The Effect of Neoadjuvant vs Adjuvant Chemotherapy on Final Outcome of Patients with Triple Negative Breast Cancer

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Abstract

Background: Triple negative breast cancer (TNBC) accounts for about 10% to 20% of breast cancers, does not respond to endocrine treatment, and is more aggressive. Two chemotherapy methods suggested include neoadjuvant chemotherapy (NAC), performed before surgery, and adjuvant chemotherapy (AC), performed after surgery. In order to determine whether the choice of chemotherapy method has any impact on patients’ outcome, the present study aimed to compare the overall survival (OS) and disease-free survival (DFS) of TNBC patients with a 10-year follow-up.

Methods: The present study aimed to investigate the effect of neoadjuvant versus adjuvant chemotherapy on the final outcome of patients with TNBC. Women with TNBC stages II and III who referred to the Cancer Research Center of Shahid Beheshti University of Medical Sciences during 2000 and 2020 were included (N = 237) and visited or called by phone to obtain their consent and complete their information. The participants were categorized into 2 groups according to the treatment protocol they received; one group received NAC (N = 85) and the other group received AC (N = 188); patients’ age, tumor's grade and stage, lymphovascular invasion (LVI), DFS, and OS were compared between the 2 treatment types. For the statistical analysis, the statistical software IBM SPSS Statistics for Windows, Version 24.0. (IBM Corp) was used. All tests were 2-sided and P values < 0.050 were considered statistically significant.

Results: The frequency of pathologies, LVI, and type of surgery was not different between the groups (p = 0.543, p = 0.352, p = 0.935), while the frequency of age categories and tumor grade was significantly different between the groups (p = 0.003, p = 0.001). Ten-year OS and DFS were not different between the groups (p = 0.771, p = 0.506). The Multivariate Cox analysis results showed clinical stage, pathologic grade, age >70, and LVI as significant predictors of death.

Conclusion: These results showed that the choice of chemotherapy method, performed before or after surgery, does not influence the 10-year OS and DFS of TNBC patients.

Keywords: Breast Cancer, Triple Negative Breast Cancer, Neoadjuvant Therapy, Chemotherapy, Adjuvant, Disease-Free Survival, Survival Rate

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Introduction

Breast cancer is the most common type of cancer worldwide with an incidence of about 2.1 million women worldwide in 2018; it is the first cause of cancer-related death among women (1). The national databases of Iran report its incidence at 33.21 per 100,000 women, mortality rate of 14.2 per 100,000, and 5- and 10-year survival rate of 81% and...
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77%, respectively (2, 3). Despite the decreasing trend in Europe (4), the mortality rate of breast cancer vary according to disease characteristics, such as stage, grade, lymphovascular invasion (LVI), metastasis, and type of breast cancer (5).

Risk stratification and treatment choice depend predominantly on the tumor’s characteristics, especially the molecular subtypes (6). About 10% to 20% of cases are negative for the 3 receptors (estrogen, progesterone, and human epidermal growth factor receptor 2), known as triple-negative breast cancer (TNBC), the treatment of which is more challenging; chemotherapy is considered the main treatment in these patients (7).

TNBC is more common in younger women and some races, like African American and Hispanic women (consisting about 40% of all breast cancer types) (8). Some variants are biologically more aggressive, have higher risk of lymphocytic infiltration, distant metastases, high grade, and large tumors; thus, the patients’ prognosis remain poor (9), while some suggest that TNBC respond to chemotherapy better than other subtypes. Chemotherapy can be given to the patients either before surgery, known as neoadjuvant chemotherapy (NAC), aimed to reduce the tumor size and lymph node involvement to make it more operable, or after surgery, known as adjuvant chemotherapy (AC) (10). Some have suggested that NAC can improve patients’ survival, especially in cases with pathologic complete response (PCR) (11-13), while the meta-analysis of randomized clinical trials has indicated no difference in distant metastasis and mortality rates between these 2 types, although NAC resulted in a higher rate of local metastasis (14). Due to the discrepancies in the results of previous studies and the lack of evidence in this regard in our country, the present study aimed to compare the overall survival (OS) and disease-free survival (DFS) of TNBC patients with a 10-year follow-up.

Methods

All patients who referred to the Cancer Research Center of Shahid Beheshti University of Medical Sciences (SBMU) during 2000 and 2020 and were diagnosed with TNBC were considered as the study population. The protocol of the study was approved by the ethics committee of the Cancer Research Center of Shahid Beheshti University of Medical Sciences (code: IR.SBMU.CRC.REC.1399.034).

Of 3210 patients with breast cancer without ductal carcinoma in situ, the results of IHC showed TNBC in 372 cases (11.58%), included into the study. Patients with TNBC stage I and IV (N = 99) were excluded from the study (as patients with stage I did not require chemotherapy and all patients with stage IV were scheduled for chemotherapy); therefore, 273 patients with TNBC stage II or III consisted the final sample of the present study. The researcher visited or called the patients, explained the study objectives to the patients or their family members, and asked for their consent for participation. After obtaining a verbal consent from the patients or their parents (in case the patient passed away), the researcher asked about the missing information. The recorded information included patients’ age, tumor’s grade and stage, LVI, date of diagnosis, and date of recurrence or death (for estimation of OS and DFS) for each patient. OS was defined as the time from the date of diagnosis until the date of the last follow-up or death (due to any reason). Disease-free survival (DFS) was defined as the time from the date of diagnosis until the date of recurrence. Also, PCR of NAC was recorded according to the results of pathologic report.

The participants were categorized into 2 groups according to the chemotherapy protocol they received, selected by the surgeon according to the disease stage (tumor’s size, breasts’ size, and lymph node involvement); group 1 received NAC before surgery (N = 85) and group 2 received AC after surgery (N = 188). Chemotherapy regimen was similar in both groups and included a combination of taxane- and anthracycline-based regimens. The type of surgery included breast conserving surgery (BCS) or modified radical mastectomy (MRM), decided by the surgeon, according to tumors and breasts’ size, as well as patients’ conditions. The groups were similar in terms of lymph node involvement.

Statistical Analysis

Results of the categorical variables were described by percentage and compared between the 2 groups using a chi square test. Age was the only numeric variable in this study that had a normal distribution; thus, it was presented by mean ± standard deviation and compared between the 2 groups using an independent samples t test. The Kaplan Meier method was used for estimation of OS and DFS and the log-rank test for comparison of the survival rates between the 2 study groups (NAC and AC). Prognostic factors affecting the survival rate were predicted by applying the Cox proportional hazard model. For the statistical analysis, the statistical software IBM SPSS Statistics for Windows, Version 24.0. (IBM Corp) was used. All tests were 2-sided and P values 0.05 were considered statistically significant.

Results

Among 273 women, 85 received NAC before surgery and 188 AC after surgery. Mean ± syandard deviation of participants’ age was 42.93 ± 12.14 and 47.97 ± 11.73 years, respectively. The frequency of pathologies, LVI, disease stage, and type of surgery were not different between the groups (p = 0.543, p = 0.352, p = 0.891, p = 0.935), while the frequency of age categories and tumor grades were significantly different between the groups (P = 0.003 and p = 0.001; Table 1). The majority of patients in AC group had grade III (63.8%), while more than half of the NAC group had grade II cancer (p = 0.001; Table 1). In NAC group, 6 patients in clinical stage II and 4 patients in clinical stage III had PCR.

The Kaplan Meier estimation of 5 and 10-year OS and DFS showed no significant difference between the groups (Figs. 1 and 2).

Five-year OS for NAC and AC were estimated at 79% and 84% and 10-year OS at 79% and 72%, respectively (p = 0.771) (Fig. 1). Five-year DFS for NAC and AC were estimated at 90% and 88% and 10-year DFS at 90% and
The univariate cox proportional hazard model analysis performed on age categories, type of chemotherapy, type of surgery, clinical stage, pathologic grade, and LVI showed no significant difference between the hazard of the type of chemotherapy and surgery type; however, age categories, clinical stage, pathologic grade, and LVI showed significant differences between diverse categories. The multivariate cox analysis, performed on the groups different on univariate analysis, showed significant differences between the hazard of various categories according to clinical stage, pathologic grade, and LVI. Prognosis was worse in the age group >70 years, compared with other age groups, while the hazards of other age groups were not different (Table 2). The mean duration of the follow-up was 59.13 months in AC group and 52 months in NAC group without significant differences between the groups (p = 0.264).

### Discussion

In the present study, the results of the retrospective investigation of patients with breast cancer showed the prevalence of TNBC at 11.58%, which is consistent with the overall rate of 10% to 20%, reported previously (15) and the results of the study by Abdollahi et al in Tehran, reporting TNBC in 14% of cases (16), although the results of national registries in Iran have not reported breast cancer subtypes separately, as far as the authors are concerned (17-19).

TNBC is biologically more aggressive with a lower OS compared with non-TNBC patients (20). Chemotherapy is the mainstay of treatment for TNBC and patients with stages II and III can receive chemotherapy either before or after surgery, NAC or AC, according to the surgeon’s preference and decision (21). For studying the effect of treatment type on patients’ survival rates, we allocated the patients into 2 groups, according to the type of chemotherapy.
they received, decided by the physician and according to
disease characteristics. The results of our study showed that
OS and DFS of the 2 groups were not different, while the
disease stage and tumor grade had significant effects on pa-
tients’ OS, based on the results of the cox regression anal-
ysis. These results are in line with the results of a meta-
analysis of 4756 women that indicated no difference in dis-
tistant metastasis and mortality rates between these 2 types of
chemotherapies in a median follow-up of 9 years (14). Nev-
evertheless, in another meta-analysis of 36,480 TNBC pa-
tients, the results showed worse OS in NAC group, com-
pared with AC, after a median follow-up of 4.12 years (HR =
1.59) (22), which is contrary to the results of the present
study, although the duration of follow-up differed and we
reported 10-year outcomes for all patients. Therefore, the
results of studies are controversial in this regard. In the
study on the National Cancer Database of the United States,
the results indicated significantly worse 5-year OS in NAC
versus AC patients (73.4% vs 76.8%) (13), which is close to
that reported by the present study (79% and 84%). Ac-
cording to the results of studies, several factors play a role
in patients’ survival, variation of which can result in dis-
crepancy in the results of studies.

The results of the present study showed that age was a
significant predictor of patients’ prognosis and patients
aged 70 years old had a worse prognosis compared with
other age groups. Also, disease stage and grade were sig-
ificant predictors of patients’ prognosis. These results are
in line with the previous evidence referring to the worse
prognosis in the elderly and in higher disease stage/grade
(23); however, the main objective is focused on amendable
factors (24). One of the factors that has been considered of
significant importance in the patients’ survival and recur-
rence is the PCR after NAC and it has been suggested that
patients with PCR have a significantly better 5-year OS
and DFS of the 2 groups were not different, while the
cancers mentioned earlier.

One of the limitations of the present study was the retro-
spective nature of the study, which resulted in loss of some
cases, because of the lack of access to the patients. Moreo-
ver, patients’ enrollment into the study was not randomized
and we included all patients who referred to our center by
census method, according to the inclusion criteria. Also, the
allocation of patients into the 2 groups was non-random, as
this was a retrospective analysis and the treatment was
based on the physician’s choice. It has to be considered that
the studied patients were selected among referrals to 1 cen-
ter in 1 city, and thus generalizing the results to the whole
population should be done with great caution.

Conclusion
These results showed that the choice of chemotherapy
method, performed before or after surgery based on the
physician’s choice, does not influence 5- and 10-year OS
and DFS of TNBC patients, and both methods resulted in
acceptable OS and DFS. Therefore, the chemotherapy
method should be chosen by the physician according to dis-
case characteristics and medical conditions of each patient
individually. Further studies are required in Iran for definite
conclusion about this statement.
Ethics Approval and Consent to Participate

The protocol of the study was approved by the Ethics Committee of Cancer Research Center of Shahid Beheshti University of Medical Sciences (code: IR.SBMU.CRC.REC.1399.034). Each patient who enters the university affiliated hospitals is informed on sharing their data for future researches.

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Conflict of Interests

The authors declare that they have no competing interests.

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