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Chemotherapy regimen choice and patient outcomes in early-stage triple-negative breast cancer: a retrospective analysis

Sanaz N. Ghafouri*, Rebecca W. Nayeri*, Nicholas P. McAndrew and Sara A. Hurvitz

Abstract

Background: Triple-negative breast cancer (TNBC) is associated with a poor prognosis when compared to hormone receptor–positive breast cancers. Anthracycline-based regimens (ABRs) are mainstay for treatment of non-metastatic TNBC. However, anthracyclines are associated with an increased risk of potentially life-threatening adverse effects. We sought to evaluate outcomes in patients with early TNBC treated with ABRs *versus* those treated with anthracycline-sparing regimens (ASRs).

Methods: All patients treated for stage I–III TNBC who had undergone curative-intent surgery at a large academic medical center between January 2013 and May 2018 were included in this retrospective study. Event-free survival (EFS) and disease-free survival (DFS) were the primary endpoints, with overall survival (OS) as a secondary endpoint and were defined as per standardized STEEP criteria. Kaplan–Meier, multivariable Cox regression, and log-rank tests were used to define key survival and treatment-related differences between subjects treated with ABRs *versus* ASRs.

Results: One hundred thirty-two patients met inclusion criteria with a median follow-up of 55.9 months. Twenty-seven patients (20%) had disease recurrence and 20 (15%) died. Patients in the ABR group were more likely to have nodal involvement (chi-square $p = 0.011$). Patients treated with ABRs ($n = 26$, 20%) compared with ASRs ($n = 106$, 80%) had significantly shorter median EFS (32.4 months *vs* not reached (NR), $p < 0.001$), DFS (26.2 months *vs* NR, $p < 0.001$), and OS (49.2 months *vs* NR, $p < 0.001$). The shorter survival observed in the ABR group persisted after adjusting for nodal status and on multivariate analysis. Of the 26 ABR-treated patients, 9 (35%) had an anthracycline added after suboptimal response to an ASR. Regardless of reason for anthracycline inclusion, the survival outcomes were similar. No cardiac or secondary leukemic events were observed in either group.

Conclusion: ABRs were associated with shorter EFS, DFS, and OS, even after adjusting for certain high-risk clinical features.

Keywords: anthracyclines, chemotherapy, recurrence, survival, triple-negative breast cancer

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Introduction

Breast cancer is the most common cancer and the second-most common cause of cancer-related deaths in women in the United States.[1] Breast cancer is a heterogeneous disease, with expression of estrogen receptor (ER), progesterone receptor (PR), and/or amplification of the gene for human epidermal growth factor receptor 2 (HER2), significantly affecting prognosis and choice of systemic therapy. Triple-negative breast cancer (TNBC) is characterized by a lack of expression of ER and PR, and normal expression of HER2.[2] TNBC accounts for approximately 10–15% of all breast cancers diagnosed in the United States,

translating to 25,000 to 30,000 cases each year, with disproportionately higher rates in younger women, women of color, and BRCA1 carriers.[3–5] TNBC itself represents a heterogeneous subgroup of breast cancers, with at least six different molecular subtypes.[6] TNBC is associated with early recurrence, typically within 5 years of diagnosis, and tend to manifest as visceral or brain metastases rather than bone metastases.[7] Treatment options are limited in TNBC as these tumors lack a therapeutic target. Therefore, in the early-stage setting, cytotoxic chemotherapy remains the standard of care, though the optimal regimen has not been clearly defined. Subgroup analysis of the anthracyclines in early breast cancer (ABC) trials suggested an improved invasive disease-free survival (iDFS) in the taxane, anthracycline, and cyclophosphamide (TaxAC) groups compared to docetaxel and cyclophosphamide (TC) groups in those with TNBC, lending support to the routine use of anthracycline-based regimens (ABRs), combined with taxanes, in this disease subtype.[8] However, as encouraging results of ASRs for early-stage TNBC have been reported over the past several years, the necessity of ABRs have been called into question.[9] For example, a combined analysis of two prospective cohorts including 190 patients with TNBC treated with neoadjuvant docetaxel and carboplatin reported a pathologic complete response (pCR) rate of 55%.[10] Three-year recurrence-free survival (RFS) and OS were 79% and 87%, respectively.[11] Furthermore, 3-year RFS and OS for patients who achieved pCR were 90% and 94%, respectively. Importantly, to date at least six randomized phase-2 or phase-3 trials have compared ASRs with ABRs in early-stage TNBC.[12–17] All of these trials demonstrated either similar or improved outcomes in patients who received ASRs. In addition, given their association with life-threatening adverse effects (cardiotoxicity, myelodysplasia, and secondary leukemia), some have questioned whether the benefits of ABRs outweigh their risks. We sought to compare outcomes in patients with early TNBC treated with ABRs *versus* those treated with ASRs.

Materials and methods

Subjects

This was a retrospective cohort study including patients diagnosed with TNBC between January 2013 and May 2018 at the University of California, Los Angeles (UCLA)-associated oncology practices in Southern California who had undergone curative-intent surgery. Inclusion criteria included those with a diagnosis of invasive TNBC, stage I–III, according to the Joint Committee on Cancer (AJCC), 8th edition (2018) staging system. Patients with distant metastases were excluded from the study. Patients with a personal history of prior cancers other than *in situ* carcinoma of the cervix or non-melanomatous skin cancers, a personal history of chemotherapy prior to the diagnosis of TNBC, or a personal history of prior chest wall radiation were also excluded from this analysis.

The Institutional Review Board (IRB#18-000568) at the UCLA Office of the Human Research Protection Program (OHRPP) reviewed this protocol and determined it to be exempt prior to the commencement of the study; the need for informed patient consent was waived, given the database was de-identified.

Baseline characteristics recorded included gender, race/ethnicity, age at initial diagnosis, menopausal status, germline mutation status, tumor stage, tumor grade, surgery and radiation type, chemotherapy regimen (ASR and ABR), and timing of chemotherapy (neoadjuvant, adjuvant, or both). The timing in months from date of diagnosis until relapse and/or death, as well as chemotherapy-related toxicities including cardiac toxicity, leukemia, and myelodysplastic syndrome were recorded as well.

Definitions and criteria

Pathologic diagnosis, ER status, PR status, and HER2 status were determined by core biopsy prior to systemic therapy or surgery. ER and PR status were determined by standard immunohistochemistry (IHC) techniques. In concordance with ASCO/CAP guidelines, tumors where less than 1% of nuceli were immunoreactive were considered to have negative hormone receptor status.[18] HER2 status was assessed by IHC and by fluorescence *in situ* hybridization (FISH) confirmation if 2+ by IHC.[19] Patients were classified as baseline node positive if they were clinically node positive prior to receiving neoadjuvant chemotherapy (NAC) or if they had nodal involvement at time of surgery if they did not receive neoadjuvant chemotherapy (NAC). Pathologic complete response was defined as no invasive carcinoma in the breast or lymph nodes (ypT0/is ypN0) after neoadjuvant therapy.

Data collection and validation

Data were collected in a de-identified manner from the Epic Health System database of 8,000 patients diagnosed with an ICD-10 code principal diagnosis of breast cancer within a UCLA-affiliated medical center from January 2013 to May 2018. Human subjects' names were kept in a password-protected database. There were no patient identifiers. From there, the eligible patients were identified, validated, and data were extracted *via* manual chart review. Final data extraction and cutoff was performed in November 2020. Data from each patient were validated by two independent researchers. Information was entered into STATA without personal health information.

Endpoints and statistical analyses

Categorical data were compared using chi-square tests. *P* values <0.05 were considered statistically significant. Univariate analysis was used to estimate the effects of clinical and pathologic characteristics on receipt of ABR *vs* ASR. To identify variables independently associated with the use of NAC or ABR, a multivariate analysis was performed. All variables with a p value <0.20 in the univariate analysis were included in as candidate variables in the multivariable logistic regression model, allowing for interaction. Overall survival (OS), defined from the date of diagnosis to the date of death from any cause, event-free survival (EFS), defined as date of diagnosis to the date of progression or death, and disease-free survival (DFS), defined as time from date of surgery to date of progression or death, were estimated using Kaplan–Meier method. All analyses were performed with STATA (StataCorp LLC. College Station, TX). EFS and DFS were the primary endpoints, with OS as a secondary endpoint and pCR rate as an exploratory endpoint for those undergoing neoadjuvant therapy. All were defined as per standardized STEEP criteria. Kaplan–Meier, multivariable Cox regression, and log-rank tests were used to define key survival and treatment-related differences between subjects treated with ABRs *vs* ASRs.

Results

After considering the eligibility requirements, ($n=132$) patients were included in the study, and among these 20% ($n=26$) received an ABR and 80% ($n=106$) received an ASR. Patient demographic and histopathologic characteristics are shown in Table 1. The median follow-up for the study was 55.8 months. Ninety-three (70%) of the patients in the study had node-negative disease, and among those who were node positive, 28 (72%), 7 (18%), and 4 (10%) were N1, N2, and N3, respectively. Most patients had a pathologic tumor stage of T1 (45%, $n=60$), with the remainder representing T2 (39%, $n=51$), T3 (12%, $n=16$), and T4 (3%, $n=4$). One patient had pathologic T0 residual disease after receiving neoadjuvant chemotherapy. Twenty percent

Table 1. Patient and baseline tumor characteristics by treatments given.

Characteristic	ABR 26 (20%)	ASR 106 (80%)	Total 132
Mean age (range)	54 (31–72)	55 (26–81)	55 (26–81)
Race/ethnicity			
Asian	7 (27%)	11 (10%)	18 (14%)
Black	2 (8%)	11 (10%)	13 (10%)
Hispanic	1 (4%)	8 (8%)	9 (7%)
Non-Hispanic White	2 (8%)	6 (6%)	8 (6%)
Other (including mixed race)	14 (54%)	70 (66%)	84 (64%)
Post-menopausal	16 (62%)	69 (65%)	85 (64%)
BRCA1/2	6 (23%)	20 (19%)	26 (20%)
Stage 2/3	21 (81%)*	56 (53%)	77 (58%)
T-stage			
T1	5 (19%)	56 (53%)	61 (45%)
T2	14 (54%)	37 (35%)	51 (39%)
T3	5 (19%)	11 (69%)	16 (12%)
T4	2 (8%)	2 (2%)	4 (3%)
Node positive	13 (52%)*	26 (25%)	39 (30%)
Grade III	23 (88%)	91 (86%)	114 (87%)
NAC only	8 (31%)	41 (39%)	49 (37.1%)
Adjuvant only	7 (27%)	53 (50%)	60 (45.5%)
NAC and adjuvant	11 (42%)	12 (11%)	23 (17.4%)
Platinum	14 (54%)	40 (38%)	54 (41%)

ABR: anthracycline-based regimen; ASR: anthracycline-sparing regimen.
*represents p value <0.05.

Table 2. Baseline characteristics for patients who received ABR after initiating an ASR due to suboptimal response to ASR.

Characteristic	ASR→ABR 9
Mean age (range)	51 (36–72)
Race	
Asian	3 (33%)
Black	0 (0%)
Hispanic	0 (0%)
White	5 (56%)
Other	1 (11%)
Post-menopausal	4 (44%)
BRCA1/2	2 (22%)
Stage 2/3	8 (89%)
Node positive	4 (44%)
Grade 3	7 (78%)
NAC	9 (100%)
Platinum	9 (100%)

ABR: anthracycline-based regimen; ASR: anthracycline-sparing regimen.

(26/132) of the study group had germline BRCA mutation. Twenty patients had a BRCA1 and 6 patients had a BRCA2 mutation.

Of the patients who had received an ABR, 35% (9/26) had the anthracycline added due to suboptimal clinical response to an ASR. The demographic and histopathologic characteristics for these patients are outlined in Table 2. Significantly more patients treated with an ABR had node-positive disease (chi-square $p = 0.011$) and higher overall stage disease (chi-square $p = 0.010$) as compared to those treated with an ASR.

Platinum agents were used in 41% of all patients ($n = 54$) and in 38% of patients receiving an ASR (40/106). Platinum usage was also associated with higher overall stage, with 76% (41/54) of this cohort having stage II or III disease, (chi-square $p < 0.001$). The association between nodal status and platinum therapy was of borderline significance (chi-square $p = 0.05$). Seventy-three percent (19/26) of *BRCA1/2*-positive patients received platinum-based therapy (chi-square $p < 0.001$). Ninety-nine percent (131/132) of patients received taxane as a part of their chemotherapy regimen, with one exception receiving adjuvant cyclophosphamide, methotrexate and 5-fluorouracil (CMF).

Seventy-two of the 132 patients (54.5%) received neoadjuvant therapy with or without adjuvant chemotherapy, with 49/132 patients (37.1%) receiving all chemotherapy in the neoadjuvant setting, and 23/132 (17.4%) of patients receiving both neoadjuvant and adjuvant chemotherapy. Sixty of 132 patients (45.5%) received all chemotherapy in the adjuvant setting. Of the patients who received neoadjuvant chemotherapy, 46% (33) and 19% (14) received platinum and anthracyclines, respectively. Of the platinum-based neoadjuvant therapy subgroup, 88% (29/33) were ASRs. There was a statistically significant association between node-positivity and neoadjuvant therapy, (chi-square $p < 0.001$). In addition, 75% (54/72) of patients receiving neoadjuvant therapy had stage-II or III disease, which is significant compared to the adjuvant cohort (chi-square $p < 0.001$).

Regardless of the timing of the chemotherapy regimen, 51% of the patients had a mastectomy, and 49% had a lumpectomy. Seventy-three percent of all patients (97/132) also had adjuvant radiation as part of their treatment.

Of the 132 patients in the analysis, 27 (20%) of patients experienced disease recurrence and 20 (15%) died. The median EFS, DFS, and OS for all 132 patients were not yet reached (NR). The patients treated with ABRs compared with ASRs had significantly shorter median EFS (32.4 months *vs* NR, $p < 0.001$), DFS (26.2 months *vs* NR, $p < 0.001$), and OS (49.2 months *vs* NR, $p < 0.001$) (Figure 1(a), 2(a), and 3(a)).

Stratifying by nodal status, EFS was significantly shorter in the ABR as compared to the ASR group in the node-positive patients (32.4 months *vs* NYR, hazard ratio (HR) = 4.34, 95% confidence interval (CI): 1.44–13.00, $p = 0.009$). The respective median EFS for the node-negative cohorts within the ABR group and the ASR group were 33.2 months *versus* NR (log-rank, $p < 0.001$) in favor of the non-anthracycline cohort, with a HR = 10.49, (95% CI: 3.48–31.60, $p < 0.001$). The median EFS for the 9 patients who received anthracycline for non-response was 32.4 months *versus* EFS of 33.2 months for those treated with

an ABR from the outset. The median DFS and OS for those treated with an ABR from the outset were 32.6 and 49.2 months, respectively.

Median DFS for node-positive patients was 26.2 months in the ABR group *versus* NR in the ASR group (log-rank, $p = 0.005$). In the node-negative patients, median DFS for the ABR and ASR groups were 32.6 months and NR, respectively (log-rank, $p < 0.001$; in favor of the ASRs (HR = 10.9 (95% CI: 3.62–32.96, $p < 0.001$)). In addition, within the ABR cohort, those with higher stage disease were more likely to have shorter EFS and worse survival outcomes, HR = 5.83, (95% CI: 2.44–13.94, $p < 0.001$).

Median OS was significantly longer for patients who had received ASR *versus* ABR (49.2 months *vs* NR, HR = 9.14, 95% CI: 3.63–22.98). Node-positive patients who received ABR had worse OS than ASR counterparts, with median OS 49.2 months *versus* NR (HR = 3.65, 95% CI: 1.18–11.25; $p = 0.024$).

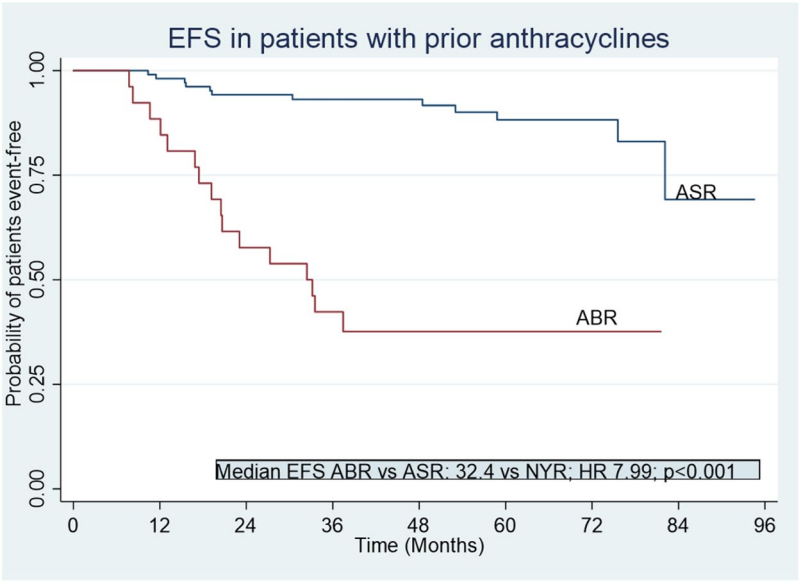

Figure 1. Event-free survival for patients according to schedule of chemotherapy and regimen used. Kaplan–Meier cumulative survival curves for EFS comparisons between patients who received ABR *vs* ASRs.

Results of univariate cox regression analysis for EFS, DFS, and OS are shown in Table 3. Stage, neoadjuvant chemotherapy, ABR, and requiring mastectomy were found to have a statistically significant association with worse EFS, DFS, and OS. Age, grade, and receipt of adjuvant radiation had no significant association on EFS, DFS, or OS (Table 3).

In the multivariate cox regression analysis, the only variables that had a statistically significant association with worsening EFS, DFS, and OS after adjusting for other confounding variables were use of ABR and requiring surgical mastectomy. In the multivariate model, ABR was associated with worse EFS (HR = 3.63, 95% CI: 1.38–9.56, $p = 0.009$), DFS (HR = 4.23, 95% CI: 1.78–10.04, $p = 0.001$), and OS (HR = 3.80, 95% CI: 1.39–10.36, $p = 0.009$). In addition, history of surgical mastectomy was associated with worse outcomes (Table 4).

Pathologic complete response rate was evaluated in patients who had received NAC. Thirty-one of the 72 patients (43%) who received NAC experienced pCR. Overall, pCR was associated with improved EFS (HR = 0.27, 95% CI: 0.09–0.83, $p = 0.022$), DFS (HR: 0.27, 95% CI: 0.09–0.82, $p = 0.021$), and OS (HR = 0.29, 95% CI: 0.08–0.99, $p = 0.048$). Of these 31 patients, 12 (39%), 13 (42%), and 6 (19%) were stage I, II, and III at diagnosis, respectively. The rate of pCR was lower in the ABR group (21.4%) as compared to the ASR group (48.2) but this was not found to be statistically significant, chi-square, $p = 0.069$). Notably, none of the four patients who received neoadjuvant anthracycline for non-response attained pCR. The odds of achieving a pCR for patients who received an ABR *versus* an ASR was not significantly different (odds ratio (OR) = 0.29, 95% CI: 0.07–1.16, $p = 0.080$). This remained non-significant after adjusting for node status (OR = 0.41, 95% CI: 0.07–2.46, $p = 0.332$). However, the ABR cohort with high stage disease had significantly worsened pCR rates (OR = 0.18, 95% CI: 0.04–0.89, $p = 0.035$).

Finally, no cardiomyopathies, myelodysplastic syndromes, or secondary leukemias were observed in either group in the 55.8-month follow-up.

Discussion

While anthracyclines remain a mainstay of therapy for TNBC in the curative setting, the toxicity associated with this class of agents may be irreversible and, in some cases, life-threatening. Moreover, a growing number of studies are demonstrating promising outcomes for anthracycline-free regimens in early-stage disease, leading some to question whether anthracyclines are needed for all patients in the curative setting. While there have

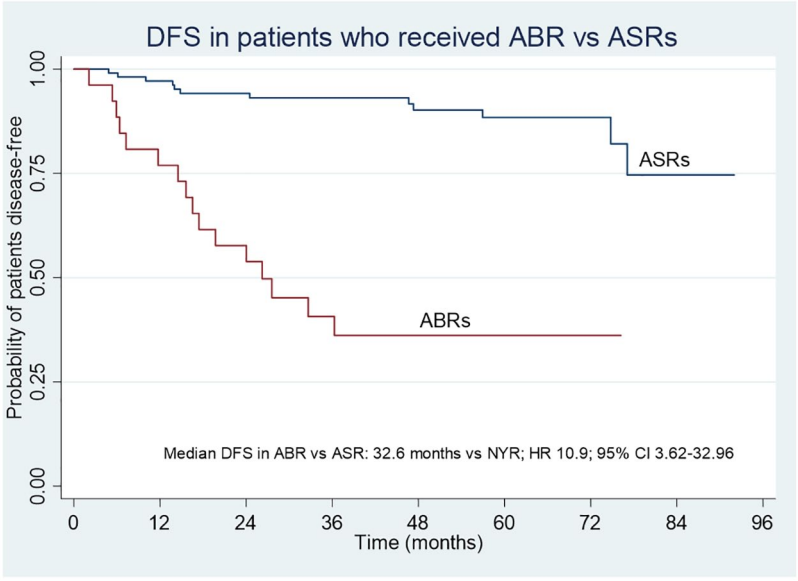

Figure 2. Disease-free survival for patients according to schedule of chemotherapy and regimen used. Kaplan–Meier cumulative survival curves for DFS comparisons between patients who received ABR *vs* ASRs.

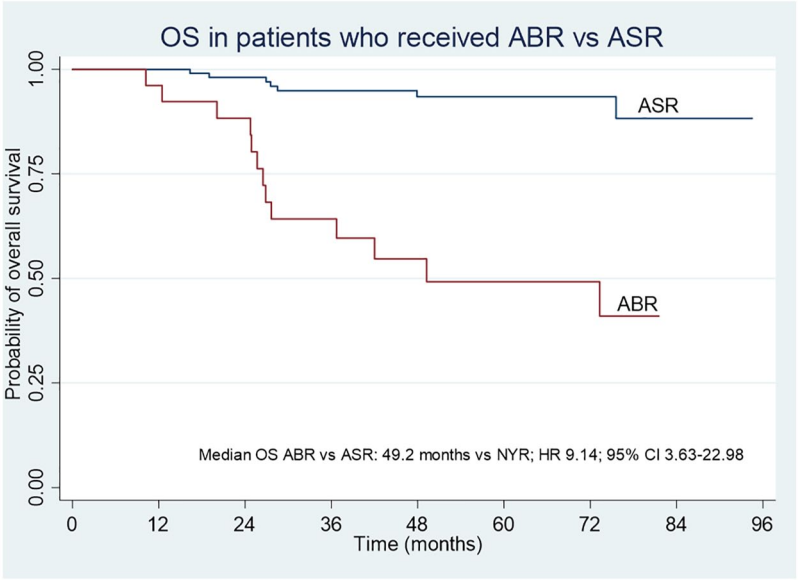

Figure 3. Overall survival for patients according to schedule of chemotherapy and regimen used. Kaplan–Meier cumulative survival curves for OS comparisons between patients who received ABR *vs* ASRs.

been studies showing benefits with the addition of anthracyclines, it remains unclear which component of the regimen has the most substantial clinical impact. Studies by Carey *et al.*[20] have favored ABR, particularly anthracycline and cyclophosphamide in combination, in that they showed greater clinical and pathologic response rates in the neoadjuvant setting for TNBC compared to other subtypes of breast cancer. In the NSABP B-27 trial, NAC with anthracycline-cyclophosphamide-based regimen was compared to the same regimen plus additional cycles of docetaxel in all-comers with advanced breast cancer, and showed a nearly doubled pCR in the latter subgroup; however, there were no long-term improvements in DFS or OS.[21] In a study of 1016 women conducted by the US Oncology Research (USOR) group, participants were randomized to achieve either four cycles of doxorubicin and cyclophosphamide or four cycles of docetaxel and cyclophosphamide and followed for 7 years. The DFS and OS were superior for the anthracycline-sparing group, (OS HR = 0.69, 95% CI: 0.50–0.97, $p = 0.032$). Interestingly, subgroup analysis indicated ER/PR-negative disease benefits more from the anthracycline-free therapy.[22] More recently, the USOR and NSABP collaborated on three trials referred to as the Anthracycline in early Breast Cancer (ABC) trials. These were all prospective trials that collectively enrolled 4242 patients with HER2-breast cancer and randomly assigned them to docetaxel plus cyclophosphamide or a triple regimen of doxorubicin, taxane, and cyclophosphamide. This endeavor represents the largest prospective randomized trial to test whether anthracyclines improve outcomes when added to taxane-based therapy. With just over 3 years follow-up, the overall trial reported a modest 2.5% absolute improvement in invasive DFS with the use of an anthracycline. The benefit associated with anthracyclines appeared to be strongest in the triple-negative subset, most notably in those with nodal involvement. The use of platinum-based therapy was not allowed on these studies.[8] To date, multiple prospective randomized clinical trials have failed to demonstrate a benefit in pCR, DFS, or OS with the addition of anthracyclines in the treatment of early-stage TNBC.[23] Importantly, the recently published PATTERN trial compared the use of an anthracycline-free taxane/platinum regimen to a taxane/ABR in the adjuvant setting for TNBC. It demonstrated a statistically significant improvement in DFS for patients who received an ASR and failed to demonstrate a difference in OS among the two study populations.[24]

Our study showed that patients who received an ASR did well regarding survival and pCR, and potentially better than those receiving an ABR. It is crucial to note that in this single-center, retrospective analysis, patients who received an ABR were more likely to have high-risk clinical features

Table 3. Cox regression univariate analysis for EFS, DFS, and OS.

Variables	EFS		DFS		OS	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Advanced age	0.89 (0.37–2.14)	0.796	0.68 (0.32–1.43)	0.307	0.93 (0.38–2.22)	0.862
Stage 2–3	7.61 (1.76–32.84)	0.006*	3.92 (1.49–10.31)	0.006*	15.31 (2.05–114.44)	0.008*
High grade	2.92 (0.39–21.79)	0.297	2.10 (0.50–8.84)	0.313	2.96 (0.40–22.11)	0.291
NAC (*vs* AC)	4.03 (1.35–12.06)	0.013*	2.82 (1.23–6.47)	0.014*	2.81 (1.02–7.73)	0.046*
ABR (*vs* ASR)	7.48 (3.05–18.34)	<0.001*	8.10 (3.73–17.55)	<0.001*	9.14 (3.63–22.98)	<0.001*
Lumpectomy (*vs* mastectomy)	0.22 (0.07–0.67)	0.007*	0.33 (0.15–0.75)	0.008*	0.15 (0.04–0.52)	0.003*
Radiation	3.30 (0.77–14.25)	0.109*	3.18 (0.96–10.53)	0.059*	3.30 (0.76–14.24)	0.109*

EFS: event-free survival; DFS: disease-free survival; OS: overall survival; CI: confidence interval; ABR: anthracycline-based regimen; ASR: anthracycline-sparing regimen; HR: hazard ratio.
*Variables that have *p* value < 0.20, which will be included in the Table 4 multivariate analysis.

Table 4. Cox regression multivariate analysis for EFS, DFS, and OS using variables from Table 3 which have *p* value < 0.20.

Variables	EFS		DFS		OS	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Stage 2–3	2.92 (0.60–14.20)	0.183	1.60 (0.53–4.80)	0.404	5.68 (0.68–47.29)	0.108
NAC (*vs* AC)	1.64 (0.51–5.21)	0.405	1.48 (0.61–3.62)	0.389	1.01 (0.35–2.90)	0.991
ABR (*vs* ASR)	3.63 (1.38–9.56)	0.009*	4.23 (1.78–10.04)	0.001*	3.80 (1.39–10.36)	0.009*
Lumpectomy (*vs* mastectomy)	0.29 (0.09–0.96)	0.043*	0.37 (0.14–0.95)	0.039*	0.22 (0.06–0.84)	0.027*
Radiation	3.32 (0.69–16.06)	0.135	3.34 (0.89–12.60)	0.075	3.68 (0.78–17.42)	0.100

EFS: event-free survival; DFS: disease-free survival; OS: overall survival; CI: confidence interval; ABR: anthracycline-based regimen; ASR: anthracycline-sparing regimen.
*Variables that have a significant association with respective survival time considering confounding variables, based on *p* value of <0.05.

such as more node-positive and advanced-stage disease, than those who received ASR. While inferior survival in the ABR groups persisted even after adjusting for nodal status, stage of the disease, and suboptimal response to ASR, the small sample size of this cohort and non-randomized nature of this study requires cautious interpretation of these results and selection bias may still be a confounding factor of this retrospective study. Interestingly, one would imagine that patients who received an ABR for residual disease or non-response after an ASR inherently have higher risk disease. However, these patients did surprisingly well in our analysis, potentially highlighting the importance and feasibility of response-adapted therapy. Sharma *et al.* studied neoadjuvant docetaxel plus carboplatin *versus* a four-drug ABR including paclitaxel, carboplatin, doxorubicin, and cyclophosphamide. They found no significant difference in rate of pCR, regardless of node status.[12] Given the ability to assess individual response to a therapeutic regimen at the time of surgery, saving anthracycline use only in non-responders may help reduce toxicity and overall drug exposure for patients who respond optimally to a more tailored regimen.

This study has several important limitations, including a relatively small sample size, and a retrospective, non-randomized design resulting in an unbalanced number of patients who received ABRs *versus* ASRs, as well as important

differences between these two populations with regard to individual disease characteristics. For example, a large majority (80%) of our patients received an ASR. This is in contrast to a recent study investigating real-world treatment patterns in early-stage TNBC, which demonstrated that the majority of patients who received either neoadjuvant or adjuvant chemotherapy received an ABR.[25] In addition, the pCR rates in our study of 48.2% and 21.4% in the ASR and ABR groups respectively trend in favor of the ASR group. However, this finding was ultimately not statistically significant likely due to the small sample size of our ABR cohort. Furthermore, given the small, retrospective nature of this study, a detailed evaluation of long-term subclinical toxicity associated with each regimen was not possible. We also acknowledge that the lack of analyses on patient characteristics such as medical comorbidities, the Eastern Cooperative Oncology Group (ECOG) performance status, and concomitant medication use are additional limitations of this study.

In conclusion, our findings suggest that ASRs in early-stage TNBC may be associated with improved, and at the very least not worsened, survival outcomes compared to patients who receive ABRs. This finding holds true after adjusting for high-risk clinical features. These findings support preliminary, randomized phase-2 data suggesting ASRs are associated with similar pCR rates to ABRs.[26] More studies are needed to evaluate the role of platinum-containing ASRs a neoadjuvant, response-adapted model, to help physicians more precisely tailor therapy for these high-risk patients.

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Author contributions

Sanaz N. Ghafouri: Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

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Nicholas P. McAndrew: Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

Sara A. Hurvitz: Writing – original draft; Writing – review & editing.

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