and 8
F 5-Fluorouracil	600	1 and 8

*Cycles were repeated intravenously every 21 days

motherapy between June 1993 and December 2000 in Gazi University Hospital. The results are evaluated retrospectivelly from computer and file records. All patients had cytologically or histologically confirmed stage IIIA (30 patients – 33.0%) or stage IIIB (61 patients – 67.0%) breast carcinoma. The median age of 91 patients was 47.0 years (range: 27–76). Fifty-two (57.1%) of them were premenopausal and 39 (42.9%) were postmenopausal. Forty-three (47.3%) patients treated with FAC or CA, 33 (36.3%) with FEC or CE and 15 (16.5%) with CMF combination as neoadjuvant setting. Chemotherapy regimens are shown in Table 1. Tumor response was evaluated after three or four cycles of chemotherapy. Response and toxicity were judged by standard WHO criteria [24]. Responders were defined as complete response (CR, disappearance of assesible disease) or partial response (PR, reduction of more than 50% of the lesion of the two largest tumor diameter). Stable disease (SD) meant less than 25% increase in tumor size. Progressive disease (PD) was defined by an increase of more than 25% in tumor size. Chemotherapy modality was changed in patients with progressive or stable disease. Eighty-three patients (91.2%) underwent surgery and 75 (90.3%) of them were treated with modified radical mastectomy and 8 (9.7%) of them were treated with conservative surgery. After surgery, all patients received both adjuvant chemotherapy and radiotherapy (Tab. 2). Patients with positive ER/PR status and some with unknown ER/PR status were also treated with adjuvant hormonal therapy (54.2%). Thirty-one patients (37.3%) received taxans as adjuvant treatment. Others received CMF or anthracycline based combination as adjuvant treatment (Tab. 2).

Statistical methods. Chi-Square, Fisher's exact test and Kruskal Wallis test were used in statistical analysis. Overall survival was calculated from the date of diagnosis and disease-free survival was calculated from the date of surgery using the method of Kaplan and Meier [20]. The log-rank statistics was used for univariate comparisons of survival end points [23]. p values <0.05 were considered as significant. Statistical procedures were performed by using SPSS for windows version 9.0 software program.

Table 2. Characteristics of patients receiving different neoadjuvant chemotherapy regimens

Characteristics	CMF	FEC/CE	FAC/CA
n	15	33	43
Age	46.0(28–76)	48.0(28–73)	47.0(27–70)
Menopausal status			
Pre-	7(46.7%)	18(54.5%)	27(62.8%)
Post-	8(53.3%)	15(45.5%)	16(37.2%)
ER/PR receptor status			
+	4(26.7%)	15(45.5%)	15(34.9%)
–	1(6.7%)	3(9.1%)	12(27.9%)
?	10(66.6%)	15(45.5%)	16(37.2%)
Stage at presentation			
IIIA	2(13.3%)	13(39.4%)	15(34.9%)
IIIB	13(86.7%)	20(60.6%)	28(65.1%)
Adjuvant chemotherapy			
CMF	8(53.3%)	6(18.2%)	2(4.7%)
FEC/CE	1(6.7%)	12(36.3%)	0(0%)
FAC/CA	3(20.0%)	2(6.1%)	18(41.8%)
Taxans	0(0%)	10(30.4%)	21(48.8%)
No adjuvant chemotherapy	3(20.0%)	3(9.0%)	2(4.7%)
Adjuvant radiotherapy			
Yes	13(86.7%)	32(97.0%)	38(88.4%)
No	2(13.3%)	1(3.0%)	5(11.6%)
Clinical response to neoadjuvant chemotherapy			
Complete response (CR)	0(0%)	2(6.1%)	3(7.0%)
Partial response (PR)	9(60.0%)	25(75.8%)	37(86.0%)
Stable disease (SD)	0(0%)	3(9.1%)	1(2.3%)
Progressive disease (PD)	6(40%)	3(9.1%)	2(4.7%)
Overall response (CR+PR)	9(60.0%)	27(81.9%)	40(93.0%)
Adjuvant tamoxifen			
Yes	6(40.0%)	19(57.6%)	20(46.5%)
No	6(40.0%)	11(33.3%)	21(48.8%)
Pathological stage after surgery			
Pathological complete response	2(13.3%)	1(3.0%)	5(11.6%)
Stage-I	1(6.7%)	2(6.1%)	4(9.3%)
Stage -IIA	1(6.7%)	5(15.2%)	5(11.6%)
Stage -IIB	6(40.0%)	17(51.5%)	19(44.2%)
Stage -IIIA	2(13.3%)	4(12.1%)	5(11.6%)
Stage -IIIB	0(0%)	1(3.0%)	3(7.0%)
No surgery	3(20.0%)	3(9.1%)	2(4.7%)
Axillary status after surgery			
Positive axillary lymph node	8(66.7%)	19(63.3%)	26(63.3%)
Negative axillary lymph node	4(33.3%)	11(36.7%)	15(36.7%)

Results

Table 2 shows patients' characteristics of different neoadjuvant treatment groups. There was no significant differ-

ence between three groups (FAC/CA, FEC/CE, CMF) according to age, disease stage at presentation, ER/PR status and menopausal status (p>0.05). In CMF group no patient was treated with taxan as adjuvant setting. However, ten patients (30.3%) in FEC/CE group and 21 patients (48.8%) in FAC/CA group were treated with taxans as adjuvant setting. The median follow-up duration of 91 patients was 33 months (range: 6–116 months). The median follow-up were 28.0 months (range: 12–116 months) in CMF group, 30.0 months (range: 6–77 months) in FEC/CE and 36.0 months (range: 13–76 months) in FAC/CA groups (p>0.05). Clinical overall response (CR+PR) was observed in 76 out of 91 patients (83.5%). Five of them (5.5%) attained CR and 71 of them attained PR (78.0%). Overall response rate was lower in CMF group (60%), when compared to FEC/CE (81.8%) and FAC/CA group (93.0%) (p<0.05). However, there was no significant difference in overall response rate between FEC/CA and FAC/CA groups (p>005). Three patients (7.0%) in FAC/CA group, 2 patients (6.1%) in FEC/CE group had clinical CR. No patient attained clinical CR in CMF group (0%). Clinical response rates are shown in Table 2.

Pathological examination of breast and axillary lymph nodes revealed no residual tumor in 8 patients (9.6%). Five patients (11.6%) in FAC/CA group, 1 patient (3.0%) in FEC/CE group and 2 patient (13.3%) in CMF group had pathological CR (p>0.05). At the time of analysis, 48 patients (52.7%) died with progressive disease. Twenty-one patients (48.8%) in FAC/CA group, 16 patients (48.5%) in FEC/CE group and 11 patients (73.3%) in CMF group died (p>0.05).

Median overall survival (OS) and median disease free survival (DFS) were 45 months (range: 38.8–51.1 months) and 22.0 months (range: 14.2–29.7 months) in 91 patients, respectively. Figure 1 and Figure 2 show the curves of OS and DFS in 91 patients. Median OS and DFS were 77.5 months (range: 61.2–93.8 months) and 68.9 months (range: 52.9–84.8 months) in stage IIIA and 33 months (range: 21.2–44.7 months) and 15 months (range: 8.9–21.0 months) in stage IIIB patients, respectively (p<0.001). Figure 3 and Figure 4 show the curves of OS and DFS according to disease stage. Median OS and DFS were 28.0 months (range: 14.8–41.1 months) and 12 months (range: 5.3–18.6 months) in CMF, 45 months (range: 16.8–73.1 months) and 23.0 months (range: 0.0–48.6 months) in FEC/CE, 46.0 months (range: 41.1–50.8 months) and 22.0 months (range: 11.1–32.8 months) in FAC/CA groups, respectively (p>0.05). Figure 5 and 6 show the curves of OS and DFS according to neoadjuvant chemotherapy types.

Median OS and DFS were 28.0 months (range: 14.8–41.6 months) and 12.0 months (range: 5.3–18.6 months) in CMF group and 45.0 months (range: 38.7–51.2 months) and 23.0 months (range: 11.4–34.5 months) in patients treated with anthracycline-based chemotherapy (FEC/CE+FAC/CA),

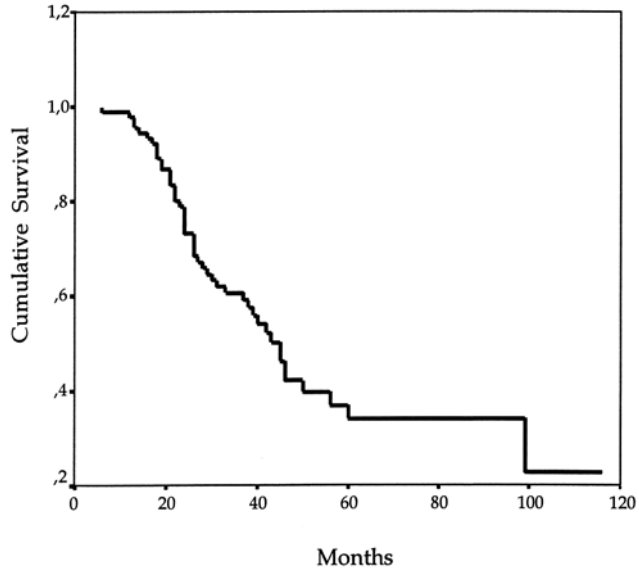

Figure 1. Overall survival in 95 patients.

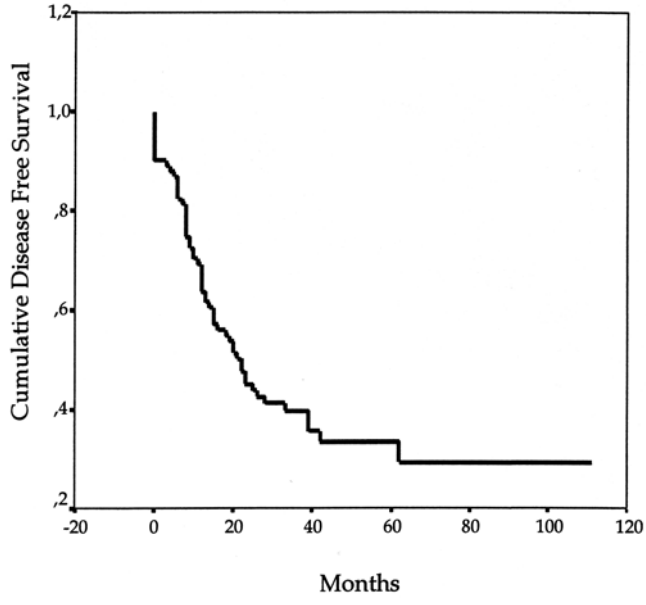

Figure 2. Disease-free survival in 95 patients.

respectively. However, the differences were not statistically significant (p>0.05).

Median OS and DFS were found to be higher in patients who had a clinical response (OS: 46.0 months (range: 35.0–56.9 months), DFS: 26.0 months (range: 13.9–38.0 month)) when compared to patients who had no clinical response (OS: 19.0 months (range: 17.1–20.8 months), DFS: 16.8 months (range: 0–35.5 months)), p<0.001).

Median OS and DFS were found to be higher in axillary lymph node negative patients (OS: 105.9 months (range: 95.2–116.8 months), DFS: 93.8 months (range: 80.1–107.5

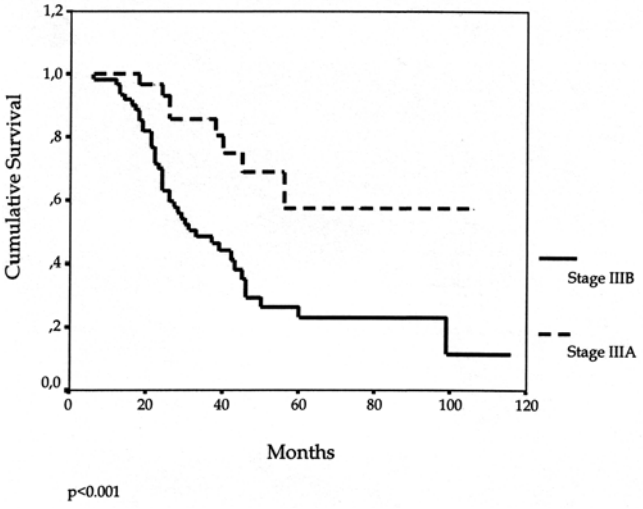

Figure 3. Overall survival according to disease stage.

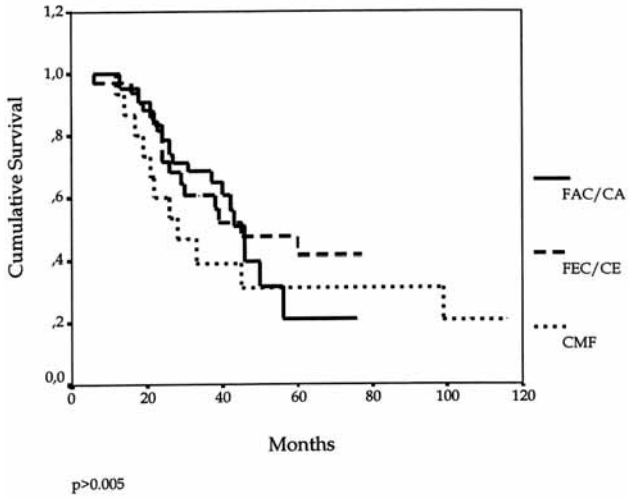

Figure 5. Overall survival according to neoadjuvant chemotherapy.

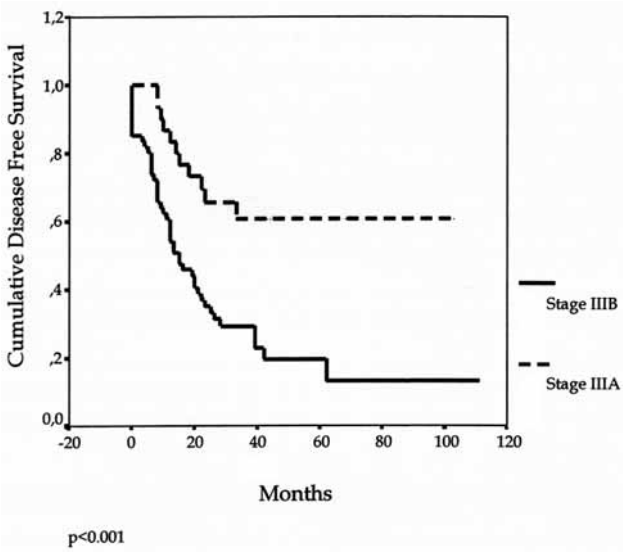

Figure 4. Disease-free survival according to disease stage.

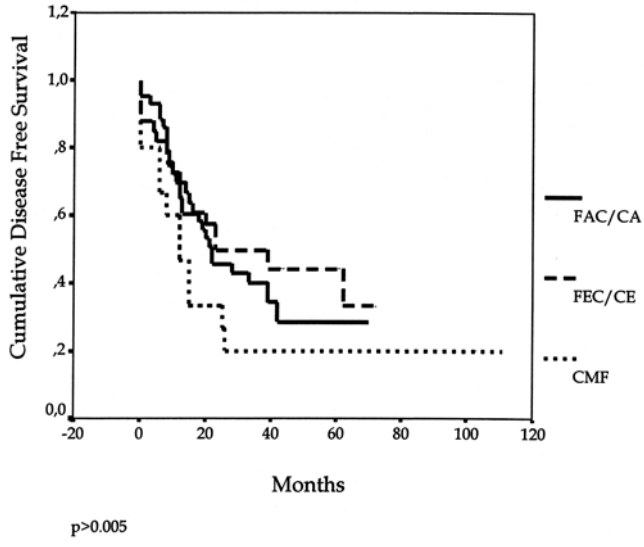

Figure 6. Disease-free survival according to neoadjuvant chemotherapy.

months)), when compared to the axillary lymph node positive patients (OS: 38.0 months (range: 26.0–49.9 months), DFS: 15.0 months (range: 8.9–21.0 months)), p<0.001).

In the group of the patients treated with anthracycline-based neoadjuvant chemotherapy, OS and DFS were not different from the patients treated with taxans (OS: 42.0 months (range: 24.9–59.0 months), DFS: 28.0 months (range: 8.1–47.9 months)) and without taxans (OS: 46.0 months (range: 24.4–67.5 months), DFS: 10.8 months (range: 17.7–60.2)), p>0.05 as adjuvant setting.

Toxicity profile of neoadjuvant chemotherapy regimens is shown in Table 3. Grade 1–2 nausea and vomiting were observed in 72.0% of FAC/CA, in 63.6% of FEC/CE and in 33.3% of CMF treatment (p>0.05). Grade 1–2 alopecia occured in 69.7% of FAC/CA, in 63.6% of FEC/CE and in 20.0% of CMF treatment (p>0.05). Grade 3 leukopenia was observed in 11.6% of FAC/CA and in 6.0% of FEC/CE groups. However, non of them was febrile and required hospitalization. No patient had grade 3 leukopenia in CMF group. Two patients in FAC/CA and one patient in FEC/CE group had grade 1–2 cardiac toxicity (decreasing in left ventricular ejection fraction without clinical signs).

Discussion

Neoadjuvant chemotherapy has been increasingly used in LABC treatment before local therapy. However, there are still many arguments regarding this treatment modality [12, 29]. Neoadjuvant chemotherapy reduces tumor volume

preopereatively and makes surgery possible for inoperable disease after chemotherapy. Moreover, this therapy may eliminate early systemic micrometastases, avoid rapid growth of metastases after local treatment and prevent emergence of resistant clones [25]. Anthracycline-based combinations seem to be most favorable treatment choice in LABC patients as neoadjuvant setting. Such as FAC and its homologue with epirubicin, FEC have been widely used, resulting in 60% to 90% overall response rates for LABC patients [2, 11, 18, 31]. Another conventional combination, CMF, shows similar overall response rates compared with anthracycline-based combinations [15, 21].

Although our study was not a randomised trial, there was no significant difference in the pretreatment characteristics including age, disease stage at presentation, menopausal and ER/PR status among patients receiving FAC/CA, FEC/CE and CMF as neoadjuvant setting (Tab. 2). In our study, overall response rate was found to be lower in patients treated with CMF (60%) than in patients treated with anthracycline-based chemotherapy ($p<0.05$). Overall response rates were similar in FEC/CE (81.8%) and FAC/CA (93.0%) groups. These results are comparable with most of the reported series in the literature [2, 11, 15, 18, 21 31]. Anthracycline-based regimens seem to be superior than CMF regimen in terms of overall response rate.

An important advantage of neoadjuvant chemotherapy is to test in vivo tumor response in order to modify treatment or introduce new drugs for adjuvant modality For example, patient who does not have a sufficient response to anthracycline-based neoadjuvant chemotherapy, may be selected for taxan based regimen or novel systemic therapy to increase survival rates in adjuvant setting.

It has been shown that patients who achieve CR or PR have a better outcome than patients who have stable or progressive disease [26]. Similar to these findings, in our study, patients who had a clinical response (CR+PR) showed higher OS and DFS than patients who had no clinical response.

Some experimental and clinical data suggest that neoadjuvant chemotherapy may have survival benefits for LABC patients [27]. However, large randomized clinical trials have not yet confirmed the advantage of neoadjuvant chemotherapy over adjuvant chemotherapy as far as overall survival [14, 28]. Because of the different application of sequential modalities after neoadjuvant chemotherapy, variety of chemotherapy regimens in adjuvant setting and heterogeneity of patient population, determining the real effect of neoadjuvant chemotherapy on survival and comparing one regimen with each other in terms of prolongation of survival becomes difficult. Achievement of a complete pathological response to neoadjuvant chemotherapy has been shown to be an excellent indicator of OS and DFS [13]. However, pathologic CR exists in less than 20% of patients [13, 22]. Therefore, most of the investigators has already focused on increasing pathologic complete remission rate of LABC patients rather than investigating long-term survival effect of this regimens. New drugs such as taxans are currently under investigation as neoadjuvant setting to improve pathologic CR [10, 30].

In our study, pathologic CR rate was observed in 8 out of 91 patients (9.6%). Five patients (11.6%) in FAC/CA, 1 patients (3.0%) in FEC/CE and 2 patient (13.3%) in CMF group showed pathological CR. Our results were not different compared with other series reported in the literature [8, 9, 16]. Unfortunatelly, because a very small number of our patients had pathological CR, it was not possible to make survival analyses for these patients. As reported in our study, clinical CR rate of neoadjuvant chemotherapy does not usually reflect the pathological examination of patients after surgery. In the present study, while clinical CR was observed in 5.5% of 91 patients, pathological CR was observed in 9.6% of patients. This finding is similar to most of reports in the literature [1, 8, 9, 16]. For example, ANDERSON et al [1] showed clinical complete response in 27% of patients but in 17% with pathological examination.

The secondary aim of our analysis was to evaluate long term outcome of patients treated with different types of neoadjuvant chemotherapy. Although there is no agreement in a standard treatment for LABC patients, neoadjuvant chemotherapy followed by surgery and radiation therapy as well as adjuvant chemotherapy and/or endocrine therapy have been recommended in several clinical reviews [3, 5, 7]. In our centre, neoadjuvant chemotherapy, radical mastectomy, adjuvant radiotherapy and adjuvant chemohormone therapy has been standard modality for LABC patients approximatelly for 8 years. In our study, small percentage of patients underwent conservative surgery (8.6%), others were treated with modified radical mastectomy (Tab. 2). In the present study, most of the patients' characteristics were similar in patients receiving FEC/CE, FAC/CA and CMF regimen (Tab. 2). No patient was treated with taxans in CMF group, 21 patients (48.8%) in FAC/CA group and 10 patients (30.3%) in FEC/CE group were treated with taxans as adjuvant setting (Tab. 2). Patients who were treated with taxan as adjuvant setting were selected according to prognostic criterion after surgery. In our centre, when CMF regimen was administered to patients, taxans were not available, therefore no patient in this group could receive taxans as adjuvant setting. However, as depicted in Figure 5 and 6, there was no difference in OS and DFS among patients treated with FEC/CE, FAC/CA and CMF. Although patients receiving anthracycline-based neoadjuvant chemotherapy and taxans as adjuvant setting showed higher overall response rate, there was no statistically significant survival advantage of these regimens over CMF. This may be related with complex treatment modality of the patients. For example, most of the patients who had no clinical response to CMF regimen as neoadjuvant setting eventually

Table 3. Toxicity of neoadjuvant chemotherapy regimens

Toxicity	Neoadjuvant chemotherapy					
	FAC/CA (%)		FEC/CE (%)		CMF (%)	
Grade	1–2	3–4	1–2	3–4	1–2	3–4
Anemia	3(6.9)	0(0)	2(6.0)	0(0)	1(6.6)	0(0)
Leucopenia	21(48.8)	5(11.6)	14(42.4)	2(6.0)	2(13.3)	0(0)
Thrombocytopenia	1(2.3)	0(0)	1(3.0)	0(0)	0(0)	0(0)
Nausea-vomiting	31(72.0)	8(18.6)	21(63.6)	5(15.1)	5(33.3)	2(13.3)
Constipation	3(6.9)	0(0)	2(8)	0(0)	0(0)	0(0)
Mucositis	4(9.3)	0(0)	3(9.0)	0(0)	3(20.0)	0(0)
Alopecia	30(69.7)	8(18.6)	21(63.6)	5(15.1)	3(20.0)	1(6.6)
Hepatotoxicity	2(4.6)	0(0)	1(3.0)	0(0)	1(6.6)	1(6.6)
Cardiac	2(4.6)	0(0)	1(3.0)	0(0)	0(0)	0(0)

p>0.05

received anthracycline-based regimens both in neoadjuvant and adjuvant setting and underwent surgery.

As expected, median OS and DFS were higher in stage IIIA patients, when compared with stage IIIB patients ($p<0.001$) (Fig. 3 and 4). Median OS and DFS were also higher in patients who had a CR or PR, when compared with patients who had no response (SD or PD) after neoadjuvant chemotherapy ($p<0.001$). When we divided the patients receiving anthracycline-based neoadjuvant chemotherapy into two groups – treated with and without adjuvant taxans – we did not observe any significant difference according to OS and DFS ($p>0.05$). After neoadjuvant chemotherapy regimens, patients who had negative axillary lymph node showed higher OS and DFS, when compared to patients who had positive axillary lymph node. Status of axillary lymph nodes seems to be the most important predictor factor for survival with neoadjuvant chemotherapy.

There was no major toxicity resulting in treatment-related death. Hematological toxicity, nausea, vomiting and constipation were equal in three groups. Alopecia and cardiac toxicity in FAC/CA, FEC/CE groups and mucositis in CMF group were slightly higher. However, these were not statistically significant (Tab. 3).

In conclusion, anthracycline-based regimens seem to be more effective as neoadjuvant setting in terms of clinical response. However, no additional survival advantage was obseved in anthracycline-based regimens than in CMF. As expected, disease stage and clinical response to neoadjuvant chemotherapy regimens are correlated with prolonged OS and DFS. Axillary lymph node status at pathological examination after surgery remains a major prognostic factor for neoadjuvant chemotherapy regimens. At the present time, new studies have already focused to increase pathological complete reponse and to decrease axillary lymph node involvement with different combination regimens especially these including taxans. In order to clarify whether neoadjuvant regimens have an additional effect on prolongation of survival and which regimen has better effect on survival beyond well known positive effect of these regimens on survival, further well designed studies are needed.

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