The comparison of anthracycline-based and non-anthracycline-based regimens in adjuvant chemotherapy of HER2-positive non-metastatic breast cancers

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Aim of the study: This study aimed to assess the efficacy of anthracycline-based (AB) and non-anthracycline-based (nAB) adjuvant therapies in the human epidermal growth factor receptor 2 (HER2)-positive non-metastatic BC (nMBC) patients.

Material and methods: This retrospective study included women with HER2-positive BCs (stage I–III) treated with trastuzumab from 2008 to 2017. The patients were divided into two groups, including 196 patients in group AB and 67 in group nAB.

Results: Cox's proportional hazard regression analysis showed no unfavourable predictors for five-year overall survival (OS) and disease-free survival (DFS) except for stage and hormone therapy. The OS rate was 67.9% in group AB and 80.6% in group nAB (p = 0.630). The DFS rate was 61.6% in group AB compared with 67.1% in group nAB (p = 0.447).

Conclusions: The results showed no difference between the efficacies of AB and nAB regimens in HER2-positive nMBCs in adjuvant setting. Therefore, selecting the nAB regimen can reduce the serious damage caused by the AB regimen.

Key words: breast cancer, HER2, trastuzumab, anthracycline, adjuvant therapy.

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Introduction

The most common cancer in women in the developed or developing countries is breast cancer (BC), with a peak in the age of 40–50 years in Asia [1]. The human epidermal growth factor receptor 2 (HER2) is overexpressed in approximately 15%–25% of invasive BCs and is associated with a high risk of disease recurrence and reduced survival [2, 3]. Trastuzumab alone and in combination with chemotherapy has been identified to have a good safety record and to be active in advanced HER2-positive disease [4, 5]. Adjuvant systemic chemotherapy has significantly improved the prognosis of BC patients [6]. Data from randomised trials including adjuvant therapy have reported that the risk of recurrence and death of disease is significantly reduced when adjuvant chemotherapy and/or hormonal therapy is added to the treatment [7]. Various factors have recently prompted a re-assessment of the role of non-anthracycline-based (nAB) regimens in the early stage of BC [8]. This debate has been triggered by recent data demonstrating the efficacy of nAB regimens in various disease settings and highlighting the importance of anthracycline-related toxicity [8]. The benefits of anthracycline-based (AB) regimens came with a number of clinically significant, long-term toxicities, in particular direct myocardial toxicity, which could lead to the later development of congestive cardiac failure and bone marrow damage resulting in leukaemia and myelodysplastic syndromes [9]. High histological grade, oestrogen receptor (OR)-negative, progesterone receptor (PR)-negative, or HER2-positive are risk factors involved in the recurrence, especially in the early recurrence, among which OR is the most significant prognostic factor involved in early recurrence [10].

The aim of this study was to evaluate the efficacy of AB and nAB adjuvant therapies in HER2-positive non-metastatic BC (nMBC) patients.

Material and methods

This retrospective study was approved by the Ethics Committee of Kermanshah University of Medical Sciences, Kermanshah, Iran. Patients referring to the Breast Cancer Research Centre, Tehran University of Medical Sciences, Tehran, Iran, during 2008–2017 were included in this study.

Patients

The patients were divided into two groups (196 patients were treated with AB regimen [group AB] and 67 with nAB regimen [group nAB]). The clin-

icopathological and demographic factors were extracted for every patient based on the pathological and clinical reports. The median follow-up time was 42 months (range: 12–125 months). Of patients, 25% were treated with modified radical mastectomy and 75% were treated with breast conservation therapy. Radiotherapy was done based on the stage of disease, including 50 Gray (Gy) in 25 fractions plus 5 Gy in five fractions as a boost for the necessary items. Chemotherapy regimens were AC4T4 (cyclophosphamide-adriamycin [AC]) used every three weeks for four cycles, followed by paclitaxel (T) given every three weeks for four cycles, or anthracycline-based regimens and TC (docetaxel and cyclophosphamide) given every three weeks for four cycles, or nAB regimen. Out of all patients, 15% had preoperative chemotherapy and 12% were inoperable or had inflammatory BC. All patients had Karnofsky Performance Score (KPS) of 0 and 1. Only 0.5% patients had local recurrence and 99.5% had distant metastases. Out of all patients, 15% had neoadjuvant chemotherapy and 100% had adjuvant hormone therapy.

The inclusion criteria consisted of the female patients aged > 20 years; HER2-positive (HER2 3+ or HER2 2+ and fluorescence in situ hybridization (FISH) positivity) and non-metastatic patients (stage I–III). The exclusion criteria consisted of the patients with stage IV; the patients receiving Trastuzumab therapy as adjuvant therapy for less than one year, and the patients with the ejection fraction (EF) less than 45%.

Survival and recurrence

Overall survival (OS) was defined as the time from the diagnosis to death by any cause, and disease-free survival (DFS) was defined as the time from the diagnosis to recurrence and/or metastasis, whichever was the earliest. OS and DFS were determined for five years. Breast tumour recurrence was defined as a comeback of cancer to the same place as the original (primary) tumour or to another place in the body. Distant metastasis was defined as recurrence at a distant site from the primary cancer.

Statistical analyses

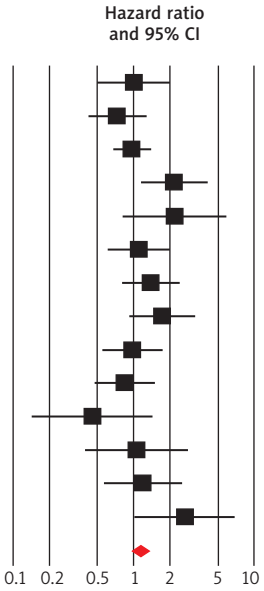
The analysis was done by IBM SPSS (version 22) software (IBM Corp., Armonk, NY, USA). Chi-square test and t-test were used for the analysis of categorical and contin-

Table 1. The comparison of baseline variables between the patients with anthracycline-based (AB) and non-anthracycline-based (nAB) chemotherapies

	Group AB *n* = 196	Group nAB *n* = 67	*p*-value
Age (year), *n* (%) Mean ±SD ≥ 50	85 (43.4) 47.8 ±11.6	24 (35.8) 46.2 ±10.8	0.174 0.325
Type of pathology IDC/DCIS/LC, *n* (%)	182 (92.8)/7 (3.6)/7 (3.6)	65 (97)/1 (1.5)/1 (1.5)	0.470
Stage I/II/III, *n* (%)	39 (19.9)/88 (44.9)/69 (35.2)	27 (40.3)/26 (38.8)/14 (20.9)	0.003
Lymph node metastasis Yes, *n* (%) N0/N1/N2/N3	132 (67.3) 64/63/60/9	28 (41.8) 39/14/10/4	< 0.001 0.002
Tumour size (cm), *n* (%) Mean ±SD < 2/2–5/> 5,	3.2 ±1.6 35 (17.9)/138 (70.4)/23 (11.7)	3.0 ±1.5 13 (19.4)/49 (73.1)/5 (7.5)	0.463 0.615
Grade, *n* (%) I/II/III	9 (4.6)/110 (56.1)/77 (39.3)	4 (6)/24 (35.8)/39 (58.2)	0.016
Vascular invasion, *n* (%) Yes	106 (54.1)	33 (49.3)	0.294
Laterality, *n* (%) Right	100 (51)	35 (52.2)	0.488
Ki67 index, % (*n* = 207) Mean ±SD ≤ 20	28.4 ±20.2 64 (44.1)	29.7 ±18.4 24 (38.7)	0.669 0.285
ER, *n* (%) Positive	119 (60.7)	44 (65.7)	0.284
PR, *n* (%) Positive	101 (51.5)	37 (55.2)	0.352
Radiotherapy, *n* (%) Yes	167 (85.2)	50 (74.6)	0.040
Hormone therapy, *n* (%) Yes	133 (67.9)	40 (59.7)	0.143

IDC – invasive ductal carcinoma; DCIS – ductal carcinoma in situ; LC – lobular carcinoma; N – number of lymph node; SD – standard deviation

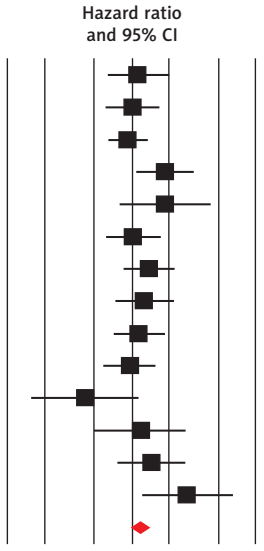
Variables	Statistics for each study			
	Hazard ratio	Lower limit	Upper limit	*p*-value
Chemotherapy group, AB vs. nAB	1.001	0.509	1.968	0.998
Age, ≥ 50 vs. < 50 yrs	0.731	0.420	1.273	0.268
Type of pathology, IDC or DCIS vs. LC	0.974	0.673	1.410	0.889
Stage, 1 or 2 vs. 3	2.149	1.120	4.124	0.021
Lymph node metastasis, yes vs. no	2.173	0.816	5.786	0.120
Tumour size, < 2 or 2–5 vs. > 5 cm	1.106	0.603	2.029	0.745
Grade, 1 or 2 vs. 3	1.376	0.799	2.369	0.250
Vascular invasion, yes vs. no	1.722	0.907	3.270	0.097
Laterality, right vs. left	0.976	0.553	1.724	0.933
Ki67 index, ≤ 20 vs. > 20	0.839	0.474	1.485	0.547
ER, positive vs. negative	0.454	0.143	1.442	0.180
PR, positive vs. negative	1.055	0.400	2.784	0.914
Radiotherapy, yes vs. no	1.186	0.562	2.503	0.654
Hormone therapy, yes vs. no	2.655	1.040	6.777	0.041
	1.130	0.955	1.336	0.153



CI – confidence interval; NA – not available; IDC – invasive ductal carcinoma; DCIS – ductal carcinoma in situ; LC – lobular carcinoma; AB – anthracycline-based chemotherapy; nAB – non-anthracycline-based chemotherapy; ER – estrogen receptor; PR – progesterone receptor

Fig. 1. Forest plot of the random-effect of hazard ratio of variables affecting the overall survival. Hazard ratios (HRs) are presented as the risk of the left-side category vs. the right-side category

Variables	Statistics for each study				
	Hazard ratio	Lower limit	Upper limit	*z*-value	*p*-value
Chemotherapy group, AB vs. nAB	1.118	0.627	1.995	0.378	0.706
Age, ≥ 50 vs. < 50 yrs	1.011	0.617	1.656	0.043	0.965
Type of pathology, IDC or DCIS vs. LC	0.926	0.648	1.324	–0.421	0.674
Stage, 1 or 2 vs. 3	1.851	1.074	3.191	2.216	0.027
Lymph node metastasis, yes vs. no	1.839	0.791	4.275	1.415	0.157
Tumour size, < 2 or 2–5 vs. > 5 cm	1.024	0.616	1.702	0.091	0.927
Grade, 1 or 2 vs. 3	1.380	0.862	2.208	1.343	0.179
Vascular invasion, yes vs. no	1.251	0.726	2.157	0.806	0.420
Laterality, right vs. left	1.150	0.708	1.867	0.565	0.572
Ki67 index, ≤ 20 vs. > 20	0.961	0.586	1.576	–0.158	0.875
ER, positive vs. negative	0.417	0.153	1.138	–1.708	0.088
PR, positive vs. negative	1.177	0.514	2.694	0.386	0.700
Radiotherapy, yes vs. no	1.437	0.760	2.716	1.116	0.264
Hormone therapy, yes vs. no	2.776	1.179	6.537	2.336	0.019
	1.178	0.999	1.389	2.051	0.051



CI – confidence interval; NA – not available; IDC – invasive ductal carcinoma; DCIS – ductal carcinoma in situ; LC – lobular carcinoma; AB – anthracycline based chemotherapy; nAB – non-anthracycline based chemotherapy; ER – estrogen receptor; PR – progesterone receptor

Fig. 2. Forest plot of the random-effect of hazard ratio of the variables affecting disease-free survival. Hazard ratios (HRs) presented as the risk of the left-side category vs. the right-side category

uous data, respectively. OS, DFS, and adverse events were the outcomes of this study. The comparison between OS and DFS in the two groups was performed by GraphPad Prism 5 software. The log-rank test was run to compare the Kaplan-Meier curves for OS and DFS. Also, Cox's proportional hazard regression analysis was used to evaluate the effects of various parameters on the primary analysis. A *p*-value (two-tailed) less than 0.05 showed a statistically significant difference. Confidence interval (CI) was 95% in all analyses. A forest plot of the random-effects model was made by Comprehensive Meta-Analysis software version 2.0 (CMA 2.0) for hazard ratios (HRs).

Results

This study included 263 female patients with BC, 169 in group AB and 67 age-matched in group nAB (Table 1).

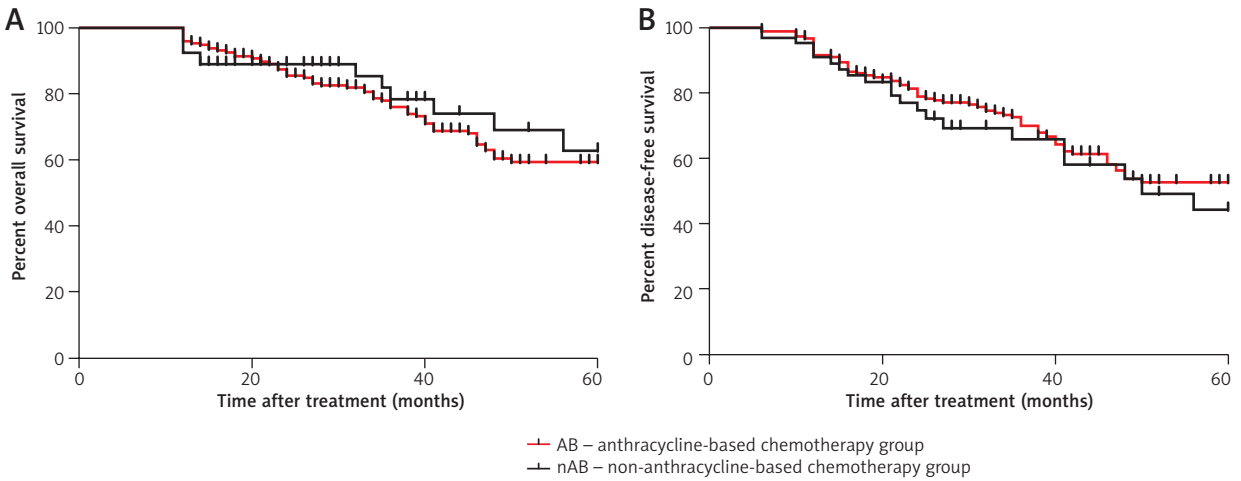


Fig. 3. A) 5-year overall survival and **B)** 5-year disease-free survival for patients with breast cancer in two groups

Table 2. The comparison of adverse events between the patients with anthracycline-based (AB) and non-anthracycline-based (nAB) chemotherapies

Adverse events	Group AB, *n* = 196	Group nAB, *n* = 67	*p*-value
Neutropaenia (grade 3–4)	10 (5.1)	1 (1.4)	0.232
Alopecia (grade 3–4)	194 (98.5)	47 (70.1)	< 0.001
Nausea and vomiting (grade 3–4)	10 (5.1)	1 (1.4)	0.232
Diarrhoea (grade 3–4)	2 (1)	2 (3)	0.279
Cardiovascular complications	7 (3.6)	1 (1.4)	0.407

Among the variables included, stage, lymph node metastasis, grade, and radiotherapy had different significant rates in the two groups ($p < 0.05$).

Cox's proportional hazard regression analysis was used to evaluate the effect of various parameters on the primary analysis. The hazard ratios of the variables affecting OS and DFS are shown in Figures 1 and 2, respectively. There were no unfavourable predictors for OS and DFS except for stage ($p = 0.021$ and $p = 0.027$, respectively) and hormone therapy ($p = 0.041$ and $p = 0.019$, respectively).

The OS rate and mean were 67.9% and 39.1 months in group AB vs. 80.6% and 30.1 months in group nAB ($p = 0.630$), respectively (Fig. 3). The DFS rate and mean were 61.6% and 36.9 months in group AB vs. 67.1% and 28 months in group nAB ($p = 0.447$). No significantly increased risk was seen in group AB, compared to group nAB, for either the five-year DFS (HR 0.82, 95% CI 0.49–1.37) or the five-year OS (HR 1.15, 95% CI 0.64–2.06).

Table 2 presents the comparison of adverse events between both groups. Among the mentioned adverse events, grade-3–4 alopecia was significantly higher in group AB than group nAB ($p < 0.001$).

Discussion

HER2 over-expression is an independent index for predicting poor prognosis and short DFS in BC patients. HER2-over-expressed patients are resistant to CMF regimen chemotherapy, but sensitive to AB or anthracyclines plus taxanes regimen. HER2 expression can be taken as a marker for therapies in BC [11]. The present study assessed the impact of two regimens (AB and nAB chemotherapies) on HER2-positive nMBC patients in an adjuvant setting. The study showed that OS and DFS were similar in both chemotherapy regimens. Considering the results obtained from the randomised controlled trials, there are limitations to the evidence supporting the use of nAB regimens [8]. Many studies have indicated an association between anthracyclines and HER2 expression [12]. One study reported that the use of AB chemotherapy declined, and the majority of patients with BC were instead receiving taxane-based chemotherapy. However, the potential impact on patient outcomes is unknown. The nAB regimens are likely to benefit patients in that the cardiac toxicity rates will decrease [13]. The AB regimens are the most commonly used chemotherapies that have been shown to be associated with cognitive impairment and brain changes in clinical studies [14].

Several studies have reported that HER2-positive BC is particularly sensitive to anthracycline treatment [11, 15, 16]. Trastuzumab improves the overall survival of HER2-positive BC women but is associated with cardiotoxicity, especially when administered after anthracyclines [17]. Adjuvant chemotherapy with anthracyclines improves the disease-free and overall survival compared to nAB adjuvant chemotherapy regimens in the treatment of early BC [15]. A meta-analysis showed that the added benefits of adjuvant chemotherapy with anthracyclines appear to be confined to women who have overexpressed HER2 or amplified BCs [15].

Slamon *et al*. [2] reported that adding one year of adjuvant trastuzumab significantly improved DFS and OS among HER2-positive BC women. The risk–benefit ratio favoured the nAB regimen (docetaxel and carboplatin plus 52 weeks of trastuzumab) over the AB regimen (doxorubicin and cyclophosphamide followed by docetaxel every three weeks) plus trastuzumab, given its similar efficacy, fewer acute toxic effects, and lower risks of cardiotoxicity and leukaemia. Almost all current adjuvant therapies incorporated the use of anthracyclines on the basis of the meta-analysis by the Early Breast Cancer Trialists' Group, which showed an improved efficacy of AB chemotherapy regimens over regimens without anthracycline [18]. Analyses of HER2 status among approximately 5200 patients who participated in eight large, randomised adjuvant trials comparing AB with nAB chemotherapy regimens showed that only HER2-positive BC women derived an incremental benefit from anthracycline use [19, 20]. The results of this study were similar to previous studies.

In conclusion, the results showed no difference between the efficacies of AB and nAB regimens in HER2-positive nMBCs in an adjuvant setting. Therefore, nAB regimen can reduce the serious damage caused by AB regimen.

The authors declare no conflict of interest.

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