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Original study

Factors affecting the disease-free and overall survival following neoadjuvant chemotherapy in patients with local advanced breast cancer

Lokal ileri meme kanserli hastalarda neoadjuvan kemoterapi sonrası hastalıksız ve genel sağkalımı etkileyen faktörler

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ABSTRACT

Locally-advanced breast cancer (LABC) is termed as locally expanding tumor in breast not metastatic to distant organs. LABC therapy is a 'multimodal therapy' including systemic (chemotherapy) and local - regional (surgery and radiotherapy) therapy.

Before and after treatment results of post-therapy followed - up 96 patients who clinically diagnosed with stage III breast cancer and were applied neoadjuvant chemotherapy in 9 years (September 2005 - January 2013) in Izmir Katip Celebi University Atatürk Training and Research Hospital were analyzed retrospectively.

The median patient age at diagnosis was detected 49 years (25 - 86), 22.9% (n = 22) under 40 years of age, 77.1% (n = 74) were over the age of 40 at diagnosis. For diagnosed patients, histological type of tumor was invasive ductal carcinoma in 85.4% (n = 82), invasive lobular carcinoma in 5.2% (n = 5), mixed type (+ invasive ductal invasive lobular) carcinoma in 4.2% (n = 4). In the other 5 patients showed a rare histological type of tumor morphology.

For breast cancer patients presenting with locally advanced tumors, NACT should be a standard treatment. Although overall survival of patients are the same, NACT provides apparent advantage on disease-free survival.

Keywords: Breast cancer, neoadjuvant chemotherapy, disease-free, survival.

ÖZET

Lokal ileri meme kanseri (LİMK) uzak organlara metastaz yapmamış, memede lokal olarak büyümüş tümör olarak tanımlanmaktadır. Lokal ileri meme kanseri tedavisi, sistemik (kemoterapi) ve lokal-bölgesel (cerrahi ve radyoterapi) tedaviyi içeren bir 'multimodal tedavidir'.

İzmir Katip Çelebi Üniversitesi Atatürk Eğitim ve Araştırma Hastanesi'nde, 9 yıl içinde (Eylül 2005-Ocak 2013) evre III meme kanseri tanısı alan ve neoadjuvan kemoterapi (NAKT) uygulanan, tedavi sonrası izlemdeki 96 hastanın tedavi öncesi ve sonrası sonuçları retrospektif olarak incelendi.

Tanı anındaki ortanca hasta yaşı 49 (25-86) idi, ve hastaların % 22.9'u (n = 22) tanı anında 40 yaşın altında, % 77.1'i (n = 74) 40 yaşın üzerindeydi. Tümörün histolojik tipi, tanılan hastaların % 85.4'ünde (n = 82) invaziv duktal karsinom, % 5.2'sinde (n = 5) invaziv lobüler karsinom, % 4.2'sinde (n = 4) mikst tip (invaziv duktal+invaziv lobüler) karsinom idi. Kalan beş hastada nadir görülen bir histolojik tipte tümör morfolojisi saptandı.

Lokal ileri tümörle başvuran meme kanseri tanılı hastalarda, NAKT standart tedavi olmalıdır. Hastaların genel sağkalımı benzer olmasına rağmen, NAKT hastalıksız sağkalım üzerinde belirgin avantaj sağlar.

Anahtar kelimeler: Hastalıksız sağkalım, meme kanseri, neoadjuvan kemoterapi.

INTRODUCTION

Locally advanced breast tumors, which have not yet spread to another region other than the regional lymph nodes and breasts or exhibited distant metastasis, are called local advanced breast cancers (LABC). While LABC has an incidence of 5 - 15% in countries where LABC screening methods are commonly used, the rate reaches up to 50% in places where screening methods are not available and the level of relevant awareness and education is low (1). Based on data from the Breast Diseases Association Federation (BDAF), the rate in our country is around 20% (2). The LABC treatment is "multimodal treatment" consisting of systemic (chemotherapy) and locoregional treatment (surgery and radiotherapy). Neoadjuvant chemotherapy (NACT) has become the standard treatment is LABC. Studies show that there is no survival difference between definitive or neoadjuvant administration of chemotherapy in patients diagnosed with LABC (3, 4). NACT has various advantages including determination of the tumor's sensitivity to chemotherapy, prevention of ineffective treatment and micrometastasis, ensuring tumor reduction, thereby allowing breast conservative surgery (BCS) in certain cases (5, 6). However it also bears certain disadvantages such as development of resistance to medication, impairment in correlation between the prognosis and pathology, change in the biological properties of the primary tumor, delayed local treatment (3 - 7%).

The evaluation of the response to NACT includes both clinical (ycTNM) and pathological (ypTNM) assessments. The clinical and pathological complete responses are prognostic markers of survival. WHO (World Health Organization- International Union Against Cancer- WHO- UICC) and RECIST (Response Evaluation Criteria in Solid Tumors) criteria are used to assess the clinical response (7). Pathological complete response is the histopathological absence of residual focus detected in the breast or axillary lymph node. Pathological assessment of response to chemotherapy was found to be superior to the clinical assessment of response.

MATERIAL AND METHOD

Pre- and post-treatment results of 96 patients, who were diagnosed with clinical stage III breast cancer at Izmir Katip Celebi University Ataturk Training and Research Hospital General Surgery Clinic betwen 2005 September– 2013 January and received NACT and who could be followed up, were retrospectively investigated. Patients were informed on the trial, advanced pathological investigations, and data to be obtained from the file. Consent from the Ethical Committee of Izmir Katip Celebi University Ataturk Training and Research Hospital (number: 30.2.İKÇ.0.05.06.00 / 123, Date: 31.05.2013).

Patients

Patients, who were histologically documented to have breast cancer with biopsy material and disease stage varying between stage IIIA, Stage IIIB and IIIC, were included in the trial. Early stage and metastatic breast cancer patients were excluded from the study. A retrospective assessment of the patient files was conducted to detect the age, menopausal status, site of metastasis, status of hormone receptor, the clinical and pathological status, whether surgery was administered, the tumor diameters of patients who received surgery and the duration of survival as of 1st January 2013.

Investigations

The disease stage at the time of diagnosis was detected by clinical examination, ultrasonography, computed tomography and bone scintigraphy. Routine, required blood biochemistry and hemogram procedures were administered prior to each chemotherapy cycle.

The assessments of the hematological, hepatic and renal toxicities emerging during chemotherapy were performed based on these results.

Pathological investigations

ER (estrogen receptor), PR (progesterone receptor), KI - 67 proliferation indices were assessed in tumor biopsies obtained at the time of diagnosis. ER, PR and KI - 67 proliferation indices were investigated in patients, who were detected to have residual tumor via surgery performed following dose-dense treatment.

Statistical analysis

The results were assessed using "Statistical Package for Social Science (SPSS) 16.0" software. In conducting the analyses, those with normal distribution among the continuous numeric values were expressed as mean ± standard values (SD) while those with abnormal distribution were expressed as median, minimum-maximum values. Nominal values were expressed as a rate (%). T-test and Mann-Whitney U - test was used for comparison of the numeric values in independent samples while Chi - square test was used for comparing nominal data. Comparisons in dependent groups were made with paired sample t-test or Wilcoxon test depending on whether the data were distributed normally. Correlation analyses were conducted with the Spearman correlation test. $P < 0.05$ was considered significant for intergroup comparisons.

RESULTS

While the median age of diagnosis was detected to be 49 years (25-86), 22.9% of the patients (n=22) were below the age of 40, 77.1% were above 40 years (n=74). 51 patients were menopausal and 45 patients were pre-menopausal at the time of diagnosis. Pre-NACT clinical and post-NACT pathological tumor node metastasis (TNM) classification is presented in Table 1.

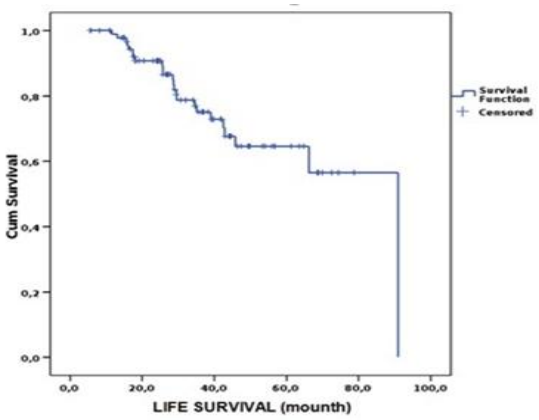
Table 1: Pre-NACT stage and clinical distribution and post-NAC pathological sage of patients

		n	%
Stage	Stage IIIA	19	20.0
	Stage IIIB	71	74.7
	Stage IIIC	5	5.3
Clinical N (Nod)	N0	18	18.9
	N1	31	32.6
	N2a	42	44.2
	N2b	4	4.2
Clinical T (Tumor)	T1	3	3.2
	T2	9	9.5
	T3	9	9.5
	T4a	24	25.3
	T4b	25	26.3
	T4c	4	4.2
	T4d	21	22.1
Pathological T	T1	13	14.0
	T2	25	26.9
	T3	23	24.7
	As microscopic foci	21	22.6
	No residual tumor	11	11.8

Since a patient's preoperative mammography (MMG) was not available, the patient was not included in stage classification. The tumor focus, detected by imaging methods during diagnosis was multicentric in 43% (n=41) and exhibited as a single mass in 57% of the patients (n=55). The median follow-up was 27.7±18.9 months (5.7-90.9 months). 85.4% (n=82), 5.2% (n=5), 4.2% (n=4) of the diagnosed patients had histologic type invasive ductal carcinoma, invasive lobular carcinoma and mixed type (invasive ductal + invasive lobular) carcinoma, respectively. The other five patients were detected to have tumor of rare histologic type morphology. 28 patients had (31.5%) positive lymphovascular invasion (LVI). Among 83 patients, in whom the tumor histological grade (HG) was investigated, 3 patients were consistent with HG I, 58 patients were consistent with HG II and 22 patients with HG III. Immunohistochemically, 40.4% of the patients were strongly ER positive, 16% were weak to moderately positive and 43.6% were negative. 31.2% patients were strongly PR positive, 22% were weak to moderately positive and 46.2% were negative. In 29.0% (n=27), 12.9% (n=12), 12.9% (n=12) and 45.2% (n=42) of the patients, cerbB2 was 3+, 2+, 1+ and cerB2 negative, respectively. 18.9% of the patients, who underwent axillary dissection (n=18), no axillary lymphadenopathy (LAP) was detected (Table 2). 66% of the patients received TEC protocol (Taxanes, Adriamycin, Cyclophosphamide) while 26% were administered FEC (5-fluorouracyl, adriamycin, cyclophosphamide) protocol. A large portion of the patients were not administered neoadjuvant trastuzumab due to the fact that they were followed up during an out-of-indication period although 32 patients in total were HeR2 (human epidermal growth factor receptor 2).

Only 3 of the HER2 positive patients diagnosed within the last one year could receive neoadjuvant trastuzumab. A majority of the patients (n=52) were detected to receive preoperative 6-8 courses of chemotherapy while 45.83% (n=44) of the patients received 3 to 5 courses of CT. 51 patients were administered CT following operation. 25.7% of the patients (n=26) were administered postoperative trastuzumab (Table 3). 93.7% (n=89) of the patients underwent MRM (modified radical mastectomy) or simple mastectomy while 6.3% underwent (n=6) breast conservative surgery (BCS). One patient refused to have surgery. 88.5% of the patients received radiotherapy (RT) and 62.4% received hormone therapy (HT).

The Kaplan-Meier analysis revealed an overall 9-year survival rate of 75% for 96 cases included in the trial (Graphic 1).



Graphic 1: General survival.

The sing-variate analysis detected that only the presence of recurrence (P=0.001) was an independent risk factor with an unfavorable effect on overall survival (Log Rank Chi-Square: 27,071 P<0.05). While the overall survival was prolonged in patients with pathological complete response both in the axilla and breasts, the prolongation was not statistically significant (P >0.05) (Table 4).

Table 2: Patient and tumor properties.					
		n	**%**	**Median**	**Range**
Exitus		24	25.0		
Age				49	25-86
	≤40	22	22.9		
	>40	74	77.1		
Menopause status	Premenopausal	45	46.9		
	Menopause	51	53.1		
Histologic type	IDC (invasive ductal carcinoma)	82	85.4		
	ILC (invasive lobular carcinoma)	5	5.2		
	Invasive micropapillary carcinoma	1	1.0		
	Mixed (IDC+ILC)	4	4.2		
	Other	4	4.2		
Vascular invasion	yes	28	31.5		
	Yok	61	68.5		
Histologic grade	Grade I	3	3.6		
	Grade II	58	69.9		
	Grade III	22	26.5		
Estrogen receptor	Negative	41	43.6		
	weakly positive	15	16.0		
	strongly positive	38	40.4		
Progesterone receptor	Negative	43	46.2		
	Weakly positive	21	22.6		
	Strongly positive	29	31.2		
C-erbB2 intensity	Negative	42	45.2		
	1+	12	12.9		
	2+	12	12.9		
	3+	27	29.0		
Pre-CT TM size	<2 cm	5	5.7		
	2-5 cm	29	33.0		
	≥5 cm	54	61.4		
Post-CT tumor size	<= 2 cm	45	48.4		
	>2 cm	48	51.6		
Post-CT axillar positivity (clinical N)	Negative	18	18.9		
	Positive	77	81.1		
Recurrence	No	58	60.4		
	Yes	38	39.6		
First site of recurrence	Local recurrence	5	13.2		
	Contralateral breast	1	2.6		
	Local recurrence +Contralateral breast	2	5.3		
	Distant organ metastasis	23	60.5		
	Distant metastasis+ local recurrence	5	13.2		
	Contralateral breast+ distant metastasis	2	5.3		
Surgical treatment	BCS	6	6.3		
	MRM	89	93.7		

Table 3: Distribution of the NACT protocols and the clinical response rates.

NACT Protocol	n	%	Complete response	Partial response	Stable Response	Progression
FEC*	25	26	1	15	7	2
TEC**	63	66	14	40	8	1
ET	2	2	0	2	0	0
4 courses of FEC + 4 courses of Docetaxel	1	1	0	1	0	0
TC	1	1	0	1	0	0
4 AC* + 4 P**	1	1	0	0	1	0
4 courses of AC + 4 courses of TH**	2	2	0	1	0	0
3 courses of TEC + 3 courses of TC + H	1	1	0	2	0	0
Total	96	100	15	62	16	3
Percentage			15.6	64.6	16.7	3.1

*FEC: 5-fluorourasil. Adriamycin. cyclophosphamide
**TEC: Taxanes. Adriamycin. cyclophosphamide
*** AC: Adriamycin. cyclophosphamide
****TH: Taxanes. Herceptin

Table 4: Prognostic factors effective on overall and disease-free survival.

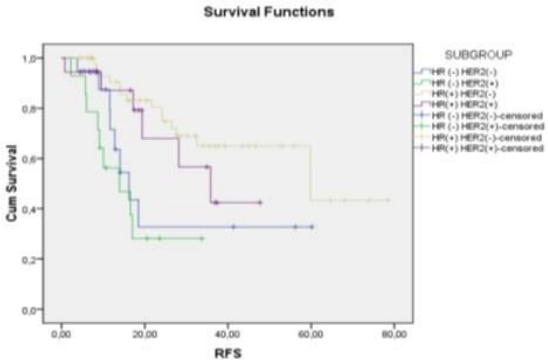
	Overall survival (%)	*P value	**P value	Disease free survival %	*P value	**P value
Age		0.634	0.581		0.694	0.169
≤40	81.8			72.7		
>40	73.0			67.6		
Pre-CT tumor stage		0.515	0.614		**0.033 ** **	0.971
T0-2	100.0			100.0		
T2-4	79.3			63.9		
Post-CT tumor size		0.239	0.613		0.150	0.566
<= 2 cm	82.2			80.0		
>2 cm	66.7			58.3		
Pre-CT axillary involvement		0.906	0.716		0.461	0.953
Negative	66.7			55.6		
Positive	76.6			71.4		
Pathologic T		0.074	0.957		0.347	0.568
T1	76.9			76.9		
T2	84.0			64.0		
T3	47.8			52.2		
As microscopic foci	81.0			76.2		
No residual tumor	90.9			90.9		
Histologic type		0.089	0.337		0.296	0.989
IDC (invasive ductal carcinoma)	79.3			70.7		
ILC (invasive lobular carcinoma)	60.0			60.0		
Invasive micropapillar carcinoma	100.0			100.0		
Mixed (IDC+ILC)	0.0			25.0		
other	75.0			75.0		

Histologic Grade		0.237	0.826			
Grade I	100.0					
Grade II	81.0					
Grade III	68.2					
Vascular invasion		0.255	0.613		0.394	0.775
no	78.7			64.3		
yes	60.7			73.8		
Estrogen Receptor (ER)		0.100	0.687		0.325	0.104
Negative	63.4			63.4		
Weakly positive	73.3			60.0		
Strongly positive	86.8			76.3		
Progesterone Receptor (PR)		0.179	0.748		0.198	0.753
Negative	72.1			62.8		
Weakly positive	90.5			81.0		
strongly positive	69.0			69.0		
Tecurrence*		**0.001 ****	-			
No	98.3					
Yes	39.5					
First site of recurrence		0.386	0.093			
Local recurrence	80.0					
Contralateral breast	0.0					
Local recurrence +contralateral breast	0.0					
Distant Organ Metastasis	36.7					

38 patients developed (39.6%) local/regional recurrence and distant organ metastasis. The most common site of distant metastasis was the brain (60%, n=15) followed by the lungs (52%, n=13), the bones (48%, n=12), the liver (32% and n=8) and pleura (32%, n=8). 47.4% (n=8) had multi-organ involvement. The Kaplan-Meier survival analysis revealed a diseasefree survival rate of 68.8%.

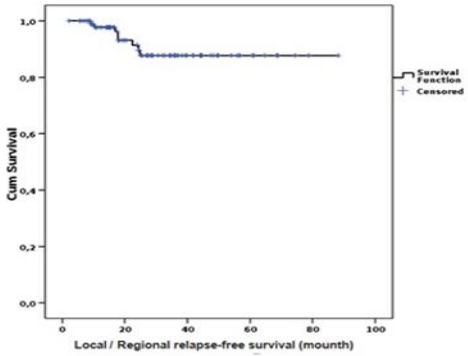
The singe-variate analysis of the variables included in the model identified pre-CT stage to be a risk factor for disease-free survival. The disease-free survival of operable patients with nipple involvement was observed to be significantly shorter relative to those with no nipple involvement (median 18.4 month and 59.8 months; 95% CI; P=0.009). Patients with multicentric tumor foci had a significantly shorter disease-free survival compared to those with no multicentric foci (28.7 months and 57.3 months, 95% CI; P<0.00019. Patients with perinodal infiltration had a shorter disease-free survival compared to those without perinodal infiltration, although the difference was not statistically significant. All the other variables were detected to be insignificant risk factors in single- and multivariate analysis (P>0.05).

Assessing the disease-free survival by the breast cancer subtype, the shortest disease-free survival was detected respectively in HR(-) HER 2(+) and HR(-) HER2(-) patients (median 13.9 months and 16.2 months) while the longest disease-free survival was observed in HR(+) HER2(-) patients (59.8 months). The difference in disease-free survival between different breast cancer subtypes was observed to be statistically significant (P=0.001) (Graphic 2).



Graphic 2: Relation between subtypes of breast cancer and survival without disease.

Eight patients (8.3%) were observed to have local/regional recurrence. The Kaplan Meier analysis revealed a recurrence-free survival rate of 92% (Graphic 3). The single-variate analysis detected response to chemotherapy (P=0.026) and ER positiveness (P=0.020) to be risk factors with an unfavorable effect on local/regional recurrence-free survival.



Graphic 3: Local/ Regional relapse-free survival.

Those who did and did not receive a taxane combination as the NACT regimen were also compared; no difference was detected with respect to pathological response, local/regional recurrence and distant metastasis (Table 5).

Table 5: Pathological response to treatment. local/regional recurrence and distant metastasis by treatment regimen.

	Patients who don't receive taxane-containing CT		Patients who receive taxane-containing CT		Total		P
	n	%	n	%	n	%	
Pathologic response							
-Partial + stable response	15	93.8	32	94.1	47	94.0	1.000*
-Pathologic compete response	1	6.3	2	5.9	3	6.0	
Local/regional recurrence							
-Yes	3	18.8	4	11.4	7	13.7	0.664*
-No	13	81.3	31	88.6	44	86.3	
Local/regional recurrence and distant metastasis							
-Yes	6	37.5	13	37.1	19	37.3	0.980**
-No	10	62.5	22	62.9	32	62.7	
Total	16	31.4	35	68.6	51	100.0	

DISCUSSION

The Local Advanced Breast Cancer (LABC) term essentially describes stage III breast cancers. Diagnosis at late state and failure to conduct an effective treatment results in a high rate of mortality associated with breast cancer. Today, based on the data from the Turkish Breast Diseases Association Federation (TBDAF) breast cancer registration, involving more than 17.000 patients, the mean tumor diameter was 2.7 cm at the time of diagnosis and the clinical stages were as follows respectively: stage 0 5%, stage I 25%, stage II 52%, stage III 16% and stage IV 2% (2). Only 34% of the surgical treatment administered in all patients is BCS. In our trial, 5.3% (n= 5), 74.7% (n= 71) and 20% (n= 19) of the patients were stage III C (n= 5), stage IIIB (n= 71) and stage IIIA respectively and only 6.3% of the patients receiving surgery was administered BCS.

Upon Fisher's claim that breast cancer was a systemic disease as from the time of diagnosis and could be managed with chemotherapy, systemic therapies have primarily come to the forefront in patients with local advanced cancer and local control rates, disease-free survival and mean survival rates increased (8). Subsequent trials revealed favorable results and thus NACT has become a standard treatment for patients diagnosed with LABC for the last 20 years (9-11).

The primary regimens preferred in LABC usually include the combination treatments containing anthracylines. However following demonstration of the taxanes' (paclitaxel and docetaxel) efficacy in the treatment of metastatic breast cancer, their use in adjuvant and neoadjuvant treatment has been revealed and their efficacy demonstrated. Currently, taxanes are the main agents of metastatic, neoadjuvant and adjuvant chemotherapy. In our trial, we used taxane-based chemotherapy in 68.6% of the treatment protocols in patients receiving NACT.

The 5-year survival was reported to be 33-75% in LABC patients (12, 13) while the 5-year disease-free survival was 30- 70% (12, 13). In our trial, 9 - year overall survival was 75.9% and 9 - year disease free survival was 68.8%. Compared to the literature results, our overall and disease-free survival rates are higher.

The tumor size at the time of diagnosis is one of the most significant prognostic factors with respect to the disease course. The trials have also reported that an increase in the tumor size represented a poor

prognostic factor with respect to regional and distant recurrences and also with respect to disease-free and overall survival (2, 14-16). In our study, upon inclusion of the data in single-variate analysis, the tumor diameter was detected to have an unfavorable effect on the disease-free survival (pre- chemotherapy T stage). However there was no statistically significant difference between the tumor diameter and the overall survival.

Today, the most important criterion for prognosis of breast cancer is the presence or absence of metastasis in axillary lymph nodes and the number of metastatic lymph nodes in the presence of metastasis. Axillary lymph node metastasis is a very important prognostic indicator in cases with LABC (2, 14). Today, many centers perform sentinel lymph node biopsy (SLNB) instead of axillary dissection even in patients with LABC. However whether this should be performed before or after neoadjuvant chemotherapy is still controversial. In our trial, we didn't use SLNB in any of the patients. As for patients who underwent axillary dissection, a difference was observed due to the adequate sample size for overall and diseasefree survival of lymph node metastasis, however the difference was not statistically significant.

The pathological response to NACT in patients with LABC is considered to be an important prognostic factor in predicting the mean and disease-free survival rates (17, 18). Post-NACT complete response (PTC) rates with first generation chemotherapeutic agents vary between 5 and 15% while the rates for pathological partial response (pPC) are between 50 and 80% (19). Upon addition of taxanes to this treatment, the pT rates have reached 20 - 30% (19). Addition of trastuzumab in HER - 2 neu receptor positive patients resulted in a pTC rate above 50% (19). In our series, TEC-based CT was administered and the rate of pathological complete response and partial response was 14% and 40% respectively.

In patients with a high grade tumor, CT response is expected to be larger due to the rapid cell proliferation. In addition, a high grade in breast cancer is a poor prognostic factor and can be used alone in determining the recurrence. Among our patients, patients with a higher grade were observed to have a better response to CT, however its efficacy in overall survival and disease recurrence alone was not demonstrated.

Parameters including ER, PR, c- erb B2, p53, KI- 67, bcl-2 and tumor markers were investigated in predicting the response to chemotherapy in neoadjuvant studies. In our trial, considering that recurrent patients may have poorer prognostic factors and that the rate of poor prognostic factors could be higher in recurrent patients, pathological prognostic factors such as ER, PR, tumor size and grade were determined via comparison of recurrent and nonrecurrent patients. As a result, response to chemotherapy and positive ER were detected to be risk factors with an unfavorable effect on local/regional recurrence-free survival. There was no significant difference between the other variables. The studies performed reported that the rate of clinical response to CT and pathological complete response was higher in ER / PR negative patients (20, 21).

Over expression of HER 2 (Human epidermal growth factor receptor 2) occurs in 20- 25% of all breast cancers and is usually associated with poor clinical course (22). Still, the role of HER 2 in predicting the response to adjuvant anthracycline-based CT is complex. A recent trial showed that HER 2(-) tumors benefited more from the adjuvant anthracycline treatment relative to HER 2(+) tumors (23). In our study, the pPC rates were markedly higher for HER 2 (-) tumors relative to HER 2(+) tumors even if the same was not applicable for pTC ($p=0.024$).

In a trial by Keam et al (22), there was no significant difference between patients with high and low P53 mutation and KI 67 proliferation with respect to response to CT. In the same study, no difference was detected between the good and poor histologic-grade tumors with respect to the rate of response. Similarly, in our trial, the clinical and pathological response rates were not affected by the factors such as age, menopausal status, histological type, KI- 67 proliferation index and P53 mutation while tumors of high histological grade were associated with significantly increased nodal pTC. In addition, ER (-) and PR (-) patients were detected to have significantly higher nodal pTC rates relative to positive patients ($P= 0.007$ and $P= 0.003$, respectively).

A good response to treatment following NACT increased the rate of breast conservative surgery to 30- 40% in well selected patients (24). However, a high local recurrence rate in these patients warrants a more careful approach to BCS. BCS was performed only in 6.3% of our patients (6 cases). Since the number of patients, in whom we performed BCS, was small, our local recurrence rates are lower than the rates reported in the literature. We believe that this is advantageous for our patients.

Despite the advances in surgical and clinical approaches, the main cause of mortality in breast cancer is the metastasis to the lungs, liver, bone and the brain rather than the complications of the primary tumor. Distant metastases following breast cancer are respectively the bone, the lungs, the liver and the brain metastases (24). The literature reports indicate a brain metastasis rate of 10-25% and a mean survival of 13 months following diagnosis of metastasis in breast cancer patients (24). The site of metastasis with the poorest prognosis was the brain with a mean survival of 15.6 months.

Bone metastases don't have a direct unfavorable effect on survival. Still, occurrence of bone metastases is an indicator that the disease is systemic and these patients are in the risk group with respect to distant organ metastases which are more fatal. As a matter of fact, 53.9% of the patients with a first distant

metastasis to the bone developed a second distant metastasis in a short while.

Conclusion

Due to the fact that they are included in the risky disease group with respect to regional and distant metastasis, LABCs require close monitoring and aggressive treatment due to the associated short survival. Patients presenting with local advanced breast tumor should receive NACT as a standard treatment. Even if the overall survival is not longer, this treatment ensures a marked advantage for disease-free survival. In addition, BCS may be performed in appropriately selected patients. However selection should be made with care because patients undergoing BCS following NACT have higher rate of local recurrence.

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