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Adjuvant systemic therapies in women with operable breast cancer: A daily medical practice in a single institution

BİNNAZ DEMİRKAN[1], İLKNUR BİLKAY GÖRKEM[2], TÜLAY CANDA[3], PINAR BALCI[4], ÖMER HARMANCIOĞLU[5], SERDAR SAYDAM[5], MÜNİR KINAY[2], MEHMET ALAKAVUKLAR[1]

Dokuz Eylül University School of Medicine, Departments of [1]Internal Medicine, Division of Hematology/Oncology, [2]Radiation Oncology, [3]Pathology, [4]Radiology and [5]General Surgery, İzmir-Turkey

ABSTRACT

To investigate the impact of adherence to international guidelines about adjuvant systemic therapies on survival rates of operable breast cancer patients in daily medical practice, 298 patients who received adjuvant chemotherapy (CMF or anthracycline-based) and/or tamoxifen were evaluated retrospectively. The 3, 5 and 7.5-year Disease Free Survival (DFS) were 77%, 67% and 61% and Overall Survival (OS) were 88%, 78% and 64%, respectively. Node negative patients have statistically better survival rates than node positive ones (p= 0.0002 for DFS, p= 0.0006 for OS). The only significant variable both for DFS and OS was four or more positive nodes. While recognizing the important impact of evidence-based guidelines on survival rates of early breast cancer patients, it might be very important to stress the weakness of standard chemotherapy regimens for women with four or more positive nodes and the necessity of early recognition for the avoidance of high numbers of involved axillary ganglia. [Turk J Cancer 2005;35(3):123-131]

KEY WORDS:

Breast cancer, survival, adjuvant systemic therapy, daily medical practice

INTRODUCTION

Breast cancer is the most common cancer and second leading cause of cancer death among women in developed countries (1,2). Adjuvant systemic therapies have significantly reduced its mortality. The 1998 meta-analysis of the Early Breast Cancer Trialists Collaborative Group (EBCTCG) showed that polychemotherapy (combination chemotherapy) produced significant proportional annual reductions in mortality both for women younger than age 50 [27% (Standard Deviation [SD] 5%)] and for those aged 50 to 69 years [11% (SD 3%)]; too few patients 70 years and older were studied. For women receiving about 6 months of combination chemotherapy, these proportional reductions translated into an absolute improvement in 10-year survival of 7% to 11% for women aged 50 years or younger and 2% to 3% for those aged 50 to 69 years. The meta-analysis of all randomized trials of adjuvant tamoxifen revealed that 2-5 years of adjuvant tamoxifen have similar efficacy in all age groups including patients below age 40 (3). For trials of 1-year, 2-years, and about 5-years of adjuvant tamoxifen use, the proportional recurrence reductions during 10 years of follow-up were 21% (SD 3), 29% (SD 2), 47% (SD 3) and the corresponding proportional mortality reductions were 12% (SD 3), 17% (SD 3), and 26% (SD 4), respectively (4).

Clinical trials do identify the potential for better survival for all cancer patients, if the results can be successfully

incorporated into routine clinical practice. So, adherence to international guidelines has an important impact on public health. But evidence-based guidelines, consensus conferences and experts' opinions are rarely promptly transferred to patient care.

Only a few studies have been conducted on daily clinical practice and its relationship to evidence derived from clinical research. Several available reports show that a gap exists between the conclusions from clinical trials, summarized in international consensus conferences and patient care (5-12).

Breast cancer is a suitable model for study of daily clinical treatment practice due to its high incidence and prevalence, the complexity of multidisciplinary approaches involved in offering adequate therapies, and the availability of results from high quality randomized clinical trials to indicate evidence for given adjuvant treatments.

In our study, we have therefore performed a retrospective analysis of our results of adjuvant systemic therapies of women with operable breast cancer who were admitted to the Hematology/Oncology Unit and treated by a multidisciplinary approach in routine clinical practice according to the guidelines.

PATIENTS AND METHODS

Only women with histologically verified invasive breast cancer and who had been administered adjuvant systemic therapies over the period September 1990 – December 1999 were evaluated retrospectively by searching their medical records (for patient characteristics see Table 1).

Cases included in this study had been staged according to either the Third or Fourth Editions of the AJCC (American Joint Committee on Cancer) Manual for Staging of Cancer before initiation of therapy (Stage I-IIIA).

Patients who underwent appropriate primary surgery (either mastectomy or tumorectomy with free margins, plus axillary lymphadenectomy) were considered eligible for evaluation of adjuvant systemic therapies.

Age, ECOG Performance Status ≤1, menopausal status, nodal and steroid hormone receptor status as well as comorbid conditions and transthoracic echocardiographic findings were the clinical features that influenced the therapeutic decision according to our adjuvant systemic treatment protocol.

Patients received either 6 cycles of CMF (600/40/600 mg/m^2, IV, d1+8, q4w) or FAC (500/50/500 mg/m^2, IV, d1, q3w) or FEC (500/50/500 mg/m^2, IV, d1, q3w) or 4 cycles of AC (60/600 mg/m^2, IV, d1, q3w) as adjuvant chemotherapy.

Adjuvant tamoxifen alone (20 mg/d, PO, qd, for 2 years before 1998 metaanalysis of the EBCTCG; after then 20 mg/d, PO, qd, for 5 years) or with ovarian ablation was administered according to the hormone receptor and menopausal status. Since the status of ovarian ablation were not available in the majority of premenopausal patients at the time of the study evaluation, ovarian ablation was not part of the study protocol.

Adjuvant radiotherapy was mandatory for all the patients with breast-conserving surgery but it was applied to the patients with modified radical mastectomy if indicated (all node positive and T3N0 patients).

Efficacy parameters in the study were 3, 5 and 7.5-year DFS and OS, which were calculated from the day of primary surgery until local/distant/contralateral relapse (DFS) or death related or not to breast cancer (OS). Patients who were lost to follow-up were not included in the study.

The Kaplan–Meier method was used to calculate the percentage of women alive (or disease free) at 3, 5 and 7.5 years and the log-rank test was used to compare survival across treatment groups and nodal status. Cox proportional hazards model for outcomes related to time variables was also performed in the overall population, the two main strata [N- (node negative) and N+ (node positive)] and chemotherapy groups. To select those factors with independent significant influence on outcomes, multivariate analyses were carried out in a stepwise (Cox regression - unconditional backward) fashion. Prior to the application of these methods, univariate analyses were performed for a preliminary exploration of marked associations. Statistical analysis and survival curves were obtained using SPSS-10.0 for Windows. P values less than 0.05 were accepted as statistically significant.

Table 1
Characteristics of all the patient study population and those according to the systemic chemotherapy

Characteristic	No. of patients (%)			P value
	All	CMF	Anthracycline-based	
Total	298 (100)	98 (32.9)	158 (53)	
Age (yr)				0.006
Mean	51	52	48	
Median	49	50	47	
Age (yr)				
< 35	28 (9.4)	7.0 (7.5)	19 (12)	
35-49	122 (41)	40 (40.7)	73 (46.4)	
50-59	70 (23.5)	27 (26.4)	34 (21.5)	
60-79	78 (26.1)	24 (25.4)	32 (20.9)	
Menopausal status				0.021
Premenopausal	138 (46.3)	40 (40.8)	88 (55.7)	
Postmenopausal	160 (53.7)	58 (59.2)	70 (44.3)	
Tumor size				0.892
T ≤2 cm	71 (23.8)	21 (21.4)	35 (22.2)	
T >2 cm	227 (76.2)	77 (78.6)	123 (77.8)	
Axillary lymph nodes involved				0.001
0	84 (28.2)	36 (36.7)	28 (17.7)	
1-3	116 (38.9)	39 (39.8)	62 (39.2)	
≥4	98 (32.9)	23 (23.5)	68 (43.1)	
Tumor Grade				0.672
1	29 (9.7)	10 (10.2)	15 (9.5)	
2-3	214 (71.8)	67 (68.4)	121 (76.6)	
Unknown	55 (18.5)	21 (21.4)	22 (13.9)	
Hormone receptors				0.636
Estrogen or progesterone positive	143 (48.0)	44 (44.9)	77 (48.7)	
Estrogen and progesterone negative	113 (37.9)	35 (35.7)	70 (44.3)	
Unknown	42 (14.1)	19 (19.4)	11 (7)	
Lymphatic invasion				0.105
Negative	26 (8.8)	11 (11.2)	11 (7)	
Positive	201 (67.4)	60 (61.2)	120 (75.9)	
Unknown	71 (23.8)	27 (27.6)	27 (17.1)	
Vascular invasion				0.036
Negative	169 (56.7)	59 (60.2)	93 (58.9)	
Positive	51 (17.1)	10 (10.2)	34 (21.5)	
Unknown	78 (26.2)	29 (29.6)	31 (19.6)	
Type of surgery				0.926
Modified radical mastectomy	216 (72.5)	70 (71.4)	112 (70.9)	
Breast conserving surgery	82 (27.5)	28 (28.6)	46 (29.1)	
Hormonotherapy				0.642
Yes	169 (56.7)	49(50)	78 (49.4)	
No or unknown	129 (43.3)	49(50)	80 (50.6)	
Radiotherapy				0.846
Yes	223 (74.8)	69(70.4)	132 (83.5)	
No	75 (25.2)	29(29.6)	26 (16.5)	

RESULTS

Table 1 gives the principal clinical, pathological and treatment characteristics of all the patient study population. The number of patients with positive axillary lymph nodes and four or more positive axillary lymph nodes were 71.8% and 32.9%, respectively. Of the 84 node-negative patients, at least 62 (73,8%) fulfilled the criteria for high risk according to the St Gallen Consensus Conference definitions (age <35 years and/or histologic grade 2-3 and/or negative hormone receptors and/or tumors of >2 cm). Thirty-two point nine percent and 53.0% of the cases received CMF and anthracycline-based chemotherapy regimens, respectively. In both groups, statistically significant differences were observed in age, menopausal status, lymph node involvement and vascular invasion favoring CMF group. Of all patients 56.7% were treated with tamoxifen (all receptor positive cases and also approximately 60% of unknown ones).

After a median follow-up of 129 months, of the 298 patients, 189 (63,4%) were alive and free of disease, 23 (7,7%) were alive with disease and 86 (28,9%) have died. 73.5 % of the patients have completed 5-year follow-up. The sites of first recurrence were distant (29.5% [45% in bone, 55% in viscera]), loco-regional (4.4%), loco-regional + distant (1.0%) and contralateral breast (1.6%).

Survival curves for the overall population, the two main strata [N (+) and N (-) patients] and N1-3 / N ≥4 are shown in figures 1, 2 and 3, respectively. Table 2 depicts the corresponding 3, 5 and 7.5-year survival parameters of overall population.

In our study; the 3, 5 and 7.5-year DFS were 77%, 67% and 61% and OS were 88%, 78% and 64%, respectively. Also node negative patients had statistically better survival rates than node positive ones (log rank p = 0.0002 for DFS, log rank p = 0.0006 for OS). Among the lymph node involved group, N ≥4 ones had the worst outcome (log rank p = 0.0006 for DFS, log rank p = 0.0009 for OS). According to the systemic treatments (CMF received by the group with favorable prognostic factors versus anthracyline-based chemotherapy received by the group with unfavorable prognostic factors), OS rate was statistically significant with CMF but DFS was similar (log rank p = 0.506 for DFS, log rank p = 0.034 for OS). Univariate analysis for DFS and OS in the overall patient population revealed significance for type of surgery [breast conserving surgery (BCS)], stage, lymphatic and vascular invasions and also for four or more positive axillary lymph nodes. But multivariate tests confirmed significance for only four or more positive axillary lymph nodes (log rank p = 0.001 for DFS [HR 2.6, CI 95% 1.49 to 4.55]; log rank p = 0.003 for OS [HR 2.6,CI 95% 1.39 to 4.88]) (Table 3). Other variables (systemic treatment, radiation therapy, tumor size,

Table 2
Survival parameters (%) at 3-, 5- and 7.5-year follow-up

Follow-up	CMF	Anthracycline	N(-)	N(+)	All
Disease-free survival (years)					
3	76	77	89	73	77
5	69	67	82	61	67
7.5	63	56	80	51	61
Overall survival (years)					
3	92	87	96	85	88
5	81	75	90	72	78
7.5	73	50	80	56	64

N(-): node negative; N(+): node positive; CMF: cyclophosphamide, methotrexate, 5-fluorouracil

Table 3
P values from Cox regression analysis: overall study population

	Univariate		Multivariate	
	DFS	OS	DFS	OS
Type of surgery (BCS)	0.021	0.029	0.480	0.393
Stage	0.000	0.000	0.812	0.988
Lymphatic invasion	0.009	0.032	0.974	0.978
Vascular invasion	0.002	0.051	0.159	0.635
N ≥ 4	0.0006	0.0009	0.001	0.003

DFS: disease-free survival; OS: overall survival; N: number of positive nodes

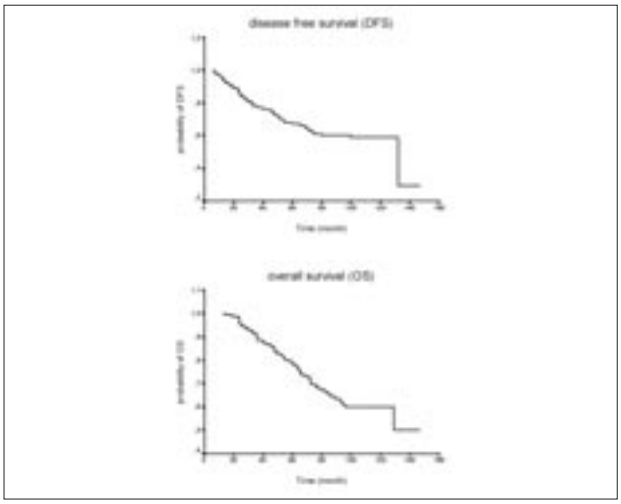

Fig 1. Disease free survial and overall survival in the entire study population

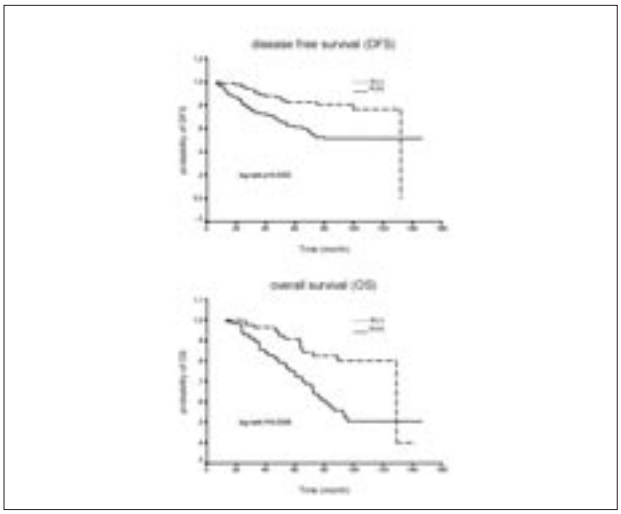

Fig 2. Disease free survial and overall survial for the entire study population according to nodal status (N): node negative versus node positive

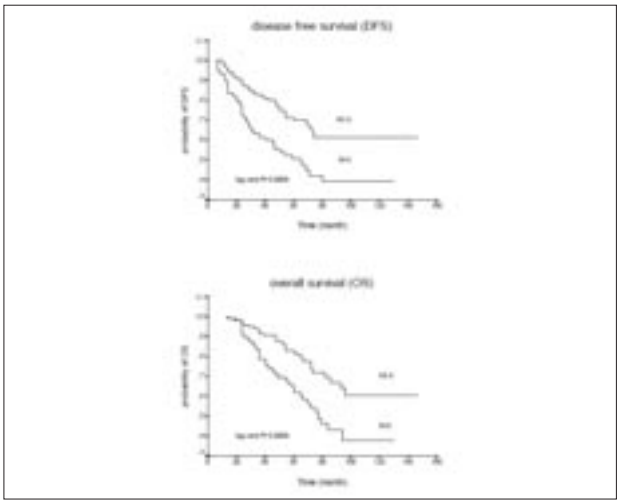

Fig 3. Disease free survial and overall survial for the node (+) population according to number of lymph node involved (N): N1-3 versus N>3

histological grade, menopausal status, age < 35 years, receptor status) did not reach significance and were excluded from the final model.

According to the separate univariate and multivariate tests performed in negative and positive node data subsets, only four or more positive axillary lymph nodes in the node-positive stratum reached statistical significance (log rank p <0.001 for DFS [HR 2.8, CI 95% 1.60 to 4.90]; log rank p = 0.001 for OS [HR 2.8, CI 95% 1.50 to 5.28]).

The significant independent prognostic variable for OS according to systemic chemotherapy regimen was again the presence of more patients with ≥4 involved lymph nodes (log rank p <0.001 for OS [HR 4.0, CI 95% 2.20 to 7.34]).

DISCUSSION

In 1976, Bonadonna et al. (13) from the Istituto Nazionale Tumori in Milan presented the results of the first randomized phase III study of adjuvant polychemotherapy versus control in node–positive breast cancer. With a follow-up of 20 years, this trial provides unequivocal evidence that CMF increases disease free survival (DFS) and overall survival (OS) in these patients (14). As the classical CMF and CMF-like protocols have been considered the gold standard for adjuvant chemotherapy for operable breast cancer, between 1990-1999, 32.9% of our patients (n=98) were treated with CMF. Because of concerns regarding cardiotoxicity, anthracyclines had not been tested in the adjuvant setting until 10-15 years ago. After the demonstration of effectiveness of 3-6 months of adjuvant therapy, this allowed for the administration of cumulative doses of anthracyclines without reaching the maximum recommended doses (13, 15-17). So, 53% of the study population (n=158) received anthracycline-based regimens. Only 14.1% of patients (n=42) with good prognostic features such as node negative, ER and/or PR positive, postmenopausal ones received endocrine therapy alone.

In the present study, 5-year DFS and OS for node-negative, node-positive and all patients were 82%, 90%; 61%, 72%; and 67%, 78%, respectively. With a statistically significant difference between the survival rates of node negative and positive patients, our results were compatible with those obtained from the randomized trials with CMF and anthracycline-based chemotherapies for operable breast cancer (18-23). But the limitation of the present study was being a retrospective analysis. A multidisciplinary team approach, as well as, prognostic factors and evidence-based guidelines were the core of treatment selection.

In regard to systemic chemotherapy, as our study was not a prospective randomized trial, CMF and anthracycline-based chemotherapy groups are not well-balanced according to known prognostic factors. There were statistically significant differences among the groups with respect to age, menopausal status, involvement of lymph nodes and vascular invasion favoring CMF group. To avoid problems of patient adherence with oral cyclophosphamide, as documented in the first trials of Gianni Bonadonna et al., we preferred IV administration of CMF (14,24,25). In regard to anthracyclines; FEC, FAC, AC and EC regimens were all devised for both node negative and positive patients in the 1990s. Dose intensity and duration of adjuvant chemotherapy are also important issues affecting survival improvement (26). 1998 and 2000 Oxford Overviews, 2000 NIH and 2001 St Gallen Consensus Panels concluded that adjuvant chemotherapy should be given 4-6 cycles (3-6 months) and superiority of FEC/FAC over CMF was shown in the randomized clinical trials (10). Today, it is well-known that 6 cycles of FEC(50) (FASG 01) used in our treatment protocol is inferior than 6 cycles of FEC(100) (FASG 05) for node-positive breast cancer patients with poor prognostic factors; but it was an acceptable regimen in the early and mid-1990s (27,28). Conventional dose escalations above standard doses will not be beneficial for doxorubicin or cyclophosphamide, while an epirubicin dose of 90-100 mg/m^2 given every third week in polychemotherapy regimens results in overall survival gains (10).

Multivariate analysis revealed that the only significant variable both for DFS and OS was presence of four or more positive axillary lymph nodes in the overall study population.

The benefit of antitumor drugs is limited, essentially, to patients with a lower tumor load, i.e. patients with negative and one to three axillary ganglia involvement. These patients could have tumors with a higher growth fraction and a lower level of acquired resistance to drugs than the four or more positive ganglia. A prospective randomized study by the GEICAM group comparing CMF with FAC chemotherapy regimens confirmed statistically better DFS and OS rates with FAC in the node-negative patient population, but not in the subgroup of positive axillary ganglia. While superiority of FAC over CMF could be the reduced dose intensity of the CMF regimen used in that study compared with classical CMF or the unknown biological features of tumor, the reason for the progressively decreased superiority of FAC over CMF in the node-positive subgroup could be increasing tumor load (23). American Intergroup Trial INT 0102 revealed the marginally better survival rates with FAC than classical CMF in the high-risk node-negative breast cancer patients (20). The International Collaborative Cancer Group Study and French Adjuvant Study Group 05 Trial pointed out the importance of dose-intensity of anthracycline which led to a significant

benefit in terms of DFS and OS among node-positive patients with poor prognostic factors (19,27).

A decade of randomized clinical trials has established the level 1 evidence-based superiority of anthracycline-based CT over CMF-like regimens. This superiority is smaller than expected, however, on average not exceeding a 4% absolute gain in 10-year survival for node-positive and a 1.7% gain at 5 years for node-negative breast cancer patients (10-12). In the last update of the EBCTCG Overview (September 2000), the results regarding anthracycline benefit, based on 14,000 women enrolled in 15 trials, continue to show the benefit of anthracycline regimens when compared with CMF in terms of reductions in recurrence (11% greater relative reduction, two-sided p-value=0.0005) and death (16% greater relative reduction, two-sided p-value<0.00001). For the node positive subset, these benefits persist for at least 10 years, with absolute gains of around 4% in recurrence and in survival. The advantage of anthracycline-based CT was found almost exclusively when a three-drug regimen was used (either CEF or CAF) (29-31).

Not only the increased risk of relapse and death associated with increasing lymph node metastasis to the ipsilateral axilla but even with endocrine-responsive disease, the higher risk of relapse and the presence of endocrine-resistant clones within the tumor have in general been taken as indications for the inclusion of cytotoxic chemotherapy in the treatment regimen.

Unfortunately, our current understanding of the optimal adjuvant chemotherapy regimen for the individual patient is still very limited. In clinical practice, the decision whether to use an anthracycline-based treatment in a given patient must always depend on the balance between the expected survival benefits for that patient and the potential risk factors for increased toxicity (i.e., mainly pre-existing heart disease) (10-12, 31,32).

Solid data are still lacking with regard to what is considered as the optimal anthracycline, optimal regimen (2- or 3-drug) and optimal number of cycles (4 or 6) (11,12,31,33,34).

In conclusion, the importance of our study was not only to answer the specific question of the impact of adjuvant systemic therapies received in daily clinical practice on operable breast cancer patients, but also to recognize the weakness of standard chemotherapy regimens for women with four or more positive lymph nodes. Because of concerns regarding high percentage of patients with ≥4 positive axillary ganglia, it might be very important to stress the necessity of early recognition by well-designed national breast cancer screening and educational programs for the avoidance of high numbers of involved lymph nodes besides new effective treatment modalities, i.e. taxanes and biological therapies.

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