BMC Cancer

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The impact of carboplatin on pathologic complete response and survival based on HER2 low and HER2 zero status in triple negative breast cancer patients receiving neoadjuvant chemotherapy: a multicenter real-world analysis

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Abstract

Background and Objectives Triple-negative breast cancer (TNBC) has a poor prognosis, and neoadjuvant chemotherapy (NACT) is the standard treatment for locally advanced TNBC. In this study, we aimed to evaluate the efficacy of adding carboplatin to NACT regarding pathological complete response (pCR) and survival in the HER2-low and HER2-zero subgroups of TNBC patients.

Materials and Methods The study included 269 patients from five medical oncology clinics. Patients were divided into two groups: HER2-low ($n=152$, 56.5%) and HER2-zero ($n=117$, 43.5%). Among HER2-zero patients, 30 (25.6%) received carboplatin, while 38 (25.0%) HER2-low patients received carboplatin. The benefit of adding carboplatin to NACT regarding pCR and survival was assessed in both HER2-zero and HER2-low groups.

Results When patients were evaluated according to HER2 status, the pCR rates were significantly higher in the HER2-zero group compared to the HER2-low group (45.2% versus 23.7%, $p<0.001$). In the HER2-zero group, patients who received carboplatin had significantly higher pCR rates (63.3% versus 39.0%, $p=0.021$). Similarly, in the HER2-low group, adding carboplatin significantly increased the pCR rates (36.8% versus 19.3%, $p=0.028$). While carboplatin improved pCR rates in both HER2 subgroups, this benefit was not observed in patients with Grade 1 tumors, HER2 score 2-FISH negative tumors, or based on *BRCA* mutation status. Patients with pCR exhibited significantly prolonged DFS and OS ($p=0.002$, $p<0.001$, respectively).

Conclusions Our research demonstrates that the addition of carboplatin increases pCR rates in both HER2-zero and HER2-low patient cohorts. We suggest that carboplatin should be considered as an addition to standard

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neoadjuvant chemotherapy for eligible TNBC patients, regardless of HER2-zero or HER2-low status, when appropriate based on individual patient factors and toxicity considerations.

Keywords Triple negative breast cancer, HER2 status, Carboplatin, Neoadjuvant chemotherapy, Pathologic complete response

Introduction

Breast cancer (BC), comprising distinct subtypes with both notable differences and shared characteristics, is a heterogeneous disease and the most common cancer among women [1]. BC is traditionally categorized based on biomarker expression into major groups: hormone receptor-positive/human epidermal growth factor receptor 2 (HER2)-negative, HER2-positive, and triple-negative breast cancer (TNBC). While sharing some similarities, these subtypes exhibit markedly different molecular features, resulting in varied survival outcomes [2]. This classification is primarily based on estrogen receptor (ER), progesterone receptor (PR), HER2, with Ki67 percentage sometimes used as an additional marker, particularly in distinguishing luminal subtypes.

Triple-negative breast cancer (TNBC) is defined as the subgroup lacking both ER and PR receptors, as well as HER2 expression [2]. Additionally, TNBC generally has a high Ki-67 level [2]. Approximately 15% of patients diagnosed with BC have TNBC [3]. Compared to other subtypes, TNBC is more commonly seen in younger women and is characterized by its aggressive nature and limited treatment options, resulting in higher mortality [4].

In locally advanced TNBC patients, neoadjuvant chemotherapy (NACT) is the standard of care. Pathological complete response (pCR), defined as the absence of invasive cancer in both the breast and axillary lymph nodes after treatment, is a key endpoint. TNBC is more sensitive to chemotherapy than other subtypes, with 30–60% of patients achieving pCR after NACT [5, 6]. It has been shown that patients who achieve pCR after neoadjuvant treatment have better disease-free survival (DFS) and overall survival (OS) compared to those with residual tumor [5, 6].

Platinum agents, particularly carboplatin, have become an important component of NACT for TNBC. The BRIGHTNESS trial demonstrated that the addition of carboplatin significantly increased pCR rates in TNBC patients [7]. Similarly, the CALGB 40603 (Alliance) study showed that patients receiving platinum-based NACT exhibit higher pCR rates than those receiving standard NACT [8]. The addition of carboplatin to NACT has been associated with significant improvements in both OS and DFS [7, 8]. While the toxicity rates are higher with carboplatin, the side effects are considered manageable [7, 8]. More recently, the KEYNOTE-522 trial established that adding pembrolizumab to carboplatin-containing neoadjuvant chemotherapy significantly improved pCR rates and event-free survival in early TNBC, further highlighting the importance of optimizing neoadjuvant regimens [9].

HER2 is an important predictive and prognostic biomarker in breast cancer, found to be positive in 15–20% of patients [10]. Following the recognition of the importance of this receptor, several HER2-targeted drugs have been developed [11–13]. A breast tumor is considered HER2-positive if it has an immunohistochemistry (IHC) score of 3+ or IHC 2+/in situ hybridization (ISH) + [14]. Tumors with an IHC score of 0, IHC 1+, or IHC 2+/ISH- are classified as HER2-negative BC [15]. Effective treatments for HER2-positive patients have not shown similar efficacy in HER2-negative patients, who typically receive similar chemotherapy regimens [14, 15].

However, this perspective has shifted following the DESTINY-Breast 04 study, which evaluated trastuzumab deruxtecan [13]. In this study, tumors with an IHC score of 1+ or IHC 2+/ISH- were classified as HER2-low, while tumors with an IHC score of 0 were categorized as HER2-zero. The study demonstrated that treatment responses differed between these two groups [13]. This new classification has clinical implications beyond HER2-directed therapies, as it potentially identifies biologically distinct tumor subgroups. Subsequently, other studies have classified patients undergoing NACT according to their HER2 status [16–21]. However, the results of these studies in TNBC patients have been inconsistent, and a clear consensus has not been reached [15–20].

It is known that adding carboplatin to NACT increases the complete response rate and positively affects DFS and OS in TNBC patients [7, 8]. The biological rationale for exploring differential effects of carboplatin based on HER2 status stems from potential variations in *DNA* repair mechanisms and platinum sensitivity between these subtypes, even within the HER2-negative spectrum. However, no study in the literature has evaluated the efficacy of adding carboplatin to NACT in early-stage TNBC patients based on HER2 status.

In our institution, carboplatin was administered as part of NACT at a dose of AUC 5–6 every 3 weeks or AUC 1.5–2 weekly, along with standard anthracycline/cyclophosphamide and taxane-based regimens. The decision to include carboplatin was based on patient

characteristics including age, performance status, and risk assessment. In this study, we aimed to evaluate the impact of adding carboplatin to NACT on pCR rates in TNBC patients according to their HER2 status (HER2-low and HER2-zero) and to investigate whether it positively affects DFS and OS.

Materials and methods

Study population and study design

Five oncology clinics from Turkey participated in our study. Patients included were diagnosed with locally advanced TNBC with known HER2 status, had undergone NACT, and had surgery with available pathology reports between June 1, 2010, and December 1, 2023. Locally advanced breast cancer was defined as stage II or III disease according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system. Patients who experienced disease progression during NACT and were not operated on, those under 18 years of age, those with metastatic disease at diagnosis, and patients with a concurrent active second malignancy (hematological or solid) were excluded from the study. Additionally, patients who, for any reason, did not receive taxane (docetaxel or paclitaxel) either before or after doxorubicin or epirubicin/cyclophosphamide were also excluded. Due to these criteria, 28 patients were excluded from the study for either not receiving anthracycline-based chemotherapy or taxane or due to incomplete data.

Demographic and clinicopathologic characteristics of the patients were obtained by retrospective review of patient files. Table 1 outlines the demographic and clinical characteristics of the patients based on their pCR status.

Definition of biomarkers and pathological assessment

Estrogen receptor (ER) and progesterone receptor (PR) status were determined by immunohistochemistry (IHC). Tumors with ≥ 1% nuclear staining were considered positive for ER and PR. HER2 status was assessed by IHC and/or fluorescence in situ hybridization (FISH). HER2 positivity was defined as IHC 3+ or IHC 2+ with FISH amplification. For the purpose of this study, HER2-zero was defined as IHC score 0, while HER2-low was defined as IHC score 1+ or IHC score 2+/FISH negative.

Ki-67 proliferation index was measured in the areas of highest proliferative activity ("hot spots") with at least 500 tumor cells counted per case. The value represents the percentage of positively stained cells, with ≥ 50% considered high Ki-67 in our study.

Pathological complete response (pCR) was defined as the absence of invasive cancer in both the breast and axillary lymph nodes (ypT0/is ypN0) after completion of neoadjuvant therapy.

Treatment details

All patients received an anthracycline (doxorubicin 60 mg/m^2 or epirubicin 90 mg/m^2) and cyclophosphamide (600 mg/m^2) combination every 3 weeks for 4 cycles, followed by or preceded by a taxane regimen (paclitaxel 80 mg/m^2 weekly for 12 weeks or docetaxel 75–100 mg/m^2 every 3 weeks for 4 cycles).

Sixty-eight patients received carboplatin in addition to the standard regimen. Carboplatin was administered either at AUC 5–6 every 3 weeks along with docetaxel or at AUC 1.5–2 weekly with paclitaxel. The decision to add carboplatin was based on factors including patient age, performance status, tumor burden, and physician preference. None of the patients received pembrolizumab or other immune checkpoint inhibitors as the study period largely predated the routine implementation of immunotherapy in early TNBC following the KEYNOTE-522 trial. Information on PD-L1 status was not available for the majority of patients.

After surgery, patients with residual disease who were candidates for further therapy received additional treatment according to the institutional guidelines and physician discretion. Data regarding specific post-operative adjuvant therapies, including capecitabine use for non-pCR cases based on the CREATE-X study, were not consistently available for analysis.

The distribution of patients receiving carboplatin was similar across participating centers, minimizing potential bias due to differences in institutional practices. *BRCA* mutation testing was performed in a subset of patients ($n = 64$) based on clinical indications and availability, recognizing that this represents a potential confounding factor in our analysis.

Ethical statement

This retrospective, multicenter study was approved by the ethics committee of Kartal Dr Lutfi Kırdar City Hospital. The ethics committee approval date was November 29, 2023, with decision number 2023/5 l4/26214. All procedures performed during the collection of data, patient file review, and study execution adhered strictly to institutional and/or national research committee ethical standards and the 1964 Helsinki Declaration and subsequent amendments.

Statistical analysis

For the descriptive statistics of the data, mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used. The distribution of variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. The Mann–Whitney U test was used to analyze independent quantitative data that were not

Table 1 Demographic and clinical characteristics of patients based on pCR status

Variable	pCR (-)	pCR (+)	p
Age at Diagnosis (years, Mean ± SD, Median)	50.4 ± 12.4, 50.0	48.6 ± 10.3, 47.0	0.261[m]
Gender (n, %)			
Female	179 (99.4%)	88 (98.9%)	0.553[x²]
Male	1 (0.6%)	1 (1.1%)	
Menopausal Status (n, %)			
Premenopausal	93 (51.7%)	49 (55.1%)	0.600[x²]
Postmenopausal	87 (48.3%)	40 (44.9%)	
ECOG Performance Score (n, %)			
0	166 (92.2%)	79 (88.8%)	0.349[x²]
I-II	14 (7.8%)	10 (11.2%)	
Ki67 at Diagnosis (≥ 50%) (Mean ± SD, Median)	59.6 ± 21.9, 60.0	66.0 ± 19.5, 70.0	0.030[m]
BRCA Status (n, %)			
Negative	22 (59.5%)	15 (55.6%)	0.197[x²]
Positive	15 (40.5%)	12 (44.4%)	
Inflammatory Breast Cancer (n, %)			
Negative	171 (95.0%)	89 (100.0%)	0.032[x²]
Positive	9 (5.0%)	0 (0.0%)	
Histopathological Diagnosis (n, %)			
Invasive Carcinoma (Ductal/NST)	160 (88.9%)	79 (88.7%)	0.422[x²]
Invasive Lobular Carcinoma	6 (3.3%)	1 (1.1%)	
Others	14 (7.8%)	9 (10.1%)	
Tumor Grade at Diagnosis (n, %)			
Grade 1	7 (3.9%)	3 (3.4%)	0.001[x²]
Grade 2	59 (32.8%)	11 (12.4%)	
Grade 3	114 (63.3%)	75 (84.3%)	
HER2 Status Before Neoadjuvant Therapy (n, %)			
Negative (Score 0)	64 (35.6%)	53 (59.6%)	0.001[x²]
Negative (Score 1)	78 (43.3%)	27 (30.3%)	
Negative (Score 2, FISH Negative)	38 (21.1%)	9 (10.1%)	
Clinical Tumor Stage (n, %)			
T1	2 (1.7%)	18 (20.2%)	0.063[x²]
T2	115 (63.9%)	58 (65.2%)	
T3	32 (17.8%)	10 (11.2%)	
T4a	5 (2.8%)	0 (0.0%)	
T4b	2 (1.1%)	3 (3.4%)	
T4d	5 (2.8%)	0 (0.0%)	
Lymph Node Stage (n, %)			
N0	39 (21.7%)	28 (31.5%)	0.168[x²]
N1	99 (55.0%)	48 (53.9%)	
N2	31 (17.2%)	11 (12.4%)	
N3	11 (6.1%)	2 (2.2%)	
Clinical Stage (n, %)			
1B	5 (2.8%)	5 (5.6%)	0.101[x²]
2A	3 (1.7%)	0 (0.0%)	
2B	43 (23.9%)	29 (32.6%)	
3B	77 (42.8%)	36 (40.4%)	
3 C	52 (28.9%)	19 (21.3%)	
HER2 Status (n, %)			
HER2-zero	64 (35.6%)	53 (59.6%)	< 0.001[x²]

Table 1 (continued)

Variable	pCR (-)	pCR (+)	p
HER2-low	116 (64.4%)	36 (40.4%)	
Carboplatin (n, %)			
Non-Recipient	145 (80.6%)	56 (62.9%)	0.002[x2]
Recipient	35 (19.4%)	33 (37.1%)	

Statistical Tests: [m]Mann-Whitney U test, [x2]Chi-square test (Fisher's exact test)

Abbreviations: pCR Pathological Complete Response, *Mean* Arithmetic Mean, *SD* Standard Deviation, *ECOG* Eastern Cooperative Oncology Group, *NST* No Special Type, *FISH* Fluorescence In Situ Hybridization

normally distributed. The chi-square test was used to analyze independent qualitative data, and when the conditions for the chi-square test were not met, Fisher's exact test was applied. The effect size was analyzed using univariate and multivariate logistic regression. Kaplan–Meier analysis was employed for survival analysis. All analyses were performed using SPSS version 28.0.

Results

Patient characteristics

The study included 269 patients from five different medical oncology clinics. The median age at diagnosis was 49 years. Of these patients, 142 (52.8%) were premenopausal, and 127 (47.2%) were postmenopausal. The Ki-67 levels were generally high, with a median value of 67.5. At diagnosis, the majority of patients were at locally advanced stages. Specifically, the proportion of patients with clinical stage 2B, 3B, and 3 C was 26.8%, 42.0%, and 26.4%, respectively, as shown in Table 1. Among the 64 patients who underwent *BRCA* testing, 37 (13.8%) were *BRCA*-negative, while 27 (10.0%) were *BRCA*-positive.

Association between clinical factors and complete response

Eighty-nine patients (33.1%) achieved pCR after NACT, while 180 patients (66.9%) did not. The pCR rates according to HER2 status and the addition of carboplatin to NACT are shown in Fig. 1. Patients who received carboplatin in addition to NACT had significantly higher pCR rates compared to those who did not receive carboplatin (48.5% versus 26.6%, $p = 0.002$). HER2-zero patients had significantly higher pCR rates than HER2-low patients (45.2% versus 23.7%, $p < 0.001$). The analysis of pCR in patients based on HER2 status and carboplatin administration is presented in Table 2.

Similarly, patients with high Ki-67 levels (≥ 50%) had significantly higher pCR rates after NACT than those with low Ki-67 levels ($p = 0.030$). However, there was no significant relationship between pCR and menopausal status, ECOG performance status, or *BRCA* mutation status ($p = 0.600$, $p = 0.349$, and $p = 0.197$, respectively).

Univariate analysis revealed that Ki-67 level, tumor grade, HER2 score, HER2-zero or HER2-low status, and the addition of carboplatin to treatment predicted pCR, as detailed in Table 3. However, in multivariate analysis, only higher tumor grade at diagnosis (OR 2.149, 95% CI 1.206–3.828, $p = 0.009$), HER2-zero status (OR 0.374, 95% CI 0.215–0.649, $p < 0.001$), and the addition of carboplatin (OR 2.376, 95% CI 1.300–4.346, $p = 0.005$) remained statistically significant predictors.

Association between clinical factors and Carboplatin-HER2 status

Of the 269 patients included in the study, 152 (56.5%) were HER2-low, while 117 (43.5%) were HER2-zero. All patients received an anthracycline (doxorubicin or epirubicin) and cyclophosphamide-based chemotherapy regimen before or after receiving taxane (docetaxel or paclitaxel). Sixty-eight patients (25.3%) received carboplatin in addition to the specified chemotherapy regimen.

When patients were evaluated according to HER2 status, the pathologic complete response (pCR) rates were significantly higher in the HER2-zero group compared to the HER2-low group (45.2% versus 23.7%, $p < 0.001$). In the HER2-zero group, patients who received carboplatin had significantly higher pCR rates (63.3% versus 39.0%, $p = 0.021$). Similarly, in the HER2-low group, adding carboplatin significantly increased the pCR rates (36.8% versus 19.3%, $p = 0.028$). Table 2 shows the effect of carboplatin on pCR according to HER2 status.

The addition of carboplatin increased pCR rates in several subgroups as illustrated in Fig. 2. Specifically, carboplatin improved pCR rates in patients younger than 50 years and in premenopausal patients ($p = 0.011$ and $p = 0.009$, respectively). Adding carboplatin also improved pCR rates in patients with Grade 3 tumors at diagnosis ($p = 0.010$); however, this effect was not observed in patients with Grade 1 or Grade 2 tumors ($p = 0.779$ and $p = 0.111$, respectively). When patients were analyzed according to HER2 scores (0, 1, and 2-FISH negative), the addition of carboplatin positively affected the pCR in HER2 score 0 and score 1 patients. However, no benefit was observed in HER2 score 2-FISH negative patients

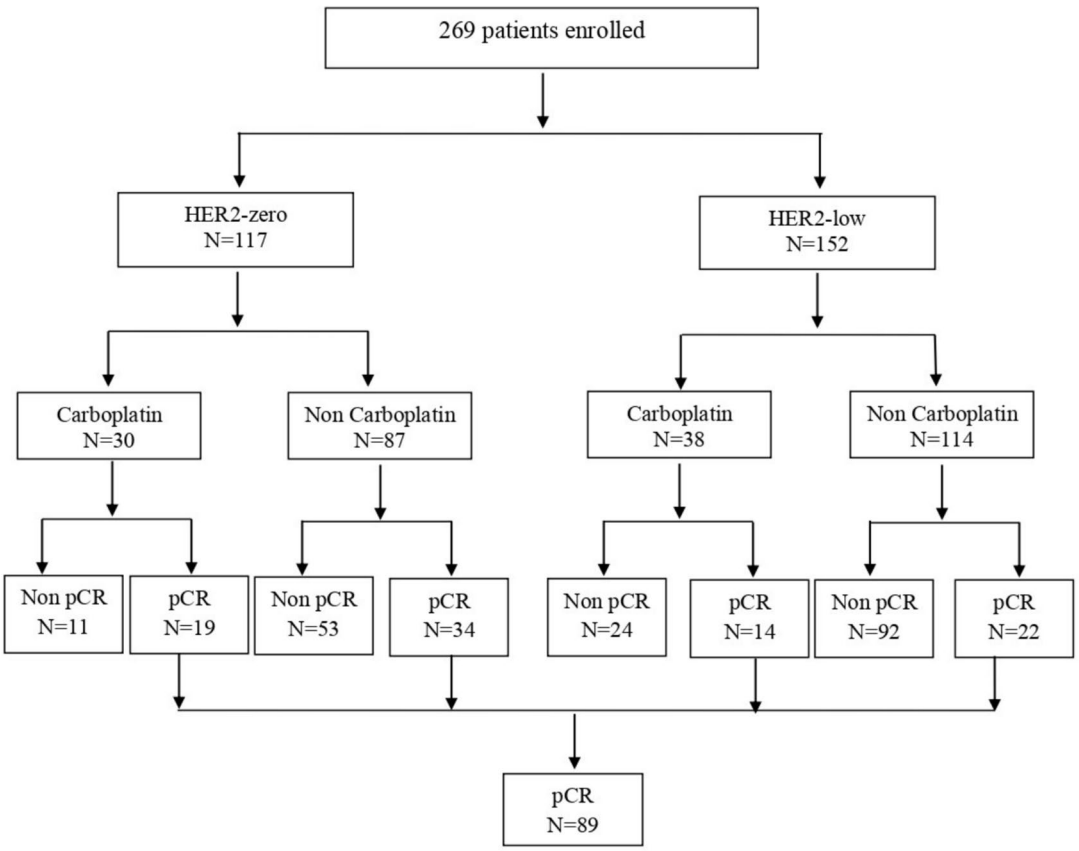

Fig. 1 Responses to neoadjuvant chemotherapy based on HER2 status and the incorporation of carboplatin into the regimen, pCR: pathologic complete response

Table 2 Effect of carboplatin on pCR according to HER2 status

HER2 Status	Carboplatin	pCR (-)	pCR (+)	p
HER2-zero	Non-Recipient	53 (60.9%)	34 (39.1%)	0.021[x2]
	Recipient	11 (36.7%)	19 (63.3%)	
HER2-low	Non-Recipient	92 (80.7%)	22 (19.3%)	0.028[x2]
	Recipient	24 (63.2%)	14 (36.8%)	

Statistical Test: [x2]Chi-square test

Abbreviation: pCR Pathological Complete Response

($p = 0.024$, $p = 0.005$, and $p = 0.420$, respectively). The addition of carboplatin did not significantly benefit pCR in *BRCA*-positive or *BRCA*-negative patients ($p = 0.195$ and $p = 0.444$, respectively). Figure 2 presents a forest plot showing the odds ratios for pCR with carboplatin across different subgroups, with statistically significant results highlighted. The forest plot clearly illustrates that certain patient subpopulations, particularly those with Grade 3 tumors, premenopausal status, and age < 50

Table 3 Clinical and pathological predictors of complete response

Variable	Univariate Analysis	Multivariate Analysis
Ki67 at Diagnosis (≥ 50% vs. < 50%)	OR: 1.015 (95% CI: 1.002—1.028), $p = 0.022$	-
Tumor Grade at Diagnosis	OR: 2.326 (95% CI: 1.329—4.073), $p = 0.003$	OR: 2.149 (95% CI: 1.206—3.828), $p = 0.009$
HER2 Score Before Neoadjuvant Therapy	OR: 0.497 (95% CI: 0.339—0.728), $p < 0.001$	-
HER2 Status (zero vs. low)	OR: 0.375 (95% CI: 0.222—0.632), $p < 0.001$	OR: 0.374 (95% CI: 0.215—0.649), $p < 0.001$
Carboplatin (Recipient vs. Non-Recipient)	OR: 2.441 (95% CI: 1.385—4.303), $p = 0.002$	OR: 2.376 (95% CI: 1.300—4.346), $p = 0.005$

Statistical Test: Logistic Regression (Forward LR)

Abbreviations: OR Odds Ratio, *CI* Confidence Interval, *pCR* Pathological Complete Response

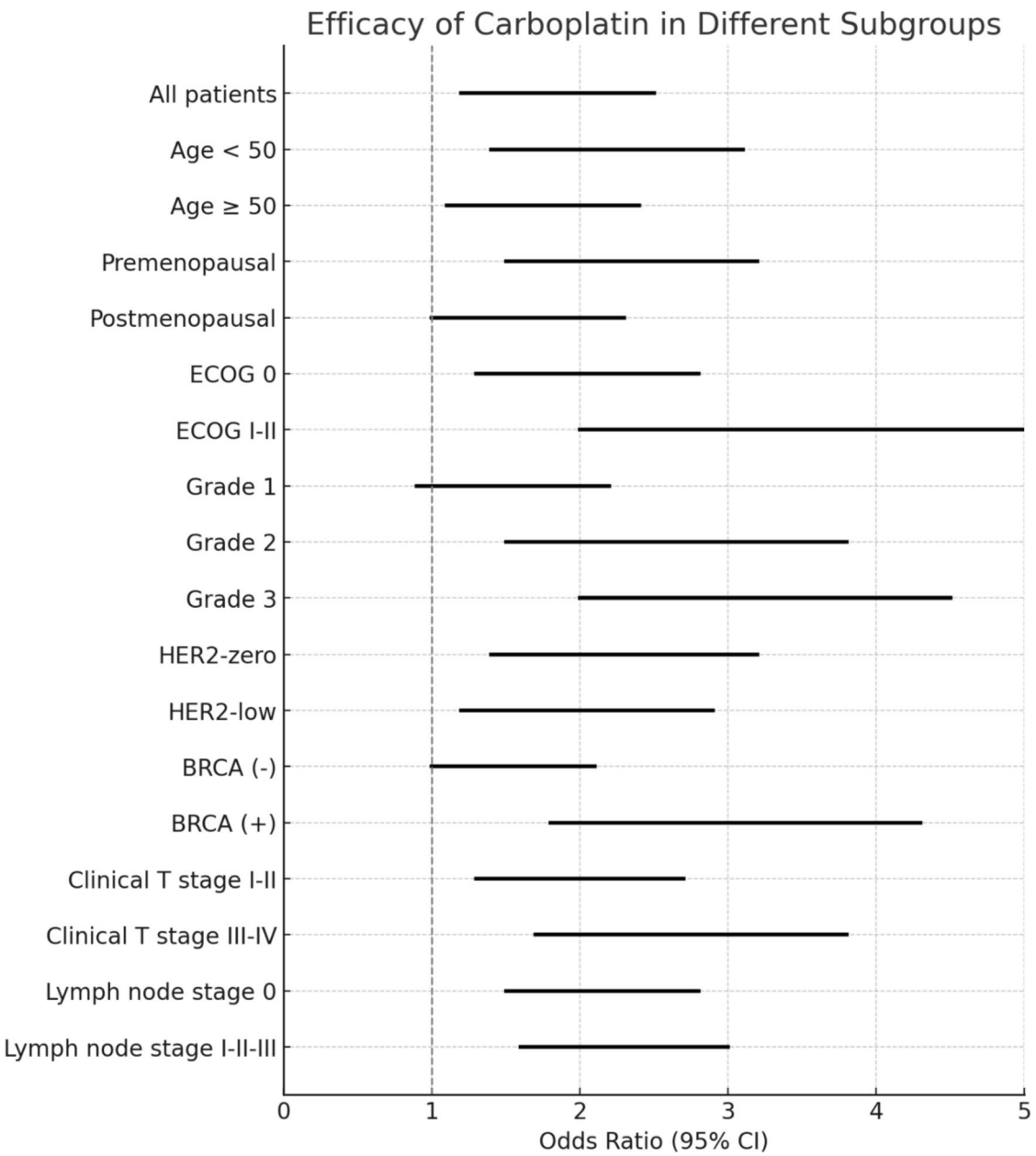

Fig. 2 Efficacy of Carboplatin Use to Differentiate Patients with and without Complete Response. ECOG: Eastern Cooperative Oncology Group, HER2: Human epidermal growth factor receptor 2

years, derived the greatest benefit from carboplatin addition, with odds ratios exceeding 3.0. This visualization highlights potential opportunities for targeted treatment intensification in specific patient populations.

Association between survival and Carboplatin-HER2 status

During the median follow-up period of 38.3 months, 50 patients died, and 76 patients experienced progression or recurrence after surgery. There was no statistically significant difference in disease-free survival (DFS) or overall survival (OS) between HER2-zero and HER2-low patients ($p = 0.114$ and $p = 0.055$, respectively). Patients with pCR exhibited substantially prolonged DFS and OS compared to those without pCR ($p = 0.002$ and $p < 0.001$, respectively). Figure 3 demonstrates the superior survival outcomes in patients achieving pCR versus those with residual disease, with Kaplan–Meier curves clearly showing this significant survival difference.

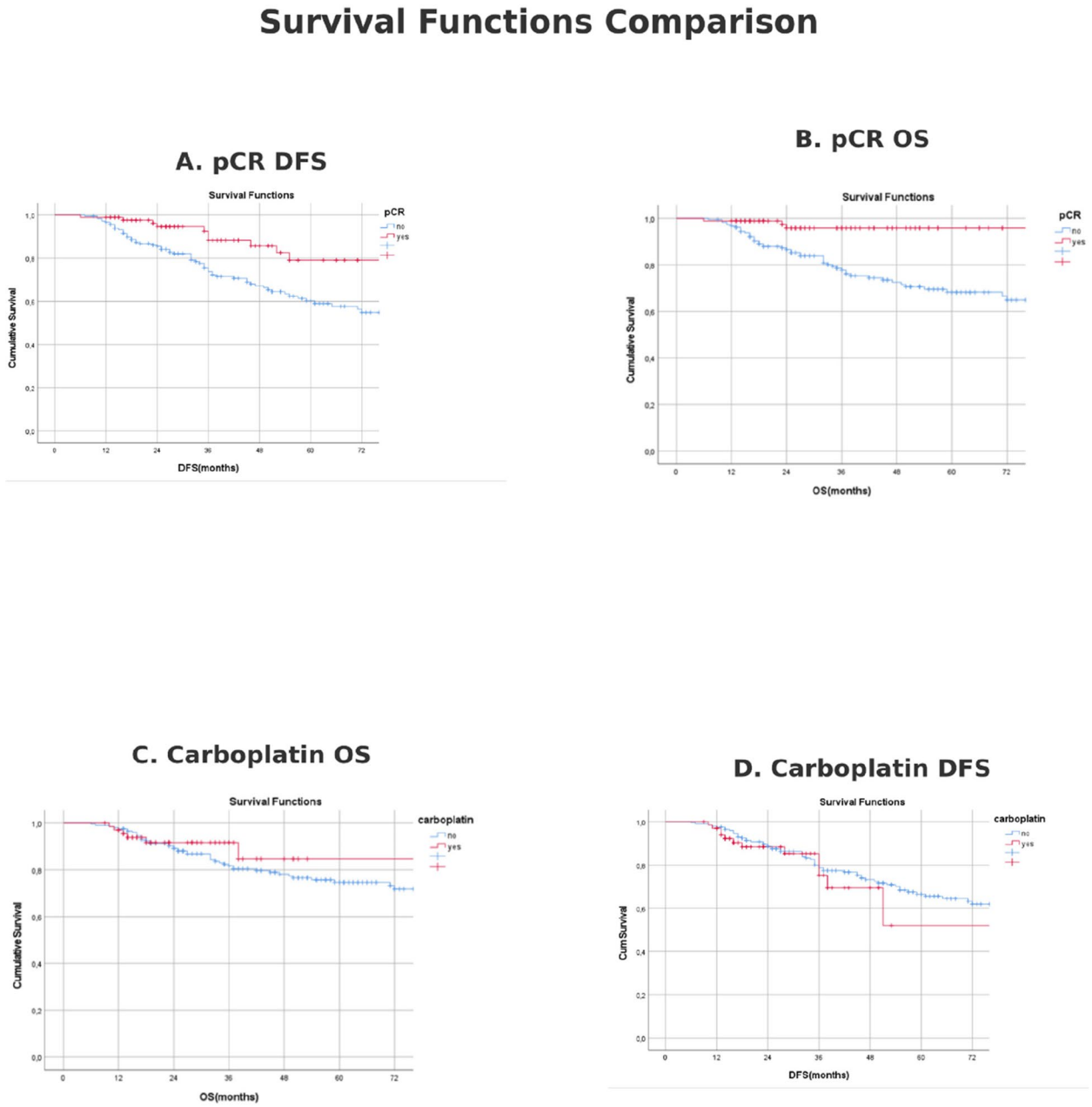

Fig. 3 Kaplan–Meier analyses of overall survival and disease-free survival based on carboplatin administration and pathological complete response status. **A** DFS according to pathologic complete response status $p = 0.002$. **B** OS according to pathologic complete response status $p < 0.001$. **C** OS according to carboplatin use $p = 0.570$. **D** DFS according to carboplatin use $p = 0.482$

In the HER2-zero subgroup analysis, 3 (10%) patients in the carboplatin-containing NACT group experienced disease progression, and 2 (6.7%) died. In contrast, 25 (28.7%) patients in the HER2-zero group who did not receive carboplatin-containing NACT experienced progression, and 13 (14.9%) died during the follow-up period. Although numerically fewer patients in the carboplatin-based treatment group experienced progression and death, these differences were not statistically significant ($p = 0.859$ and $p = 0.795$, respectively).

Similarly, in the HER2-low subgroup analysis, 9 (23.7%) patients in the carboplatin-containing NACT group experienced disease progression, and 4 (10.5%) died. In the HER2-low group that did not receive carboplatin-containing NACT, 39 (34.2%) patients experienced progression, and 31 (27.2%) died during the follow-up

period. Although numerically fewer patients in the carboplatin-based treatment group experienced progression and death, these differences were not statistically significant ($p = 0.208$ and $p = 0.664$, respectively).

Figure 3 also illustrates the survival trends between patients who received carboplatin versus those who did not. While the curves suggest a potential survival advantage with carboplatin addition, the differences did not reach statistical significance, consistent with our numerical findings. Nevertheless, the visual separation of the curves, particularly in the early follow-up period, may indicate a clinical benefit that warrants investigation in larger cohorts.

Discussion

Our study is a comprehensive real-world data-based investigation that explores the benefits of adding carboplatin to NACT in TNBC patients from various perspectives. It is well known that adding carboplatin to NACT increases pCR rates and contributes positively to DFS and OS [7, 8]. The GeparSixto and CALGB 40603 trials have established the benefit of adding carboplatin to anthracycline and taxane-based neoadjuvant regimens in TNBC. More recently, the KEYNOTE-522 trial demonstrated that the addition of pembrolizumab to carboplatin-containing neoadjuvant chemotherapy has become the current standard of care for high-risk early TNBC patients, further highlighting the importance of optimizing neoadjuvant regimens [22, 23]. However, to our knowledge, no previous study has demonstrated the differential benefits of carboplatin in the HER2-low and HER2-zero subgroups of TNBC patients receiving neoadjuvant treatment. In our study, we aimed to evaluate whether adding carboplatin to NACT in locally advanced TNBC patients, stratified by HER2-low and HER2-zero subgroups, provides benefits in terms of pCR and survival.

Our key finding is that adding carboplatin significantly increased pCR rates in both HER2-zero and HER2-low TNBC patients, with a more pronounced effect in the HER2-zero group (63.3% vs. 39.0%, $p = 0.021$) compared to the HER2-low group (36.8% vs. 19.3%, $p = 0.028$). Notably, when patients were categorized by HER2 score (0, 1, and 2-FISH negative), the 2-FISH negative cohort exhibited the minimal advantage regarding pCR from NACT. This differential benefit may reflect underlying biological differences between these subgroups. Recent molecular characterization studies have shown that HER2-zero tumors may harbor unique patterns of genomic instability and DNA repair deficiencies that could make them particularly sensitive to platinum agents [24]. In contrast, even low levels of HER2 expression in HER2-low tumors might activate alternative signaling pathways that potentially modify response to DNA-damaging agents like carboplatin [25, 26]. Tumor grade at diagnosis, HER2 status, and the addition of carboplatin were independent predictors of pCR in multivariate analysis.

Regarding survival outcomes, there was no difference in DFS or OS between the HER2-low and HER2-zero groups. Similarly, no significant differences were observed in DFS and OS between patients receiving or not receiving carboplatin in both HER2-low and HER2-zero groups. As expected, patients who achieved pCR had significantly longer DFS and OS than those who did not. It is important to note that our study was not adequately powered to detect survival differences in these subgroups due to the relatively small sample size and limited follow-up period. This is a significant limitation that must be considered when interpreting our survival results.

The importance of carboplatin in treating locally advanced TNBC is increasingly reinforced by multiple studies [8, 26, 27]. As the positive impact of pCR on DFS and OS has become more apparent, there is growing interest in treatments that enhance pCR [28]. The BRIGHTNESS trial represents one of the more pertinent studies in this area, which specifically evaluated the addition of carboplatin (with or without veliparib) to standard neoadjuvant chemotherapy in TNBC. This study demonstrated a significant improvement in pCR rates with carboplatin addition (58% vs. 31%), reinforcing our findings. Similarly, the NEOPACT trial, which evaluated docetaxel/carboplatin as a neoadjuvant regimen in TNBC, demonstrated promising efficacy with acceptable toxicity profiles [29, 30].

A meta-analysis involving 12 studies and 4,580 patients demonstrated that patients receiving carboplatin had significantly higher pCR rates and meaningful improvements in DFS and OS [27]. Another meta-analysis of approximately 3,250 TNBC patients found that those who received platinum-based chemotherapy had better DFS and OS compared to those who did not [26]. In a study examining the treatment of early-stage TNBC, adding carboplatin to NACT increased pCR rates, though more frequent chemotherapy-related side effects were observed [31].

While our analysis focused primarily on efficacy, it is essential to consider the toxicity associated with carboplatin. Previous studies have reported increased rates of hematological toxicities, including neutropenia, thrombocytopenia, and anemia, as well as higher rates of treatment modifications with carboplatin addition [7, 8, 25, 26]. This safety profile must be balanced against the potential benefits, particularly in patients with comorbidities or reduced performance status. The recommendation to add carboplatin should therefore

be individualized based on patient characteristics and risk–benefit assessment.

Similarly, in a retrospective analysis of Stage II-III TNBC patients receiving NACT, those who received carboplatin had higher pCR rates and longer event-free survival (EFS) and OS [32]. However, a meta-analysis of 3,518 patients found that while carboplatin contributed to better DFS, no significant improvement in OS was observed [33]. In our study, HER2-low patients who received carboplatin had significantly higher pCR rates than those who did not. Although patients who received carboplatin had numerically fewer recurrences and deaths, no statistically significant differences in DFS or OS were observed. The same was true for HER2-zero patients. We believe the lack of statistical significance in DFS and OS despite higher pCR rates and numerically fewer recurrences and deaths may be due to the small sample size and the relatively short follow-up period. With only 68 patients receiving carboplatin across both HER2 subgroups, our study lacks the statistical power to detect potentially meaningful survival differences.

As our understanding of HER2 biology continues to evolve, new therapeutic approaches are emerging [34]. Although HER2-zero and HER2-low breast cancers exhibit significant molecular similarities, specific molecular differences, such as *ERBB2* hemideletion rates and *ERBB2* copy number variations, may result in different treatment responses [24]. These biological differences may help explain the differential response to carboplatin observed in our study, with HER2-zero tumors potentially harboring characteristics that make them more sensitive to platinum agents.

Several limitations of our study warrant consideration. First, the retrospective design introduces potential selection biases. Second, the uneven distribution of *BRCA* mutations between groups—with testing available for only 64 patients—may represent a confounding factor, as *BRCA*-mutated tumors are known to be particularly platinum-sensitive. Third, the wide confidence intervals in our subgroup analyses, particularly for tumor grades (as seen in Fig. 2), suggest limited statistical power for detecting differences between certain subgroups, such as Grade 2 versus Grade 3 tumors. Fourth, the variability in post-surgical adjuvant treatments may have influenced survival outcomes independently of carboplatin's effect.

The strengths of our study include being the first known investigation to examine the efficacy of adding carboplatin to NACT in terms of pCR and survival in HER2-zero and HER2-low TNBC patients, as well as being a multicenter study involving clinics from different regions of our country.

Conclusion

Our study demonstrated that adding carboplatin to NACT increases pCR rates in both HER2-zero and HER2-low groups, with a potentially greater benefit in the HER2-zero population. In light of our findings, we suggest that carboplatin should be considered as an addition to standard neoadjuvant chemotherapy for eligible TNBC patients regardless of their HER2-zero or HER2-low status, when appropriate based on individual patient factors and toxicity considerations. Further prospective studies with larger sample sizes and longer follow-up durations are needed to support our results and better define the subgroups most likely to benefit from this approach.

Authors' contributions

S. Y.: Conceptualization, Methodology, Investigation, Project administration, Data curation and management, Writing- original draft T. B.: Data curation, Investigation, Writing- Review & Editing A. D.: Data curation, Investigation, Writing- Review & Editing G.A.: Data curation, Investigation, Writing- Review & Editing O.K.: Data curation, Investigation, Writing- Review & Editing A.T.: Data curation, Investigation, Writing- Review & Editing O. A.: Software, Formal analysis, Writing- Review & Editing A.A.S.: Data curation, Investigation, Writing- Review & Editing M.G.: Data curation, Investigation, Writing- Review & Editing T.C.: Data curation, Investigation, Writing- Review & Editing R.C.: Data curation, Investigation, Writing- Review & Editing M.Y.: Writing- original draft, Software, Formal analysis A.K.: Investigation, Writing- Review & Editing N.S.: Data curation, Investigation, Writing- Review & Editing N.M.: Data curation, Investigation, Writing- Review & Editing K.K.: Data curation, Investigation, Writing- Review & Editing S.S.: Data curation, Investigation, Writing- Review & Editing O.S.: Data curation, Investigation, Writing- Review & Editing M.O.: Data curation, Investigation, Writing- Review & Editing D.I.: Supervision, Methodology, Writing- Review & Editing H.S.: Data curation, Investigation, Writing- Review & Editing O.N.S.: Supervision, Project administration, Writing- Review & Editing H.O.: Conceptualization, Supervision, Writing- Review & Editing M.E.Y.: Conceptualization, Supervision, Writing- Review & Editing N.T.: Supervision, Project administration, Writing- Review & Editing.

Funding

This study was not supported by any sponsor or funder.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This retrospective, multicenter study was approved by the ethics committee of Kartal Dr Lutfi Kırdar City Hospital. The ethics committee approval date was November 29, 2023, with decision number 2023/5 l4/26214.
Patient data, were obtained retrospectively from patient records after obtaining written informed consent from the patients or their relatives.

Consent for publication

I confirm the corresponding author has read the journal policies and submit this manuscript in accordance with those policies**.**

Competing interests

The authors declare no competing interests.

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Received: 4 December 2024 Accepted: 30 April 2025
Published online: 06 May 2025

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