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# Do We Need Anthracyclines for Elderly Patients with Triple-Negative Breast Cancer?

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**Keywords**
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**Abstract**
***Objectives:*** Triple-negative breast cancer (TNBC) requires chemotherapy-based systemic treatment which is usually anthracycline-based (AB). The cardiotoxicity of AB regimens is especially relevant in the elderly population. Therefore, we retrospectively compared survival and toxicity between elderly patients with early TNBC receiving AB or anthracycline-free (AF) adjuvant chemotherapy to evaluate whether elderly patients with TNBC could be spared anthracycline-related toxicity without compromising survival. ***Methods:*** The study population comprised 221 women with TNBC older than 65 years from the SUCCESS A and SUCCESS C studies, who underwent primary surgery and received either AB (3x fluorouracil-epirubicin-cyclophosphamide followed by 3x docetaxel) or AF (6x docetaxel-cyclophosphamide) adjuvant chemotherapy according to a standardized protocol. The two groups were compared regarding clinicopathological parameters (pT, pN, grading, histological subtype, type of surgery, adjuvant radiotherapy) and side effects using chi-square tests, and regarding survival (overall survival, invasive disease-free survival, breast-cancer specific survival, distant disease-free survival) using log-rank tests and Cox regressions. ***Results:*** There was no significant difference between the two groups regarding any of the clinicopathological parameters, and no significant difference was observed in survival parameters. However, elderly patients with the AB regime had significantly more often grade 3 or 4 adverse events (75.2% vs. 50.6%, $p < 0.001$) during adjuvant chemotherapy than patients with the AF regimen. ***Conclusion:*** In our retrospective analysis of SUCCESS A and C trial, the use of AF chemotherapy in elderly patients with TNBC was associated with similar survival rates but less toxicity compared to AB chemotherapy. Further randomized controlled trials with AF regimen focusing on elderly patients with TNBC are necessary to confirm our results.



## Introduction

Breast cancer is the most common cancer in women [1]. The prevalence of breast cancer rises in the elderly population simultaneously with increasing life expectancy [2], and at the same time, oncological diseases are the leading cause of death in elderly women [3]. The dominant breast tumors in the elderly population, usually defined as age >65 years, are luminal-like tumors characterized by estrogen/progesterone positivity and low grading [4, 5]. Nevertheless, triple-negative breast cancer (TNBC) represents approximately 19% of the tumors in elderly patients [6]. TNBC has a poor prognosis, and therefore, chemotherapy is indicated as primary therapy option to achieve systemic control of the disease in the early setting [7]. Both the German guidelines

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and the guidelines of the European Society of Medical Oncology recommend anthracycline-based (AB) regimens for patients with TNBC [7, 8]. However, the most common contraindications for anthracyclines are preexisting cardiac conditions such as heart failure, cardiomyopathy, or myocardial infarction [9, 10], and especially elderly patients have a high incidence of such cardiac risk factors [11]. Consequently, the question arises if an anthracycline-free (AF) chemotherapy regimen could be an alternative treatment option for elderly patients with TNBC with similar efficacy but less toxicity compared to AB regimens.

## Methods

*Study Population*

The study population comprised all women participating in one of the two large adjuvant breast cancer trials SUCCESS A (EudraCT 2005-000490-21, NCT 02181101) and SUCCESS C (EudraCT 2008-005453-38, NCT 00847444) that were older than 65 years, had TNBC, and received either an AB chemotherapy regime consisting of three cycles of 5-fluorouracil (500 mg/m$^2$), epirubicin (100 mg/m$^2$), and cyclophosphamide (500 mg/m$^2$) every 3 weeks, followed by three cycles of docetaxel (100 mg/m$^2$) every 3 weeks (FEC-D) or an AF regime with six cycles of docetaxel (75 mg/m$^2$) and cyclophosphamide (600 mg/m$^2$) every 3 weeks (DC). Patients from the SUCCESS B study were not eligible, as this trial only included women with HER2-positive breast cancer [12]. Furthermore, we excluded patients from the randomized SUCCESS A trial that received an AB chemotherapy regime consisting of three cycles of 5-fluorouracil, epirubicin, and cyclophosphamide every 3 weeks followed by three cycles of docetaxel plus gemcitabine every 3 weeks (FEC-DG), as a comprehensive analysis showed that the addition of gemcitabine to FEC-D did not improve survival and was associated with higher toxicity [13]. Overall, 221 women with TNBC and older than 65 years could be included for the final exploratory and hypothesis-generating analysis. Every patient underwent primary surgery with complete resection of the tumor followed by adjuvant chemotherapy and radiation, if indicated according to the respective study protocol. A brief synopsis of the SUCCESS A and SUCCESS C study can be found in the online supplementary Appendix 1 (for all online suppl. material, see https://doi.org/10.1159/000544906). Both SUCCESS A and SUCCESS C were approved by the relevant Ethics Committees in Germany and conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

*Clinicopathological Parameters*

For each patient, age in years, weight in kilograms, and height in meters were documented and the BMI in kg/m$^2$ was calculated. Coding of the histopathological parameters, tumor stage (pT1, pT2, pT3, pT4), nodal status (pN0, pN1, pN2, pN3), histological grading (G1, G2, G3), hormone receptor status (positive, negative), HER2 status (positive, negative), and tumor classification by histologic type (ductal, lobular, other) were based on the standard histopathologic classification summarized in the study protocols. In addition, type of surgery (breast-conserving, mastectomy, other) and use of radiotherapy (yes/no) were documented.

*Survival*

The survival parameters, overall survival (OS), invasive disease-free survival (iDFS), breast cancer-specific survival (BCSS), and distant disease-free survival (DDFS), were estimated according to the Standardized Definitions for Efficacy Endpoints (STEEP) [14]. Survival was calculated from the date of randomization to the earliest time of occurrence of an event or to the last time that an adequate assessment occurred if no event was documented (censored patients) for all survival analyses reported here.

*Toxicity*

The occurrence of any side effects according to common toxicity criteria of adverse events (CTC-AE, version 3.0) during any of the six cycles of the adjuvant chemotherapy was documented. In addition, the incidence of dose reductions and dose delays of more than 6 days were recorded. Three patients in the AB group and 2 patients in the AF group did not receive any chemotherapy and were excluded from the safety analyses.

*Statistical Analysis*

Patient characteristics obtained in terms of categorical variables were described using frequency tables and reported in absolute numbers and percentages within the particular subgroup. Metric variables (age and BMI) were reported as median and range. The associations between AB and AF regimens and categorical parameters were analyzed by chi-square tests or Fisher's exact tests if one or more cells of the 2 × 2 contingency tables have expected frequencies less than five. Comparisons between the two chemotherapy regimens AB and AF with regard to metric variables were performed using the Mann-Whitney U test.

The survival endpoints OS, iDFS, BCSS, and DDFS were analyzed based on Kaplan-Meier estimates, illustrated using Kaplan-Meier curves, and compared between AB and AF regimens using a log-rank test. Univariable and adjusted multivariable Cox proportional hazards regression models were used to analyze the effects of chemotherapy regimen on survival with the AF regime as the reference category. The assumptions for the proportional hazards Cox regression models were tested and

met for all four survival endpoints, as there were no significant chemotherapy regimen by time interaction terms (calculated based on the multivariable Cox regression models with a time-dependent covariate; all $p > 0.30$).

Incidences of AEs were compared between the two chemotherapy regimens with chi-square or Fisher's exact tests. Furthermore, the risk for the occurrence of at least one AE grade 3 or 4 (yes/no) was evaluated using univariable and multivariable binary logistic regressions with chemotherapy regimen (AB vs. AF), age (years), BMI (kg/m$^2$), and radiation therapy (yes vs. no) as independent variables.

Data were analyzed using IBM Statistical Package for the Social Sciences (SPSS), version 29 (SPSS Inc). All $p$ values reported are two-sided, and $\alpha = 0.05$ was used as the significance level throughout; no adjustment was made to the significance level for multiple testing.

## Results

*Clinicopathological Parameters*

There were no significant differences between the group receiving AB and AF regimes in the evaluated clinicopathological parameters. The median age of the patients in both groups was 69 years. Most of the patients had pT2, pN0, G3, NST tumor treated with breast-conserving surgery and radiation. The results of the comparison can be found in Table 1.

*Survival*

Median follow-up duration for OS was 64 months, and overall 48 DFS events, including 34 deaths, were observed during the follow-up period. The 5-year OS and iDFS rates were 86.4% and 76.5%, respectively, for patients receiving the AB regimen, and 84.7% and 80.3%, respectively, for patients receiving the AF regimen. Patients receiving AB and AF regimes did not differ significantly with regard to median survival in OS (79.4 and 80.4 months, respectively; HR 1.09; 95% CI 0.55–2.19; $p = 0.799$), iDFS (74.1 vs. 68.3 months, respectively; HR 1.06; 95% CI 0.59–1.91; $p = 0.853$), BCSS (84.4 and 82.5 months, respectively; HR 0.91; 95% CI 0.40–2.08), or DDFS (79.5 and 78.8 months, respectively; HR 1.27; 95% CI 0.61–2.66; $p = 0.521$). The Kaplan-Maier survival curves for OS, iDFS, BCSS, and DDFS are shown in Figure 1.

In the adjusted multivariable Cox regression analysis (see Table 2), the chemotherapy regimen (AB vs. AF) showed no significant effect on any of the four survival endpoints. Nodal stage was a significant risk factor for all survival parameters; in addition, there was a significant effect of radiation therapy on OS (HR 0.35; 95% CI 0.13–0.96; $p < 0.05$).

*Side Effects*

The most common AEs of any grade and of grade 3/4 only according to chemotherapy regimen are shown in Table 3. No difference between the AB and AF group was observed regarding the proportion of patients with at least one AE of any grade (91.5% vs. 89.7%, $p = 0.651$). However, patients in the AB group had significantly more often at least once leukopenia, thrombocytopenia, nausea, vomiting, and neuropathy of any grade than patients in the AF group (see Table 3).

The proportion of patients with at least one grade 3/4 AE during any cycle of the adjuvant chemotherapy was significantly higher in the AB group (75.2% vs. 50.6%, $p < 0.001$). For most of the different types of grade 3/4 AEs, the proportion of patients with at least one grade 3/4 AE was numerically higher in the AB group compared to the AF groups, with the differences being significant for grade 3/4 leukopenia (Table 3). A multivariable logistic regression analysis with the incidence of at least one grade 3/4 AE during adjuvant chemotherapy (yes/no) as binary response variable including the other potential risk factors age, BMI, and radiation therapy confirmed the independent effect of the chemotherapy regimen on the probability of a grade 3/4 AE (odds ratio AB vs. AF 3.53, 95% CI 1.90–6.56, $p < 0.001$; see Table 4).

Overall, 104 and 51 SAEs were observed in patients of the AB and AF groups, respectively. Of these, 74 and 35 were considered to be serious adverse drug reactions (SARs) related to AB or AF chemotherapy treatment. The reasons for classification as SAR were hospitalization (70 cases), prolongation of hospitalization (2 cases), and important medical event (2 cases) in the AB group, and hospitalization (34 cases) and important medical event (1 case) in the AF group. There were no cases of SARs resulting in life-threatening condition or death. Both dose delays of more than 6 days (20.9% vs. 11.5%, $p = 0.071$) and dose reductions (22.5% vs. 10.3%, $p = 0.022$) were observed more often in patients of the AB group.

## Discussion

Our results provide information about the elderly population of patients with TNBC receiving either AB or AF adjuvant chemotherapy under standardized conditions of clinical trials. TNBC belongs to the breast cancer subtypes with the worst survival; therefore, an aggressive treatment is necessary in order to avoid local or distant relapse and its consequences [15]. The results of previous studies showed that elderly patients benefit from adding adjuvant chemotherapy in case of TNBC [16, 17]. As a standard, various guidelines recommend the use of AB chemotherapies for patients with TNBC [7, 8], but our

**Table 1.** Comparison of the clinicopathological parameters in elderly patients with TNBC receiving AF or AB regime

| | | Total ($N$ = 221) | AF (6x DC) ($N$ = 89) | AB (3x FEC-3x D) ($N$ = 132) | $p$ value |
|---|---|---|---|---|---|
| Age, years | Median<br>Range | 69<br>66–86 | 69<br>66–79 | 69<br>66–86 | 0.423[1] |
| BMI, kg/m$^2$ | Median<br>Range | 26.0<br>18.4–40.9 | 26.6<br>18.8–40.9 | 25.8<br>18.4–40.4 | 0.633[1] |
| Tumor stage | pT1<br>pT2<br>pT3<br>pT4 | 93 (42.1%)<br>116 (52.4%)<br>7 (3.2%)<br>5 (2.3%) | 36 (40.4%)<br>46 (51.7%)<br>5 (5.6%)<br>2 (2.2%) | 57 (43.2%)<br>70 (53.0%)<br>2 (1.5%)<br>3 (2.3%) | 0.401[2] |
| Nodal stage | pN0<br>pN1<br>pN2<br>pN3<br>Unknown | 136 (61.5%)<br>48 (21.7%)<br>23 (10.4%)<br>13 (5.9%)<br>1 (0.5%) | 59 (66.3%)<br>20 (22.5%)<br>7 (7.9%)<br>3 (3.4%)<br>0 (0.0%) | 77 (58.3%)<br>28 (21.2%)<br>16 (12.1%)<br>10 (7.6%)<br>1 (0.8%) | 0.376[2] |
| Histological type | Invasive ductal<br>Invasive lobular<br>Others | 198 (89.6%)<br>3 (1.4%)<br>20 (9.0%) | 79 (88.8%)<br>2 (2.2%)<br>8 (9.0%) | 119 (90.2%)<br>1 (0.8%)<br>12 (9.0%) | 0.644[2] |
| Grading | G1<br>G2<br>G3 | 2 (0.9%)<br>38 (17.2)<br>181 (81.9%) | 0 (0.0%)<br>16 (18.0%)<br>73 (82.0%) | 2 (1.5%)<br>22 (16.7%)<br>108 (81.8%) | 0.496[2] |
| Type of surgery | Breast-conserving<br>Mastectomy<br>Other | 169 (76.5%)<br>46 (20.8%)<br>6 (2.7%) | 64 (71.9%)<br>21 (23.6%)<br>4 (4.5%) | 105 (79.6%)<br>25 (18.9%)<br>2 (1.5%) | 0.260[2] |
| Irradiation | No<br>Yes | 46 (20.8%)<br>175 (79.2%) | 17 (19.1%)<br>72 (80.9%) | 29 (22.0%)<br>103 (78.0%) | 0.606[2] |

D, docetaxel; C, cyclophosphamide; F, fluorouracil; E, epirubicin. [1]Mann-Whitney U test. [2]Chi-square test.

results show that AB and AF regimens seem to be equally effective regarding survival in patients older than 65 years.

A pooled analysis of the adjuvant SUCCESS C and PlanB trials comparing AB and AF regimen in 5,924 patients with intermediate-to-high risk HER2-negative breast cancer of all age groups (median age 55 years) revealed no significant difference regarding OS or DFS in the overall cohort. In addition, an exploratory subgroup analysis found no significant interaction term between chemotherapy (AB vs. AF) and patient age (≤40, 40–60, >60 years), indicating that the effect of chemotherapy regimen on survival was not different among age groups [18].

There are several other studies that compared AB and AF chemotherapy in breast cancer patients in different settings [18, 19]. For example, in the NeoSTOP study the efficacy of AF and AB neoadjuvant carboplatin regimens was compared in women with TNBC of all age groups (median age 51 years). Similar to our results, OS and iDFS were not statistically different and both regimes achieved a similar rate of pathological complete remission of the tumor [16]. Contrary to these results, the KBOG 1101 study comparing FEC-D and DC in a Japanese population of 97 patients with early hormone receptor-negative BC suggested that the addition of anthracyclines could be essential for TNBC, because of the inferior OS and iDFS in patients with TNBC receiving only DC [20]. A recent large meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) evaluated anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer [19]. Across 15 eligible trials that provided individual patient data, recurrence rates were significantly lower with taxane plus anthracycline regimens than with taxane without anthracycline regimens. However, when the comparison was restricted to sequential taxane plus anthracycline regimens versus higher cumulative dose docetaxel plus cyclophosphamide regimens, as was the case in our study, the difference in recurrence rate was no longer significant [19].

Only few studies more specifically addressed the question of whether an AB regimen provides a better outcome than an AF regimen in elderly patients with TNBC, a patient subgroup rarely included in

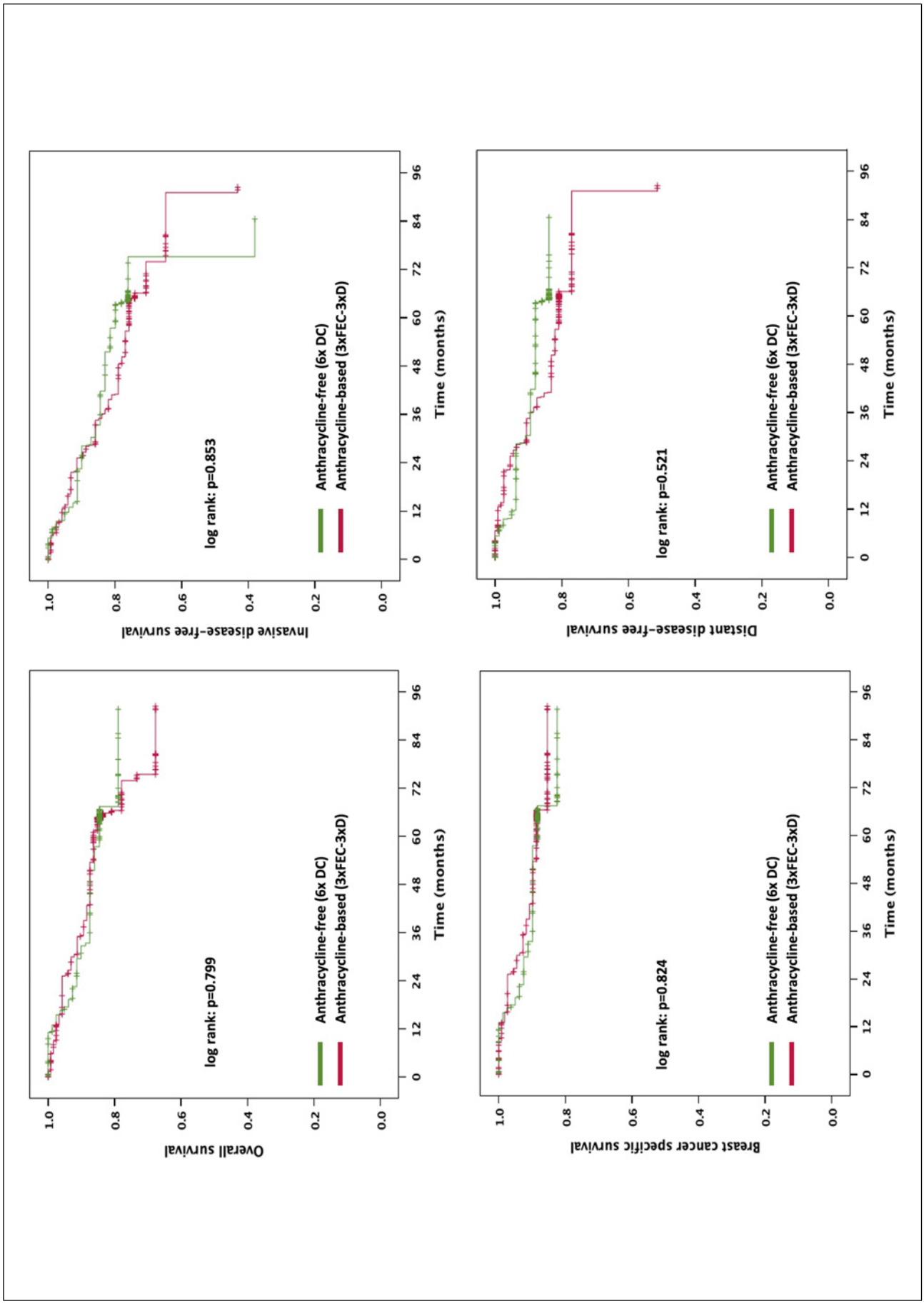


**Fig. 1.** Comparison of survival between AB and AF chemotherapy regimen in elderly patients with TNBC. D, docetaxel; C, cyclophosphamide; F, fluorouracil; E, epirubicin.

**Table 2.** Results of adjusted multivariable Cox regression models for different survival endpoints

| Parameter | Categories | OS | | iDFS | | *BCSS* | | *DDFS* | |
|---|---|---|---|---|---|---|---|---|---|
| | | hazard ratio (95% CI) | *p* value | hazard ratio (95% CI) | *p* value | hazard ratio (95% CI) | *p* value | hazard ratio (95% CI) | *p* value |
| Chemotherapy | AB versus AF | 1.00 (0.45–2.25) | 0.99 | 0.95 (0.49–1.85) | 0.875 | 0.80 (0.31–2.08) | *0.643* | *1.15* (*0.52–2.57*) | *0.731* |
| Age (years) | | 1.07 (0.98–1.16) | 0.129 | 1.04 (0.97–1.13) | 0.271 | 1.07 (0.97–1.17) | *0.163* | *1.06* (*0.96–1.17*) | *0.226* |
| BMI (kg/m$^2$) | | 1.08 (0.99–1.18) | 0.068 | 1.06 (0.99–1.14) | 0.079 | 1.04 (0.93–1.16) | *0.489* | *1.09* (*0.99–1.18*) | *0.059* |
| Tumor stage | | | 0.561 | | 0.803 | | *0.414* | | *0.649* |
| | pT2 versus pT1 | 1.92 (0.77–4.78) | 0.163 | 1.31 (0.66–2.60) | 0.434 | 3.02 (0.82–11.11) | *0.097* | *1.67* (*0.70–3.98*) | *0.248* |
| | pT3 versus pT1 | 1.35 (0.20–9.26) | 0.758 | 0.77 (0.14–4.34) | 0.768 | 1.91 (0.13–28.17) | *0.638* | *Cannot be calculated*[1] | |
| | pT4 versus pT1 | 1.49 (0.22–10.22) | 0.683 | 1.43 (0.27–7.66) | 0.679 | 2.39 (0.17–34.69) | *0.523* | *2.44* (*0.38–15.87*) | *0.350* |
| Nodal stage | | | <0.001 | | <0.001 | | *0.008* | | *0.028* |
| | pN1 versus pN0 | 2.55 (1.02–6.38) | 0.046 | 2.28 (1.08–4.81) | 0.030 | 1.16 (0.34–3.94) | *0.816* | *1.57* (*0.61–4.05*) | *0.355* |
| | pN2 versus pN0 | 3.01 (0.92–9.85) | 0.069 | 2.79 (1.08–7.21) | 0.034 | 2.92 (0.70–12.20) | *0.143* | *1.88* (*0.55–6.45*) | *0.317* |
| | pN3 versus pN0 | 11.58 (3.55–37.83) | <0.001 | 9.76 (3.58–26.58) | <0.001 | 10.55 (2.70–41.30) | *<0.001* | *7.28* (*1.98–26.68*) | *0.003* |
| Grading | | | 0.522 | | 0.429 | | *0.957* | | *0.943* |
| | G2 versus G1 | 1.18 (0.09–16.26) | 0.900 | 1.59 (0.14–18.46) | 0.710 | Cannot be calculated[1] | | *1.55* (*0.11–21.49*) | *0.742* |
| | G3 versus G1 | 2.18 (0.21–22.18) | 0.510 | 2.64 (0.28–24.94) | 0.396 | Cannot be calculated[1] | | *1.52* (*0.14–16.91*) | *0.734* |
| Histology | | | 0.238 | | 0.731 | | *0.072* | | *0.488* |
| | Lobular versus ductal | 2.35 (0.23–23.73) | 0.468 | 1.99 (0.23–17.30) | 0.534 | 3.42 (0.30–39.60) | *0.326* | *3.42* (*0.34–34.72*) | *0.299* |
| | Other versus ductal | 2.42 (0.82–7.10) | 0.109 | 1.32 (0.47–3.67) | 0.597 | 3.97 (1.14–13.82) | *0.030* | *1.50* (*0.46–4.90*) | *0.505* |
| Type of surgery | | | 0.916 | | 0.999 | | *0.997* | | *0.532* |
| | Ablative versus breast-conserving | 1.23 (0.47–3.21) | 0.676 | 1.01 (0.44–2.32) | 0.989 | 1.01 (0.31–3.27) | *0.989* | *1.77* (*0.65–4.78*) | *0.262* |
| | Other versus breast-conserving | Cannot be calculated[1] | | Cannot be calculated[1] | | Cannot be calculated[1] | | *Cannot be calculated*[1] | |
| Irradiation therapy | Yes versus no | 0.35 (0.13–0.96) | 0.042 | 0.45 (0.18–1.13) | 0.089 | 0.49 (0.13–1.91) | *0.307* | *0.88* (*0.23–3.31*) | *0.850* |

OS, overall survival; iDFS, invasive disease-free survival; BCSS, breast cancer-specific survival; DDFS, distant disease-free survival.
[1]Cannot be calculated due to subgroups without events.

randomized clinical trials. A study based on SEER-Medicare published by Schreiber et al. [21] included more than 3,000 patients older than 66 years with node-negative TNBC, of whom 1,404 patients received either a taxane plus anthracycline-containing (ATAX) or a taxane-containing (TAX) chemotherapy (cyclophosphamide usage was not reported). Univariable analysis showed significantly worse OS and BCSS in patients who received ATAX compared to TAX, but patients receiving ATAX also had significantly larger tumors. However, even when controlled for covariates including tumor stage, OS was significantly worse in the ATAX group. The authors suggested that the higher toxicity of anthracycline-containing therapies contributed to the inferior outcome in the ATAX group, as the elderly population might be particularly susceptible to

**Table 3.** Frequency (number and percent of patients) of all grade and grade 3/4 adverse events (overall, most common adverse events; CTC-AE V 3.0) according to chemotherapy treatment (AF vs. AB)

| | Any grade | | | Grade 3/4 | | |
|---|---|---|---|---|---|---|
| | AF (6x DC) ($N$ = 87[1]) | AB (3x FEC-3x D) ($N$ = 129[1]) | $p$ value[2] | AF (6x DC) ($N$ = 87[1]) | AB (3x FEC-3x D) ($N$ = 129[1]) | $p$ value[2] |
| Any adverse event | 78 (89.7%) | 118 (91.5%) | 0.651 | 44 (50.6%) | 97 (75.2%) | <0.001 |
| Anemia | 37 (42.5%) | 68 (52.7%) | 0.142 | 0 (0.0%) | 0 (0.0%) | |
| Leukopenia | 40 (46.0%) | 87 (67.4%) | 0.002 | 35 (40.2%) | 81 (62.8%) | 0.001 |
| Thrombocytopenia | 2 (2.3%) | 17 (13.2%) | 0.006 | 0 (0.0%) | 0 (0.0%) | |
| Neutropenia | 24 (27.6%) | 49 (38.0%) | 0.113 | 21 (24.1%) | 46 (35.7%) | 0.073 |
| Nausea | 32 (36.8%) | 69 (53.5%) | 0.016 | 2 (2.3%) | 8 (6.2%) | 0.322 |
| Fatigue | 41 (47.1%) | 54 (41.9%) | 0.444 | 1 (1.1%) | 5 (3.9%) | 0.405 |
| Vomiting | 8 (9.2%) | 27 (20.9%) | 0.022 | 2 (2.3%) | 4 (3.1%) | 1.000 |
| Stomatitis | 18 (20.7%) | 37 (28.7%) | 0.186 | 0 (0.0%) | 4 (3.1%) | 0.150 |
| Constipation | 20 (23.0%) | 37 (28.7%) | 0.352 | 2 (2.3%) | 2 (1.6%) | 1.000 |
| Diarrhea | 22 (25.3%) | 30 (23.3%) | 0.732 | 4 (4.6%) | 3 (2.3%) | 0.443 |
| ALT elevation | 16 (18.4%) | 25 (19.4%) | 0.856 | 1 (1.1%) | 0 (0.0%) | 0.403 |
| AST elevation | 9 (10.3%) | 15 (11.6%) | 0.769 | 0 (0.0%) | 0 (0.0%) | |
| Pain | 5 (5.7%) | 15 (11.6%) | 0.144 | 1 (1.1%) | 3 (2.3%) | 0.650 |
| Infection | 0 (0.0%) | 5 (3.9%) | 0.083 | 0 (0.0%) | 1 (0.8%) | 1.000 |
| Neuropathy | 18 (20.7%) | 50 (38.8%) | 0.005 | 0 (0.0%) | 5 (3.9%) | 0.083 |
| Arthralgia | 5 (5.7%) | 17 (13.2%) | 0.077 | 0 (0.0%) | 1 (0.8%) | 1.000 |

D, docetaxel; C, cyclophosphamide; F, fluorouracil; E, epirubicin; AST, aspartate aminotransferase; ALT, alanine aminotransferase. [1]Three patients in the AB group and 2 patients in the AF group did not receive any chemotherapy and were excluded from the safety analysis. [2]Chi-square test or Fisher's exact test (if one or more cells of the 2 × 2 contingency tables have expected frequencies <5).

**Table 4.** Results of univariable and adjusted multivariable logistic regression analyses with the incidence of any CTC-AE grade 3/4 during adjuvant chemotherapy (yes vs. no) as binary response variable

| Risk factor | | Univariable | | Multivariable | |
|---|---|---|---|---|---|
| | | odds ratio (95% confidence interval) | $p$ value | odds ratio (95% confidence interval) | $p$ value |
| Chemotherapy regime | AB versus AF | 2.96 (1.66–5.29) | <0.001 | 3.53 (1.90–6.56) | <0.001 |
| Radiation therapy | Yes versus no | 3.43 (1.70–6.92) | <0.001 | 4.70 (2.16–10.22 | <0.001 |
| Age (years) | | 1.04 (0.94–1.15) | 0.443 | 1.10 (0.98–1.23) | 0.103 |
| BMI (kg/m$^2$) | | 1.00 (0.94–1.07) | 0.928 | 0.98 (0.91–1.05) | 0.551 |

this toxicity [21]. A similar SEER-Medicare-based retrospective analysis compared ATAX versus TAX in 661 patients older than 66 years with node-positive TNBC and reported no significant difference in OS and BCSS between both regimes [22].

With increasing age, treatment goals gradually shift from reducing the risk of recurrence to maintaining the quality of life, cognitive and physical functionality, and protecting independence [9, 23]. Therefore, side effects of therapeutic treatment regimens become increasingly important in older patients. It is known that more than 62% of persons over 65 years have more than 2 chronic conditions, defined as polymorbidity, which is associated with elevated risk of death and adverse drug events [11].

This is because pharmacokinetics is different in the elderly population, mainly due to different functional reserves, polypharmacy, and by comorbidity-triggered organ dysfunctions [24].

Therefore, caution should be taken when an elderly patient is treated with cytotoxic agents, as chemotherapy-related side effects can lead to life-threatening medical conditions including febrile neutropenia, sepsis, or organ failure [24]. Anthracyclines are known for their hematological, gastrointestinal, and neurological toxicity, but cardiotoxicity is considered as the most relevant side effect, especially in the elderly [9, 10].

Our results show that the incidence of side effects (grade 3/4 adverse events) was significantly higher in the AB group with an odds ratio of 3.53 in adjusted multivariable analysis (Table 4). In particular, hematological adverse events occurred more often in the AB group than in the AF group (Table 3). Similar to our results, Narui et al. [20] reported significantly higher CTC-AE Grade 3 within the AB regime in comparison with AF, and these results are also supported by NeoSTOP and other studies [16, 18, 20]. Additional arguments for omitting AB regimes and favoring AF regimes are provided by the results from a French cohort confirming a good tolerability of DC among elderly patients with TNBC [25].

The advantage of our study is that elderly patients at all non-metastatic stages of TNBC were included and treated under standardized conditions of clinical trials. Additionally, we have two defined cohorts with specific chemotherapy regimens, thus avoiding any bias due to various treatment schemes. Furthermore, we could compare not only four different survival parameters but also the occurrence of side effects, thus combining results regarding both relevant oncological aspects in the elderly population. Limitations are the retrospective nature of our study and the fact that comparison was made between patients extracted from two different clinical trials (patients with AF regimen extracted from SUCCESS C trial only and patients with AB regimen extracted from both SUCCESS A and C trials), which implies a risk of selection bias. In addition, the number of events is limited, especially for some of the smaller subgroups. Another limitation is the lack of data on tumor-infiltrating lymphocytes that are known to have prognostic relevance in TNBC. Furthermore, more detailed information regarding geriatric assessment or comorbidities, as well as long-term follow-up data regarding cardiotoxicity or hematological malignancies, all of which might be crucial for the tolerability of chemotherapy-related side effects, is missing. Finally, the standard therapy of TNBC nowadays involves platinum agents, if Keynote 522 trial criteria are fulfilled immunotherapy, which was not included in our study [26].

## Conclusions

An adjuvant AF regimen containing 6 cycles of DC in a cohort of patients older than 65 years with TNBC showed similar survival and fewer side effects grade 3/4 according to CTC-AE in comparison with an anthracycline-taxane-based regimen. Our results suggest that the AF regimen with 6 cycles of DC could be considered a reasonable and safe alternative treatment option in elderly patients with TNBC. However, these results have to be confirmed by randomized controlled trials taking into account current standard therapeutic approaches in TNBC with platinum agents and immunotherapy.

## Statement of Ethics

A positive ethical approval of the respective leading Ethics Committee is available for both studies: SUCCESS A (EudraCT 2005-000490-21): Ludwig-Maximilian-Universität München 076/05 and SUCCESS C (NCT00847444): Heinrich-Heine-Universität Düsseldorf MC-LKP-319. All patients provided written informed consent.

## Conflict of Interest Statement

S.L. received honoraria from Lilly, Novartis, Theramex, Gedeon Richter, and Roche; V.F. received honoraria from Novartis and BD; T.F. received honoraria from Novartis and Lilly; F.M. got travel support from Lilly; K.P. obtained honoraria from Gilead, Novartis, and Pfizer, and research grants (constitutional) from AstraZeneca; H.S. got travel support from Daiichi Sankyo and Gilead, and received honoraria from Novartis; D.D. has no conflict of interest to disclose; S.H. received research funding and honoraria from Clovis Oncology, Inc., GlaxoSmithKline, Novartis, Roche, AstraZeneca, and Pfizer, and participated in advisory boards for Novartis, G.S.K., and Merck Sharp & Dome Corporation; B.R. acquired honoraria and research funding from AstraZeneca and Novartis; W.J. obtained honoraria and/or research funding from AstraZeneca, Cellgene, Chugai Daiichi Sankyo, Aisai, ExactScience, G.S.K., Janssen, Lilly, Menarini, M.S.D., Novartis, Sanofi-Aventis, Roche, Pfizer, Seagen, Gilead, and Inivata Guardant Health; E.L. received travel expenses from Lilly. W.J. was a member of the journal's Editorial Board at the time of submission.

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## Author Contributions

All authors discussed the results and implications and commented on the manuscript at all stages. S.L. designed the analysis, wrote the manuscript, and performed the evaluation and interpretation together with T.W.P.F. and E.L. The statistical

analysis was performed by T.W.P.F. V.F., D.D., F.M., H.S., K.P., and S.H. helped design the analysis and assisted the clinical interpretation of the data. B.R. and W.J. designed and conducted the SUCCESS studies, supervised the analysis, and assisted the clinical interpretation.

## Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary files. Further inquiries can be directed to the corresponding author.

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