Phase II study of adjuvant docetaxel and carboplatin with/without doxorubicin and cyclophosphamide in triple negative breast cancer: a randomised controlled clinical trial

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Aim of the study: The aim of this trial was to compare overall survival (OS), disease-free survival (DFS), and toxicity of two adjuvant regimens in triple negative patients with Iranian ethnicity.

Material and methods: In a phase II trial, patients with previously untreated triple negative breaststroke cancer were randomly assigned by using docetaxel 70 mg/m^2 and carboplatin AUC = 7 every three weeks with granulocyte colony-stimulating factor for sin courses (arm A) or doxorubicin hydrochloride 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every three weeks with G-CSF for four courses followed by docetaxel 70 mg/m^2 and carboplatin AUC = 7 every three weeks with G-CSF for four courses (arm B).

Results: A total of 119 patients were randomly enrolled in our study (60 patients in Arm A and 59 patients in Arm B) between 2011 and 2016. The mean follow-up was 40 months at the time of treatment analysis. The 2-year and 5-year DFS rates for Arm A were 92.7% vs. 85% and for Arm B were 82.6% vs. 64.4%. The 2-year and 5-year OS rates for Arm A were 96.5% vs. 91.7% and for Arm B were 90.5% vs. 81.3%. There was a significant correlation for DFS and OS in the two arms. There was no significant difference between adverse events with the two regimens.

Conclusions: In our research, less progression was found with Arm A as compared to Arm B. Adding of anthracyclines such as doxorubicin hydrochloride did not increase OS and DFS in triple negative breast cancer (TNBC) patients.

Key words: breast cancer, triple negative, carboplatin, docetaxel.

Contemp Oncol (Pozn) 2017; 21 (1): 83–89
DOI: https://doi.org/10.5114/wo.2017.66661

Introduction

Breast cancer (BC) is a chemosensitive tumour, and anthracyclines are among the most active cytotoxic agents in chemotherapy treatment [1]. Triple-negative breast cancer (TNBC) is diagnosed more frequently in younger and premenopausal women [2, 3], comprising 15–20% of all BCs [3, 4], and is defined by the lack of oestrogen and progesterone receptor expression and also human epidermal growth factor receptor 2(HER2) amplification [4, 5]. Chemotherapy is the basic treatment option for TNBC patients in the neoadjuvant, adjuvant, or metastatic settings. Despite the rather aggressive clinical behaviour of TNBC, about 30–40% of patients achieve a pathological complete response (CR) with no histological evidence of disease at the time of surgery after neoadjuvant chemotherapy, and those patients have much higher rates of survival [6, 7]. The differences in clinical response and survival after neoadjuvant chemotherapy suggest that a subset of TNBC may be inherently insensitive to cytotoxic chemotherapy [8]. Systemic adjuvant treatment with chemotherapy is almost always indicated [9]. Adjuvant therapy aids surgery in affecting cure of BC. Adjuvant treatments for BC can include chemotherapy, hormonal therapy, HER2-directed therapies, and radiation [10]. Adjuvant therapy for BC increases progression-free survival (PFS) and overall survival (OS), but does not benefit all BC patients [11]. Anthracyclines [12, 13] and taxanes [13] are the most active and widely used chemotherapeutic agents for BC, but few data on the role of anthracyclines are available [14]. Anthracyclines are the drug class most closely associated with acute and late cardiac toxicity [15]. Herein, we reported the efficacy of adjuvant docetaxel and carboplatin with or without doxorubicin hydrochloride and cyclophosphamide in treating women with stage I–III triple negative BC in Iran.

Material and methods

Participants

This randomised phase II clinical trial was approved by the Ethics Committee of Kermanshah University of Medical Sciences, Kermanshah, Iran, and registered at http://www.irct.ir (registration number: IRCT2016070325791N2).

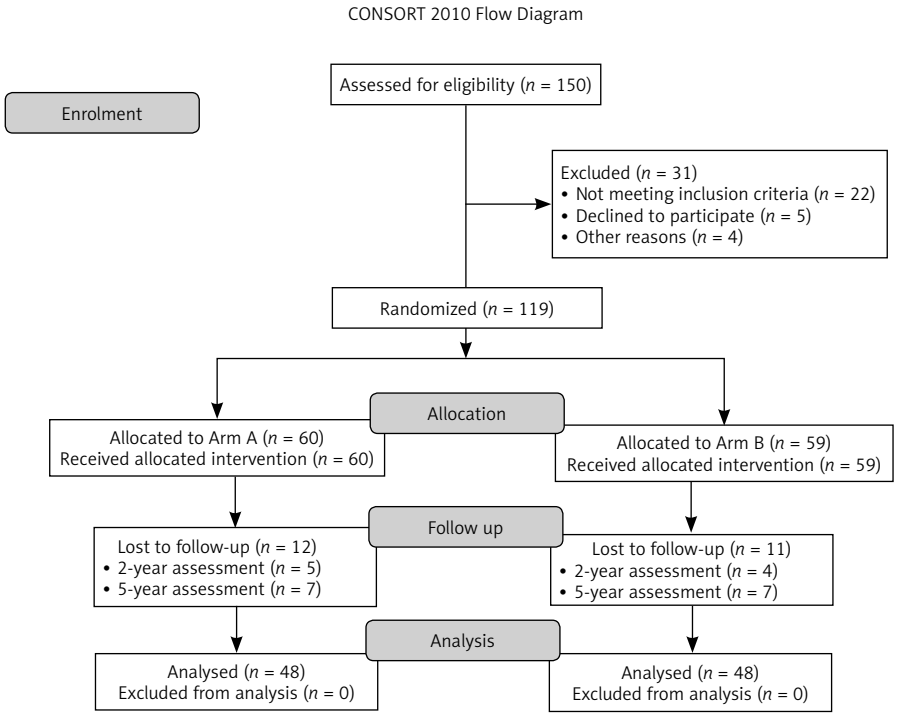


Fig. 1. Consort flow chart

The range of participants' recruitment was from Feb 2011 to Jul 2011. During Aug 2011 to Sep 2016 the patients referred to the Breast Cancer Research Centre, Tehran University of Medical Sciences, Tehran, Iran. All patients gave written, informed consent before enrolment. Figure 1 shows the consort flow chart, which details the number of participants. The patients were divided into two groups: 60 patients in Arm A, treated with adjuvant docetaxel 70 mg/m^2 and carboplatin AUC = 7 every three weeks with granulocyte colony-stimulating factor (G-CSF) for six courses; and 59 patients in Arm B, treated with adjuvant doxorubicin hydrochloride 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every three weeks with G-CSF for 4 courses followed by docetaxel 70 mg/m^2 and carboplatin AUC = 7 every three weeks with G-CSF for four courses. The mutations of BRCA 1 and 2 were not checked due to their high price, and all patients did R0 resection. The OS was defined as the time from randomisation to death, irrespective of cause, and disease-free survival (DFS) was defined as the time from randomisation to local or distant relapse or death.

Criteria

Inclusion criteria: The female patients with age > 20 years, the tumour must have been determined to be HER2-negative (IHC1+ or IHC2+ and fluorescence *in situ* hybridisation [FISH]-negative); the tumour must have been determined to be hormone receptor-negative (ER- and PR-negative).

Exclusion criteria: T4 tumours including inflammatory BC; definitive clinical or radiologic evidence of metastatic disease; required imaging studies (computed tomography [CT] scan and bone scan) must have been performed within 90 days prior to randomisation; any previous history of ipsilateral invasive BC or ipsilateral DCIS; history of non-breast malignancies (except for in situ cancers treated only by local excision and basal cell and squamous cell carcinomas of the skin) within 5 years prior to randomisation; active or history of cardiac disease, patients known to be human immunodeficiency virus (HIV) positive, hepatitis B or hepatitis C with abnormal liver function tests; history of hospitalisation in the past 12 months for diabetes; and pregnancy or lactation at the time of study entry.

Statistical analyses

The analysis was done using SPSS 19 software (IBM, SPSS Inc., Chicago, IL, USA). The categorical and continuous data were analysed using χ^2 and t-test, respectively. Outcomes for this study were OS, DFS, and toxicity. Comparison between OS and DFS for the two arms was checked by GraphPad Prism 5 software and the log-rank test was used to compare the Kaplan-Meier curves for OS and DFS. Also, Cox's proportional hazard regression analysis was used to check the effects of various parameters on the primary analysis. A p-value < 0.05 was considered to be statistically significant.

Results

A total of 119 patients were randomly enrolled to two arms (60 patients in arm A and 59 patients in arm B). The baseline characteristics of patients in the two arms are shown in Table 1. The mean follow-up was 40 months at the time of treatment analysis. There were no significant differences between the two arms regarding the start of intervention. In the patients with lymph node involve-

ment, a minimum of three and maximum of 15 lymph nodes were involved.

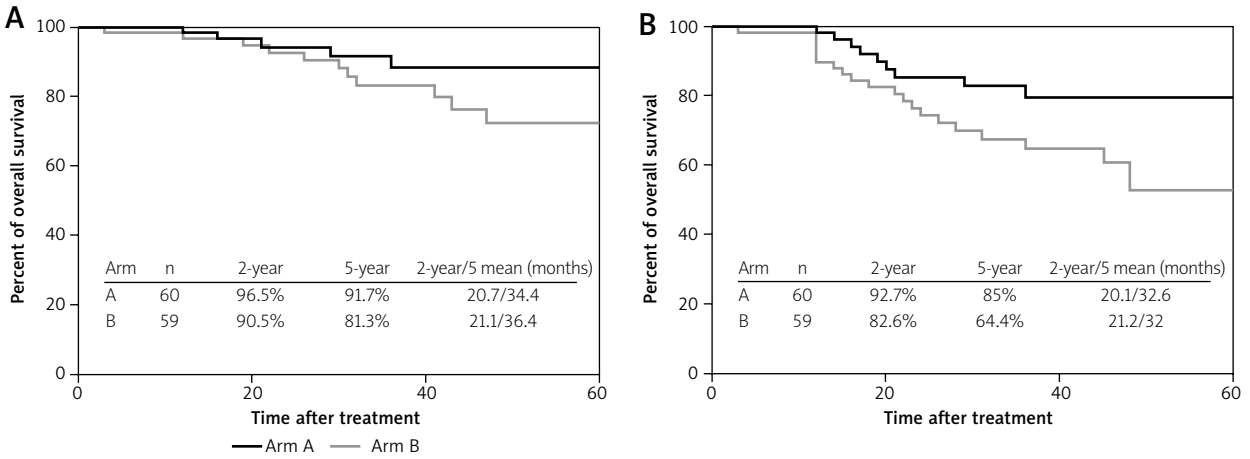
The two-year OS rate was 96.5% vs. 90.5%, and also the mean OS was 20.7 months vs. 21.1 months (arm A vs. arm B), and there was no significant difference between the two arms (hazard ratio [HR] 2.56, 95% CI: 0.58–11.30; p = 0.21) (Fig. 2). In addition, the 5-year rate and mean OS were 91.7% vs. 81.3% and 34.4 vs. 36.4 months (arm A vs. arm B); there was no significant difference between the two arms (HR 2.04, 95% CI: 0.76–5.43; p = 0.17). The 2-year rate and the mean DFS for arm A vs. arm B were 92.7% vs. 82.6% and 20.1 months vs. 21.2 months; there was no significant difference between the two arms (hazard ratio [HR] 2.09, 95% CI: 0.67–6.52; p = 0.20), whereas, the 5-year rate and the mean DFS was 85% vs. 64.4% and 32.6 vs. 32 months (arm A vs. arm B); there was significant difference between the two arms (HR 2.31, 95% CI: 1.13–4.73; p = 0.028).

Cox's proportional hazard regression analysis was used to evaluate the effects of various parameters on the primary analysis. There were no unfavourable predictors for OS (Table 2), but age and menopausal status were unfavourable predictors for DFS (Table 3).

Table 1. The correlation between variables in two arms

Variables	Arm A* (n = 60)	Arm B** (n = 59)	P-value
Age, year			
Mean ± SD	45.7 ±13.7	44.1 ±10	0.490
Range	24–85	21–72	
< 50	41 (68.3)	40 (67.8)	0.553
Menopausal status			0.474
Premenopausal	41 (68.3)	39 (66.1)	
Postmenopausal	19 (31.7)	20 (33.9)	
Laterality			0.326
Right	25 (41.7)	28 (47.5)	
Left	35 (58.3)	31 (52.5)	
Tumour size, cm			0.135
< 2	20 (33.3)	12 (20.3)	
2–5	34 (56.7)	35 (59.3)	
> 5	6 (10)	12 (20.3)	
Lymph node invasion			0.060
Yes	24 (40)	33 (55.9)	
No	36 (60)	26 (44.1)	
Vascular invasion			0.424
Yes	12 (20)	10 (16.9)	
No	48 (80)	49 (83.1)	
Perineural invasion			0.511
Yes	5 (8.3)	4 (6.8)	
No	55 (91.7)	55 (93.2)	
Stage			0.102
I	12 (20)	10 (16.9)	
II	41 (68.3)	33 (55.9)	
III	7 (11.7)	16 (27.1)	
Histological Grade			0.584
I	8 (13.3)	5 (8.5)	
II	23 (38.3)	27 (45.8)	
III	29 (48.3)	27 (45.8)	
Margin involvement			0.489
Yes	4 (6.7)	5 (8.5)	
No	56 (93.3)	54 (91.5)	
Radiotherapy			0.127
Yes	55 (91.7)	49 (83.1)	
No	5 (8.3)	10 (16.9)	
Type of pathology			0.187
IDC	52 (86.7)	55 (93.2)	
ILC	0	1 (1.7)	
MC	8 (13.3)	3 (5.1)	
Ki-67, %			
Mean ± SD	42.2 ±28.4	42.8 ±25	0.918
≤ 20	19 (31.7)	14 (23.7)	0.223

* Arm A – docetaxel and carboplatin
*** Arm B – doxorubicin hydrochloride and cyclophosphamide followed by docetaxel and carboplatin*
SD – standard deviation; IDC – invasive ductal carcinoma; ILC – invasive lobular carcinoma; MC – medullary carcinoma



Arm A – docetaxel and carboplatin
Arm B – doxorubicin hydrochloride and cyclophosphamide followed by docetaxel and carboplatin

Fig. 2. A) Overall survival and B) disease-free survival of patients with triple negative breast cancer

Table 2. Multivariate survival analysis using Cox's regression model for affecting of variables on overall survival

Variables	*P*-value	HR	95% CI
Treatment arm, arm A vs. arm B	0.636	0.748	0.225–2.488
Menopause status, pre vs. postmenopausal	0.352	0.500	0.116–2.156
Age, ≥ 50 vs. < 50 years	0.085	0.277	0.064–1.194
Laterality, right vs. left	0.138	0.329	0.076–1.428
Tumour size, < 2 vs. 2–5 or > 5 cm	0.275	0.581	0.219–1.539
LN involvement, yes vs. no	0.805	0.830	0.188–3.664
Vascular invasion, yes vs. no	0.496	2.012	0.269–15.061
Perineural invasion, yes vs. no	0.756	0.694	0.070–6.931
Stage, I vs. II or III	0.370	1.889	0.470–7.597
Grade, I vs. II or III	0.278	0.554	0.191–1.610
Margin involvement, yes vs. no	0.781	0.750	0.099–5.695
Radiotherapy, yes vs. no	0.121	3.095	0.742–12.910
Type of pathology, IDC vs. LC or MC	0.975	–	–
Ki-67 status, ≤ 20 vs. > 20%	0.326	1.943	0.516–7.311

**HRs (hazard ratios) are presented as the risk of the right-side category (i.e. right side of vs. in Parameter column) to the left-side category (i.e. left side of vs.) LN – lymph node; CI – confidence interval; DC – invasive ductal carcinoma; LC – lobular carcinoma; MC – medullary carcinoma. Arm A – docetaxel and carboplatin; Arm B – doxorubicin hydrochloride and cyclophosphamide followed by docetaxel and carboplatin*

The comparison of adverse events for the two arms is shown in Table 4. Although thrombocytopaenia was higher in arm A compared with arm B, the difference was not significant ($p > 0.05$). Therefore, the side effects were similar in the two groups.

Discussion

Both arms in this study had carboplatin because we wanted to check the efficacy of adding of an anthracycline (doxorubicin) to the taxane regimen in stage I-IIITNBC patients that more patients were stages I and II (88.3% arm A and 72.9% arm B). The results showed that adding anthracycline to the chemotherapy regimen did not increase the 5-year OS (HR 2.04, 95% CI: 0.76–5.43; $p = 0.17$) and DFS (HR 2.31, 95% CI: 1.13–4.73; $p = 0.028$). Although grade 3-4 neutropaenia and cardiotoxicity was more in anthracycline-based regimen and also thrombocytopaenia in the regimen without anthracycline, the differences were not significant. Patients suffering from TNBC have a poor prognosis mainly because no standard treatment is currently available [16]. Anthracyclines and taxanes are the most active and widely used chemotherapeutic agents in hormone receptor-negative patients for treating BC and those whose disease progresses while they are taking hormone therapy [17]. These agents are commonly used in the adjuvant setting, either in combination or sequentially [18]. Anthracycline use in early-stage BC has been steadily declining, especially for patients with stage I/II or

Table 3. Multivariate survival analysis using Cox's regression model for affecting of variables on disease-free survival

Variables	*P*-value	HR	95% CI
Treatment arm, arm A vs. arm B	0.070	0.444	0.184–1.070
Menopause status, pre vs. postmenopausal	0.022	0.283	0.097–0.831
Age, ≥ 50 vs. < 50 years	0.007	0.248	0.091–0.679
Laterality, right vs. left	0.603	0.779	0.303–2.001
Tumour size, < 2 vs. 2–5 or > 5 cm	0.456	0.752	0.355–1.592
LN involvement, yes vs. no	0.320	0.607	0.227–1.624
Vascular invasion, yes vs. no	0.128	2.706	0.752–9.742
Perineural invasion, yes vs. no	0.566	0.628	0.128–3.071
Stage, I vs. II or III	0.454	1.368	0.602–3.106
Grade, I vs. II or III	0.235	0.640	0.307–1.337
Margin involvement, yes vs. no	0.132	2.902	0.726–11.600
Radiotherapy, yes vs. no	0.114	2.399	0.810–7.106
Type of pathology, DC vs. LC or MC	0.604	1.190	0.616–2.297
Ki-67 status, ≤ 20 vs. > 20%	0.144	2.084	0.777–5.588

**HRs (hazard ratios) are presented as the risk of the right-side category (i.e. right side of vs in Parameter column) to the left-side category (i.e. left side of vs). LN – lymph node; CI – confidence interval; DC – invasive ductal carcinoma; LC – lobular carcinoma; MC – medullary carcinoma. Arm A – docetaxel and carboplatin; Arm B – doxorubicin hydrochloride and cyclophosphamide followed by docetaxel and carboplatin*

Table 4. The adverse events for treatment regimens (two arms)

Adverse events	Arm A	Arm B	*P*-value
Grade 3–4 vomiting	1 (1.7)	1 (1.7)	> 0.05
Grade 3–4 mucositis	1 (1.7)	1 (1.7)	> 0.05
Grade 3–4 diarrhoea	1 (1.7)	1 (1.7)	> 0.05
Grade 3–4 neutropenia	1 (1.7)	3 (5.1)	> 0.05
Grade 3–4 thrombocytopenia	6 (10.2)	2 (3.4)	> 0.05
Cardiotoxicity	1 (1.7)	2 (3.4)	> 0.05
Hypersensitivity reaction	1 (1.7)	1 (1.7)	> 0.05
Peripheral neuropathy	2 (3.4)	1 (1.7)	> 0.05
Sepsis	0	1 (1.7)	> 0.05

Arm A – docetaxel and carboplatin, Arm B – doxorubicin hydrochloride and cyclophosphamide followed by docetaxel and carboplatin

HER2-positive disease, and the overall analysis reported that 80% of chemotherapies were anthracycline-based in these patients from 2000 to 2010. Then, the use of anthracycline-based regimens reduced 20% in stage I/II and 6% in stage III patients, while non-anthracycline regimens (cyclophosphamide, methotrexate, and fluorouracil) increased from 5% to 35% [19]; one study from Giordano *et al*. [20] confirmed these results. Multiple trials in the 1980s and 1990s demonstrated that an anthracycline-based chemotherapy regimen was associated with lower rates of BC recurrence and improved survival when compared with non-anthracycline regimens [12]. The addition of taxanes to anthracycline-based chemotherapy as adjuvant therapy decreases the risk of recurrence (4.6%) and overall mortality (3.2%) [21]. One trial [22] compared docetaxel plus cyclophosphamide (TC) with a first-generation anthracycline regimen (doxorubicin plus cyclophosphamide, or AC) and reported superior OS for the patients treated with TC. The patients treated with TC had more fever and neutropaenia (5% vs. 2.5%), but congestive heart failure developed in one patient treated with AC and none with TC. Smith *et al*. [23] demonstrated that anthracyclines increased the risk of clinical cardiotoxicity (5.43 fold), subclinical cardiotoxicity (6.25 fold), any cardiotoxicity (2.27 fold), and the risk of cardiac death (4.94 fold) compared with non-anthracycline regimens. The trial by Chen *et al*. [24] reported that patients with neoadjuvant treatment of TNBC or HER2-positive with docetaxel, anthracycline, and cyclophosphamide (TEC) had a higher rate of neutropaenia and leukopaenia. TEC treatment had a better survival outcome and a trend of higher complete response rate compared with TC in this trial setting, especially in TNBC subtype, which deserves further validation. On univariate analysis [25], patients who had received prior adjuvant chemotherapy with anthracyclines had a significantly lower probability of response than patients who did not: 43% vs. 58% (p = 0.02). The patients who did not receive adjuvant chemotherapy had a longer survival time than the patients previously treated

with anthracycline-based (21.1 vs. 15.8 months) adjuvant chemotherapy. Also, multivariate analysis confirmed adjuvant chemotherapy with anthracyclines to be among the strongest prognostic factors associated with both poor PFS and OS. Piccart-Gebhart *et al*. [26] reported that taxanes were significantly worse compared with single-agent anthracyclines in terms of PFS, but not in terms of response rates or survival. Taxane-based combinations were significantly better than anthracycline-based combinations in terms of response rates and PFS, but not in terms of survival. A taxane-based treatment regimen may be a better option than a combined taxane/anthracycline regimen for patients with advanced BC because it produces equivalent clinical outcomes and has lower toxicity compared to other similar regimens [27]. Five randomised studies compared anthracyclines (doxorubicin, epirubicin, pegylated liposomal doxorubicin) vs. other drugs, but it did not reach the statistical significance for the endpoints of response rate, time to progression, and OS, suggesting a minor role for anthracycline in the therapeutic strategy of pretreated metastatic BC patients [28–32]. Although doxorubicin has become one of the most effective chemotherapeutic agents, it was noted early on that its use was complicated by the development of heart failure [33, 34]. Multiple large cohort trials and meta-analysis studies showed that the addition of a taxane to an anthracycline-based regimen in the adjuvant setting has improved the PFS and OS in patients with early BC. According to these, the use of anthracyclines as initial chemotherapy in early BC may continue to be replaced by taxane-based and novel regimens in the future [35]. We need a prospective, more advanced trial with clearly more rigorous reporting and data monitoring (a larger group of patients).

In conclusion, less progression was found with arm A as compared to arm B. Therefore, the addition of anthracyclines such as doxorubicin hydrochloride did jot increase OS and DFS in TNBC patients. Due to the number of TNBC patients in stages I and II, we can easily omit anthracyclines in the treatment of these patients.

The authors declare no conflict of interest.

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Submitted: 8.12.2016
Accepted: 29.01.2017