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ORIGINAL ARTICLE

Sequential adjuvant docetaxel and anthracycline chemotherapy for node positive breast cancers: a retrospective study

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Summary

Purpose: *Anthracyclines and taxanes are the most active agents in the adjuvant treatment of breast cancer (BC). They can be used simultaneously or sequentially. The optimal schedule and duration for their administration is unknown. We analyzed the efficacy of sequential adjuvant anthracycline and docetaxel administration in node positive BC patients.*

Methods: *Node positive BC patients (N=539) from 6 medical oncology centers in Turkey who received sequential adjuvant anthracycline-based regimens and taxane chemotherapy were included in this study between 2006 - 2010. One-hundred and thirty-eight (25%) patients received 3 cycles of anthracycline-based chemotherapy followed by 3 cycles of docetaxel (3+3) and 401 (75%) patients received 4 cycles of anthracycline -based chemotherapy followed by 4 cycles of docetaxel (4+4). Prognostic factors analyzed were estrogen receptor (ER), progesterone receptor (PR), HER2, tumor grade, and nodal status in relation to disease free survival (DFS) and HER2 status in relation to overall survival (OS).*

Results: *The patient median age was 48 years (range 18-79). Most common grade 3-4 toxicities were neutropenia, mucositis and arthralgia. No treatment-related toxic deaths were seen. With a median follow up of 26 months (range 1-115) 61 (11.3%) recurrences and 11 (2%) deaths were registered. Three-year DFS was 81% and OS 96% for all patients. There was no statistically significant difference between 3+3 and 4+4 groups in terms of survival (3-year DFS 88% and 79% [p=0.28] and OS 97% and 95% [p=0.60], respectively).*

Conclusion: *Sequential chemotherapy with 4+4 cycles of anthracycline and docetaxel every 3 weeks is an acceptable regimen for adjuvant treatment of node positive BC patients. Duration of chemotherapy should be planned depending on prognostic factors. In this study there was no difference between 3+3 and 4+4 groups in DFS and OS despite the presence of good prognostic factors in the 3+3 group.*

Key words: *adjuvant, anthracycline, breast cancer, docetaxel, node positive*

Introduction

Adjuvant chemotherapy reduces the risk of recurrence in radically resected BC patients [1]. Anthracycline-based combinations are generally effective and have become the cornerstone of adjuvant chemotherapy for most patients with BC [1-6].

Early studies of docetaxel in BC revealed its activity in the metastatic setting [3]. Further studies showed efficacy in the adjuvant setting, combined with or in sequence with anthracycline-based regimens, showing significant improvement in DFS for the taxane-based treatment vs the control

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anthracycline-based treatment. Docetaxel was administered in 3 or 4 cycles in these studies [7-18].

Sequential treatment with docetaxel and anthracyclines was first analyzed in the PACS 01 study [11]. In this study 3 cycles of docetaxel after 3 cycles of FEC chemotherapy were found superior than 6 cycles FEC for 5-year DFS (78.4 vs 73.2%, hazard ratio/HR=0.82 [0.69–0.99], p=0.034) and 90.7 vs 86.7% (HR=0.73 [0.56–.94], p=0.017).

Another study for adjuvant treatment of BC designed by Eiermann et al. compared anthracycline, cyclophosphamide and docetaxel combination to sequential anthracycline and docetaxel (4 cycles) [18]. At a median follow-up of 65 months, the estimated 5-year DFS was 79% in both groups (p = 0.98; HR = 1.0; 95% CI 0.8-1.16), and 5-year OS for both arms was 88 and 89%, respectively (p = 0.37; HR = 0.91; 95% CI 0.75-1.11).

Although docetaxel is an active agent for early BC, simultaneous or sequential usage and the duration of chemotherapy are not well defined.

In this study we analyzed the efficacy of sequential docetaxel with anthracycline-based chemotherapy in node positive BC patients and the effect of treatment duration.

Methods

We retrospectively evaluated the clinicopathological data of 539 node positive BC patients who received adjuvant sequential anthracycline and docetaxel chemotherapy in 6 medical oncology centers in Turkey between January 2006 and January 2010. Parameters assessed included tumor histology, grade, ER and PR status, HER2 status, menopausal status at diagnosis, type of surgery, stage, toxicities, OS and DFS and the duration of adjuvant treatment.

All patients received 3 cycles of anthracycline-based regimens and 3 cycles of docetaxel (100 mg/m^2 every 3 weeks) (3+3 group) or 4 cycles of anthracycline-based regimens and 4 cycles of docetaxel 75 mg/m^2 every 3 weeks (4+4 group). Anthracycline-based chemotherapy included CAF (cyclophosphamide 60 mg/m^2, doxorubicin 60 mg/m^2, 5-fluorouracil 600 mg/m^2), CEF (cyclophosphamide 600 mg/m^2, epirubicin 90 mg/m^2, 5-fluorouracil 600 mg/m^2), AC (doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2) or EC (epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2) every 3 weeks. Steroid receptor positive patients received tamoxifen or aromatase inhibitor therapy according to menopausal status after completion of chemotherapy.

Statistics

Statistical analyses were performed by using SPSS for Windows version 18.0.(SPSS, Chicago, IL). Baseline characteristics of the groups were compared by x^2 test (for categorical variables) or two-sample t-test (for continuous variables). Tumors with missing values were omitted from the analyses. Kaplan-Meier survival analysis was carried out for DFS and OS. Log-rank test was used to examine the statistical significance of the differences observed between the groups. Two-sided p-values of <0.05 were considered statistically significant.

Results

Patient and treatment characteristics

The patient median age was 48 years (range 18-79). At the time of diagnosis 275 (51%) patients were premenopausal and 258 (48%) postmenopausal. Patient characteristics are summarized in Table 1.

Four-hundred and sixty-one (85.8%) patients had infiltrative ductal carcinoma, 31 (5.8%) invasive lobular carcinoma and 45 (8.4%) had other subtypes (mixed, medullary, metaplastic, and mucinous). ER and PR were positive in 322 (61.3%) and 335 (63.3%) of the patients respectively. HER2 positivity was seen in 170 (33.5%) patients.

Modified radical mastectomy and axillary lymph node dissection were performed in 486 patients (90.2%) and breast-conserving surgery in 53 (9.8%). A median of 18 lymph nodes (range 1-58) were excised. The median metastatic lymph nodes number was 5 (range 1-39), and the median tumor diameter was 3.5 cm (range 0-11). Two-hundred and seventy-eight (51%) patients received CAF, 175 (32%) AC, 74 (14%) CEF and 12 (3%) EC therapy as anthracycline-based therapy.

Adjuvant radiotherapy was delivered to 497 (94%) patients and all positive ER/PR patients were administered hormonal therapy with tamoxifen or aromatase inhibitors after completion of chemotherapy.

HER2 positive patients received at least 3 cycles of anti-HER2 therapy with trastuzumab along with docetaxel every 3 weeks (first cycle 8 mg/kg, then 6 mg/kg).

3+3 group

One-hundred and thirty-eight (25%) patients received 3+3 cycles of chemotherapy. Their median age was 49.2 years (range 27-79) and 39.5% were premenopausal at the time of diagnosis. Ninety-four (68.6%) were ER or PR positive. HER2 positivity was 23.7%; other patient characteristics are shown in Table 2.

Table 1. Patient and disease characteristics and 3-year survival rates

Characteristics	*N (%)*	*3-year DFS (%)*	*p-value*	*3-year OS (%)*	*Log-rank p*
Total	539 (100)	81	-	96	-
Histology					
IDC	461 (85.8)	82	0.62	96	0.74
ILC	31 (5.8)	78		96	
Other	45 (8.4)	72		89	
ER					
Positive	322 (61.3)	85	0.009	97	0.41
Negative	203 (38.7)	75		93	
PR					
Positive	335 (63.3)	86	0.001	98	0.067
Negative	194 (36.7)	71		91	
ER or PR					
Positive	388 (73.3)	85.4	<0.001	97.6	0.118
Negative	141 (2.7)	69.2		90.6	
HER2					
Positive	170 (33.5)	72	0.032	92	0.004
Negative	337 (66.5)	84		97	
Menopausal status					
Pre	275 (51)	79.9	0.547	96	0.31
Post	258 (48)	82.5		96	
Surgery					
MRM	486 (90.2)	80	0.246	95	0.947
BCS	53 (9.8)	84		100	
Grade					
I	40 (7.4)	84	0.084	96	0.054
II	263 (52.9)	83		98	
III	36 (39)	75		91	
Stage at diagnosis					
2a	30 (5.6)	96	<0.0001	100	0.18
2b	150 (27.8)	89		97	
3a	201 (37.3)	79		98	
3b	17 (3.2)	74		100	
3c	141 (26.2)	73		91	
T status					
T1	66 (12)	94	0.077	100	0.403
T2	332 (61.5)	82		95	
T3	114 (21)	77		97	
T4	24 (4.5)	63		91	
N status					
N1	217 (40.3)	87	<0.0001	98	0.071
N2	180 (33.4)	80		98	
N3	142 (26.3)	73		91	
Adjuvant radiotherapy					
Yes	497 (94)	80	0.2	96	0.2
No	32 (6)	91		95	
Adjuvant hormonotherapy					
No	146 (28)	68	0.021	88	0.151
Tamoxifen	226 (43.3)	85		99	
Anastrozole	97 (18.6)	82		95	
Letrozole	51 (9.8)	85		97	
Chemotherapy					
3+3 cycles	138 (25.6)	86.3	0.287	97.6	
4+4 cycles	401 (74.4)	79.6		95.7	0.605

IDC: infiltrative ductal carcinoma, ILC: invasive lobular carcinoma, Other: mixed, medullary, metaplastic, mucinous, PFS: progression free survival, OS: overall survival, MRM: modified radical mastectomy, BCS: breast-conserving surgery, ER: estrogen receptor, PR: progesterone receptor

Table 2. Patient and disease characteristics and duration of chemotherapy in the 3+3 and 4+4 groups

Characteristics	*3+3 cycles (%) N=138*	*4+4 cycles (%) N=401*	*p-value*
Age, years, median (range)	49.2 (27-79)	48.2 (18-77)	0.56*
Menopausal status			
Pre	39.5	55.8	0.001§
Post	50.6	44.2	
ER			
Negative	49.3	35	0.004§
Positive	50.5	65	
PR			
Negative	39.4	35.7	0.471§
Positive	60.6	64.3	
HER 2			
Negative	76.3	62.9	0.006§
Positive	23.7	37.1	
Grade			
I	10.5	7.1	0.46§
II	51.9	53.3	
III	37.6	39.6	
Lymphatic invasion			
Positive	20.2	42.1	<0.001§
Negative	79.8	57.9	
T stage			
T1	18.2	10.3	0.03§
T2	54	64.7	
T3	21.2	21.3	
T4	6.6	3.8	
N stage			
N1	50.7	36.7	0.014§
N2	28.3	35.2	
N3	21	28.2	
Adjuvant hormonotherapy			
No	26.3	25.1	0.132§
Tamoxifen	37	45.5	
Aromatase inhibitors	26.7	29	

*two-sample t-test, §x^2-test. ER: estrogen receptor, PR: progesterone receptor

4+4 group

Four-hundred and one patients received 4+4 cycles of chemotherapy. Their median age was 48.2 years (range 18-77) and 55% were premenopausal at the time of diagnosis. Two-hundred and ninenty-four patients (75%) were ER or PR positive. HER2 positivity was seen in 37.7% of the patients. In this group, patients had significantly more unfavorable prognostic factors such as premenapausal status, HER2 positivity, more advanced T and N stage and more lymphovascular invasion compared to the 3+3 group.

Survival

Median follow up was 26 months (range 1-115). Three-year DFS was 81% for all patients (Figure 1A). Sixty-one (11%) recurrences occurred during the first 3 years. Most common metastatic sites were bone, lung and liver. Patients with positive ER and PR, negative HER2, with less than 4 metastatic lymph nodes had significantly better DFS. Menopausal status, type of surgery, and tumor grade showed no impact on DFS.

Three-year OS for all patients was 96% (Figure 1B). Eleven (2%) deaths occurred during the first 3 years. HER2 negative patients had statistically significant better OS (Table 1). Hormonal status, tumor grade, menopausal status, type of surgery, and type of adjuvant hormonal therapy had no impact on OS.

Three-year DFS was 88% for the 3+3 group and 79% for the 4+4 group (p=0.28), while OS was 97% and 95% (p=0.60), respectively.

Toxicity

No chemotherapy-related toxic deaths were registered. Most common grade 3-4 toxicity was neutropenia (N=34; 6.3%). Dose reduction was necessary for 9 patients due to grade 3-4 mucositis and grade 3-4 neutropenia. Five patients were hospitalized due to neutropenic fever. Other most common grade 3-4 toxicities were anemia, arthralgia-myalgia and diarrhea. No differences in

Table 3. Grade 3-4 toxicities and chemotherapy schedules

Toxicity	*3+3 cycles*	*4+4 cycles*	*x^2, p*
	N	*N*	
Anemia	4	7	0.48
Neutropenia	11	23	0.41
Mucositis	3	4	0.92
Arthralgia-Myalgia	3	4	0.92
Diarrhea	3	2	0.89
Chemotherapy delayed	10	13	0.62
Dose reduction	3	6	0.48
Neutropenic fever and hospitalization	2	3	0.89

toxicities were seen between 3+3 and 4+4 groups. Grade 3-4 toxicities are shown in Table 3.

Discussion

This multicentric retrospective study showed that sequential adjuvant therapy with anthracycline and docetaxel for lymph node positive BC patients is a good alternative regimen with acceptable 3-year DFS and OS. The optimal duration of this schedule is uncertain, but 4+4 and 3+3 cycles of chemotherapy showed similar survival despite the presence of adverse prognostic factors in the 4+4 cycles group.

To our knowledge no available data exist that compare 3+3 to 4+4 chemotherapy cycles in the literature; available data mostly compare taxanes to anthracyclines or simultaneous to sequential treatments. This is the first retrospective analysis comparing 3+3 and 4+4 groups. 4+4 therapy contains higher absolute drug doses and longer duration of chemotherapy compared to 3+3 cycles schedule. In our study patients belonging to the 3+3 group had good prognostic factors but DFS and OS were similar with the 4+4 patient group.

Sequential treatment with docetaxel and anthracyclines was first analyzed in the PACS 01 study [13,14]. In this study 3 cycles of docetaxel after 3 cycles of FEC chemotherapy were found superior than 6 cycles FEC for 5-year DFS (78.4 vs 73.2% HR=0.82 [0.69–0.99], p=0.034) and OS (90.7 vs 86.7%, HR = 0.73 [0.56–0.94], p=0.017). Our patients received 600 mg/m^2 cyclophosphamide and 5-fluorouracil while patients in the PACS 01 study received 500 mg/m^2. In both studies docetaxel doses were similar. In our analysis we could only determine 3-year OS and DFS because of short median follow up. Our study differed from PACS 01 study because it had two different groups with the same chemotherapy regimen (3+3 and 4+4 groups). Despite the presence

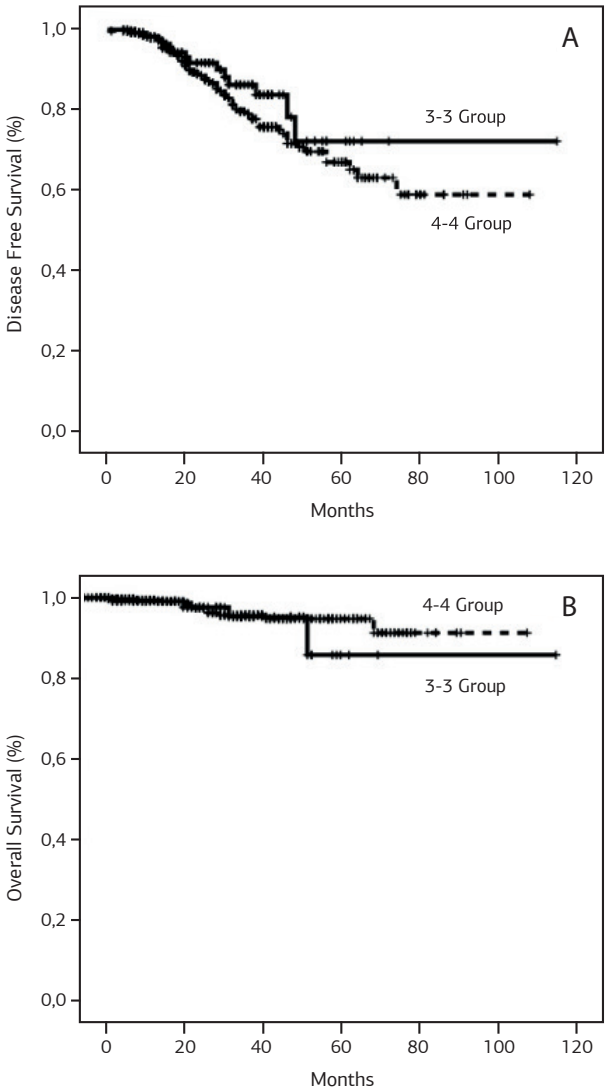

Figure 2. Kaplan-Meier survival of 3+3 and 4+4 groups. **A:** Disease free survival (p=0.28); **B:** Overall survival (p=0.60).

of adverse prognostic factors in the 4+4 group such as premenapausal patients, young patients, advanced T and N stage and HER2 positivity, the survival rates were similar in both groups.

Most recently the BCIRG 005 study designed for concomitant vs sequential docetaxel as adjuvant treatment was concluded [14]. In this study 6 courses of TAC (docetaxel, doxorubicin and cyclophosphamide) were compared with 4 cycles of docetaxel after 4 cycles adriamycin and cyclophosphamide (AC). There was no significant difference in 5-year DFS (79% in both arms) and OS (88 and 89%, respectively). Only toxicity, such as febrile neutropenia and thrombocytopenia, was greater in the TAC group.

Paclitaxel is an alternative drug for the adjuvant treatment in axillary lymph node positive BC patients. In a randomized phase III study 4 cycles of paclitaxel after 4 cycles of AC were compared with 4 cycles of AC [19]. The addition of paclitaxel to AC reduced the HR for DFS event by 17% (rela-

tive risk 0.83, 95% Cl 0.72-0.95; p=0.006). However, improvement in OS was not statistically significant in this study. Both paclitaxel and docetaxel are effective agents for adjuvant treatment in BC.

A meta-analysis [20] performed to determine the efficacy of paclitaxel and docetaxel included 17 trials and 30,672 patients. This study proved that the addition of taxanes increased significantly DFS and OS (HR 0.82, 95% CI 0.76-0.88 for DFS and HR 0.83, 95% CI 0.75-0.91 for OS). Indirect comparison of docetaxel and paclitaxel showed that the benefit of docetaxel in OS was significantly superior to that obtained with paclitaxel in lymph node positive patients (OR 0.79, 95% CI 0.63-0.98). Of note, this meta-analysis did not mention the duration of chemotherapy.

In conclusion, adjuvant treatment for node positive BC with sequential anthracycline-based and docetaxel chemotherapy seems effective, but the optimal treatment duration is uncertain. Probably, high risk patients should be treated with 4+4 cycles of chemotherapy rather than 3+3 cycles. Future randomized controlled trials may clarify the optimal schedule, treatment intensity and treatment duration.

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