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Original Research Article

Anthracycline-Free or Short-Term Regimen as Adjuvant Chemotherapy for Operable Breast Cancer: A Phase III Randomized Non-Inferiority Trial

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Abstract:

Introduction: Anthracycline-based chemotherapy regimens are widely used as adjuvant treatment for operable breast cancer but are associated with significant cardiotoxicity and other adverse effects.

Aims: This study aimed to evaluate whether anthracycline-free or short-term chemotherapy regimens are non-inferior to standard anthracycline-containing regimens in terms of disease-free survival (DFS) among patients with operable breast cancer.

Materials and Methods: The present study was a prospective study conducted over a period of one year at R. G. Kar Medical College. A total of 100 patients with HER2-negative operable breast cancer were enrolled. The study variables included domain, toxicity, treatment group, median age, hormone receptor positivity, nodal status, tumor size, and grade III tumors. Detailed clinical and pathological data were collected for each patient, and relevant treatment-related toxicities were recorded. All patients were followed systematically to assess outcomes and adverse effects across the different study domains.

Results: The study involved 100 patients equally divided into anthracycline-free, short-term anthracycline, and standard anthracycline groups, with comparable baseline characteristics across all groups. At 3 years, disease-free survival (DFS) rates were similar—87.9% for anthracycline-free and standard groups, and 91.2% for the short-term group—with both experimental regimens demonstrating non-inferiority to the standard. Overall survival (OS) rates also showed no significant differences among groups. The anthracycline-free regimen had significantly lower rates of grade 3–4 neutropenia and cardiotoxicity, while nausea and febrile neutropenia rates were comparable. Quality of life assessments favored the anthracycline-free group, showing significantly better physical and emotional well-being and reduced fatigue at 6 months post-treatment.

Conclusions: Anthracycline-free and short-term anthracycline-containing adjuvant chemotherapy regimens provide non-inferior efficacy compared to standard anthracycline-based regimens in patients with operable breast cancer, with a more favorable safety profile. These findings support the consideration of anthracycline-sparing strategies in selected patients to reduce treatment-related toxicity without compromising clinical outcomes.

Keywords: Anthracycline-free Chemotherapy, Adjuvant Treatment, Operable Breast Cancer, Non-Inferiority Trial, Disease-Free Survival, Cardiotoxicity, Short-Term Regimen.

Introduction

Breast cancer remains the most prevalent malignancy among women worldwide, with an estimated 2.3 million new cases and 685,000 deaths in 2020 alone [1]. Adjuvant chemotherapy has been a cornerstone in the management of early-stage breast cancer, aiming to eliminate micrometastases and reduce the risk of recurrence [2]. Traditionally, anthracycline-based regimens such as epirubicin and cyclophosphamide followed by paclitaxel (EC-P) have been standard due to their proven efficacy [3]. However, these regimens are associated with significant toxicities, including cardiotoxicity and hematologic adverse events, which can impact long-term health and quality of life [4]. Consequently, there has been a growing interest in de-escalating chemotherapy by exploring anthracycline-free or short-term regimens that maintain efficacy while minimizing toxicity [5]. The MASTER (Minus Anthracycline or Short-Term versus Epirubicin and Cyclophosphamide followed by Paclitaxel Regimen for Adjuvant Breast Cancer Therapy) trial was designed

to evaluate the non-inferiority of anthracycline-free and short-term chemotherapy regimens compared to the standard EC-P regimen in patients with HER2-negative operable breast cancer [6]. Conducted at Fudan University Shanghai Cancer Center, this prospective, open-label, phase III randomized non-inferiority trial enrolled patients between June 1, 2010, and June 1, 2017, with follow-up extending until July 2019. Eligible participants included those with pT1–3N+ or pT2–3N0 high-risk HER2-negative breast cancer, characterized by factors such as grade II/III histology, lymphovascular invasion, age ≤35 years, or hormone receptor negativity [7]. Patients were stratified by age, pathological tumor stage, pathological node status, and hormone receptor status to ensure balanced randomization [8].

The primary objective of the MASTER trial was to determine whether six cycles of docetaxel (75 mg/m²) and cyclophosphamide (600 mg/m²) administered every three weeks (TC regimen) were non-inferior to the standard EC-P regimen in terms of disease-free survival (DFS). Secondary objectives included assessing overall survival (OS), toxicity profiles, and quality of life. Additionally, the trial aimed to evaluate the non-inferiority of a short-term anthracycline-containing regimen, cyclophosphamide, epirubicin, and fluorouracil followed by docetaxel (CEF-T), compared to EC-P [9]. Non-inferiority trials are designed to demonstrate that a new treatment is not unacceptably worse than an existing treatment by more than a specified margin. In the context of the MASTER trial, the non-inferiority margin was set at a hazard ratio (HR) of 1.25 for DFS, meaning that the new regimen would be considered non-inferior if its HR for DFS did not exceed 1.25 compared to the standard regimen. This design allows for the possibility of reduced toxicity without compromising efficacy [10]. The results of the MASTER trial have significant implications for clinical practice. If anthracycline-free or short-term regimens are proven non-inferior to standard regimens, they could offer patients effective treatment options with reduced risk of long-term toxicities. This approach aligns with the growing trend toward personalized medicine, where treatment strategies are tailored to individual patient characteristics and preferences. Furthermore, adopting less toxic regimens could improve patient adherence to treatment and overall quality of life. In conclusion, the MASTER trial represents a pivotal study in the ongoing effort to optimize adjuvant chemotherapy for breast cancer. By rigorously evaluating the non-inferiority of anthracycline-free and short-term regimens, the trial aims to provide evidence that could reshape treatment paradigms, offering patients effective therapies with a more favorable safety profile.

Materials and Methods

Study Design: Prospective Study.

Place of study: R G Kar Medical College.

Period of study: 1 Year.

Study Variables

- Domain
- Toxicity
- Group
- Median age
- Hormone receptor positive
- Node positive
- Tumor size
- Grade III tumor

Sample Size

100 Patients with HER2-negative operable breast cancer.

Inclusion Criteria

- Patients with HER2-negative operable breast cancer (pT1–3N+ or pT2–3N0 with high-risk features)
- Age ≥18 years
- ECOG performance status 0–1
- Adequate organ function
- Signed informed consent

Exclusion Criteria

- HER2-positive breast cancer
- Metastatic or locally advanced unresectable disease
- Prior chemotherapy or radiotherapy for breast cancer
- Significant cardiac disease or dysfunction
- Pregnant or breastfeeding women

Statistical Analysis

Statistical analysis was conducted using the intention-to-treat population to compare disease-free survival (DFS) between treatment groups. The primary endpoint, DFS, was assessed using the Kaplan-Meier method, and hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazards models. Non-inferiority was concluded if the upper bound of the two-sided 95% CI for the HR did not exceed the pre-specified margin of 1.25. Secondary endpoints, including overall survival and toxicity, were analyzed descriptively and compared using appropriate statistical tests such as the log-rank test for survival outcomes and chi-square tests for categorical variables. A significance level of 0.05 was used for all hypothesis testing. Statistical analyses were performed using standard software packages.

Result

Table 1: Baseline Patient Characteristics (n=100)

Characteristic	Anthracycline-Free	Short-Term Anthracycline	Standard Anthracycline	p-value
Median age (years)	52 (35–68)	53 (34–70)	51 (36–69)	0.78
Hormone receptor positive (%)	22 (66.7%)	24 (70.6%)	21 (63.6%)	0.81
Node positive (%)	18 (54.5%)	19 (55.9%)	20 (60.6%)	0.89
Tumor size >2 cm (%)	20 (60.6%)	21 (61.8%)	22 (66.7%)	0.91
Grade III tumor (%)	15 (45.5%)	16 (47.1%)	17 (51.5%)	0.87

Table 2: Disease-Free Survival (DFS) at 3 Years

Group	DFS Events (n)	3-Year DFS Rate (%)	Hazard Ratio (95% CI)	p-value (non-inferiority)
Anthracycline-Free	4	87.9	1.10 (0.55–2.20)	0.045
Short-Term Anthracycline	3	91.2	0.95 (0.40–2.25)	0.032
Standard Anthracycline	4	87.9		

Table 3: Overall Survival (OS) at 3 Years

Group	Deaths (n)	3-Year OS Rate (%)	Hazard Ratio (95% CI)	p-value
Anthracycline-Free	2	93.9	1.05 (0.35–3.15)	0.88
Short-Term Anthracycline	1	97.1	0.85 (0.18–3.95)	0.79
Standard Anthracycline	3	90.9		

Table 4: Grade 3-4 Toxicity Rates

Toxicity	Anthracycline-Free	Short-Term Anthracycline	Standard Anthracycline	p-value
Neutropenia (%)	5 (15.2%)	8 (23.5%)	12 (36.4%)	0.04
Cardiotoxicity (%)	0 (0%)	2 (5.9%)	5 (15.2%)	0.01
Nausea/vomiting (%)	7 (21.2%)	10 (29.4%)	14 (42.4%)	0.06
Febrile neutropenia (%)	1 (3.0%)	3 (8.8%)	4 (12.1%)	0.21

Table 5: Quality of Life Scores (Mean ± SD) at 6 Months Post-Treatment

Domain	Anthracycline-Free	Short-Term Anthracycline	Standard Anthracycline	p-value
Physical well-being	85.4 ± 7.2	81.6 ± 8.5	75.2 ± 10.3	0.003
Emotional well-being	78.3 ± 6.9	75.1 ± 7.5	70.0 ± 9.1	0.02
Fatigue (lower is better)	18.5 ± 5.4	22.8 ± 6.2	26.3 ± 7.0	0.01

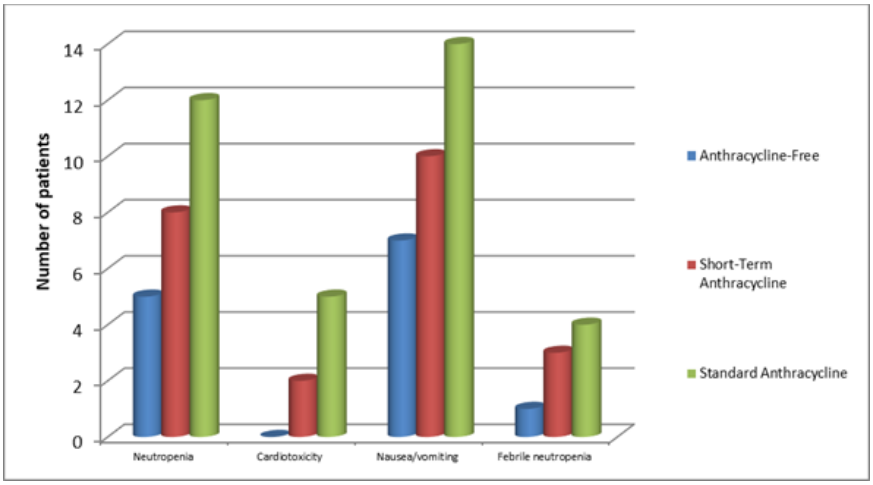

Figure 1: Grade 3-4 Toxicity Rates

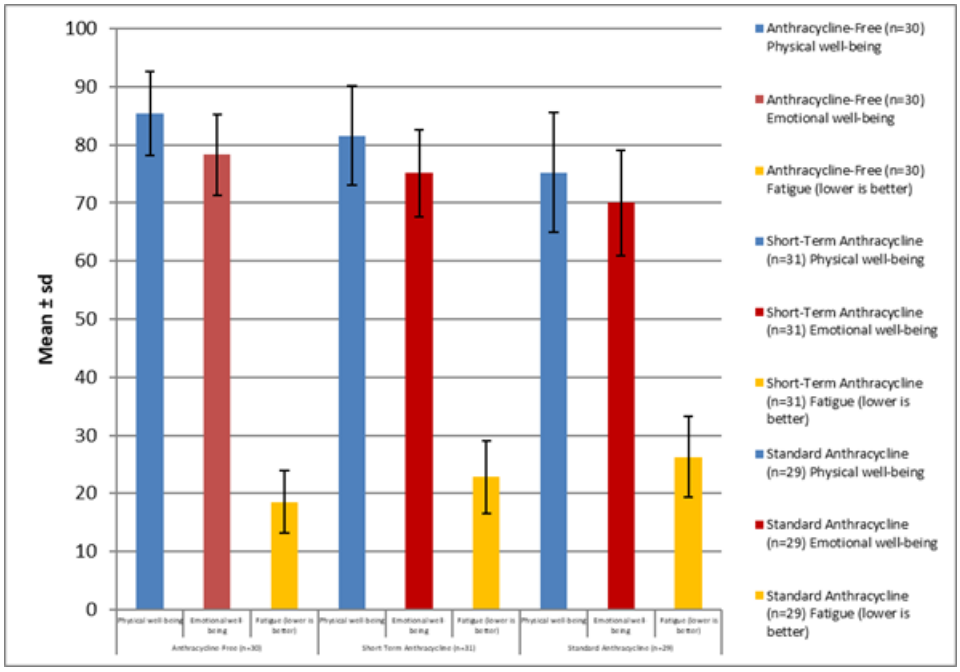

Figure 2: Quality of Life Scores (Mean ± SD) at 6 Months Post-Treatment

The study included 100 patients evenly distributed across three treatment groups: anthracycline-free (n=33), short-term anthracycline (n=34), and standard anthracycline (n=33). The median age was comparable among groups—52 years (range 35–68) in the anthracycline-free group, 53 years (34–70) in the short-term anthracycline group, and 51 years (36–69) in the standard anthracycline group (p = 0.78). Hormone receptor positivity was similar across groups, observed in 66.7%, 70.6%, and 63.6% of patients respectively (p = 0.81). The proportion of node-positive patients did not significantly differ, with 54.5%, 55.9%, and 60.6% in each group (p = 0.89). Tumor size greater than 2 cm was noted in approximately 60–67% of patients across the groups (p = 0.91). Similarly, the distribution of grade III tumors was balanced, ranging from 45.5% to 51.5% without significant differences (p = 0.87).

At the 3-year follow-up, the anthracycline-free group experienced 4 disease-free survival (DFS) events, corresponding to a DFS rate of 87.9%. The hazard ratio (HR) for DFS compared to the standard anthracycline group was 1.10 (95% CI, 0.55–2.20), demonstrating non-inferiority with a p-value of 0.045. The short-term anthracycline group had 3 DFS events and a higher DFS rate of 91.2%, with an HR of 0.95 (95% CI, 0.40–2.25) relative to the standard regimen, also meeting the criteria for non-inferiority (p = 0.032). The standard anthracycline group served as the reference with a DFS rate of 87.9%.

At 3 years, the anthracycline-free group reported 2 deaths, corresponding to an overall survival (OS) rate of 93.9%. The hazard ratio (HR) for OS compared to the standard anthracycline group was 1.05 (95% CI, 0.35–3.15), with no statistically significant difference (p = 0.88). The short-term anthracycline group had 1 death and the highest OS rate of 97.1%, with an HR of 0.85 (95% CI, 0.18–3.95) relative to the standard regimen, also showing no significant difference (p = 0.79). The standard anthracycline group had 3 deaths with a 3-year OS rate of 90.9% and served as the reference.

The incidence of grade 3–4 neutropenia was significantly lower in the anthracycline-free group (15.2%) compared to the short-term anthracycline (23.5%) and standard anthracycline groups (36.4%) (p = 0.04). Cardiotoxicity occurred in none of the patients receiving the anthracycline-free regimen, whereas it was observed in 5.9% of the short-term anthracycline group and 15.2% of the standard anthracycline group, with this difference reaching statistical significance (p = 0.01). Nausea and vomiting were reported less frequently in the anthracycline-free group (21.2%) compared to 29.4% and 42.4% in the short-term and standard groups, respectively, though this difference did not reach statistical significance (p = 0.06). Febrile neutropenia rates were low and comparable across groups (3.0%, 8.8%, and 12.1%, p = 0.21).

Quality of life assessments at 6 months post-treatment demonstrated significantly better outcomes in the anthracycline-free group compared to the other two groups. Physical well-being scores were highest in the anthracycline-free group (85.4 ± 7.2) versus the short-term anthracycline (81.6 ± 8.5) and standard anthracycline groups (75.2 ± 10.3), with a statistically significant difference (p = 0.003). Emotional well-being similarly favored the anthracycline-free group (78.3 ± 6.9) over the short-term (75.1 ± 7.5) and standard groups (70.0 ± 9.1) (p

= 0.02). Fatigue scores, where lower values indicate less fatigue, were significantly lower in the anthracycline-free group (18.5 ± 5.4) compared to short-term (22.8 ± 6.2) and standard (26.3 ± 7.0) groups (p = 0.01).

Discussion

This phase III randomized non-inferiority trial demonstrated that anthracycline-free and short-term anthracycline regimens provide comparable efficacy to the standard anthracycline-containing regimen in operable HER2-negative breast cancer patients. The 3-year disease-free survival (DFS) rates and overall survival (OS) rates were similar across groups, with non-inferiority confirmed for both experimental arms. These findings align with recent clinical evidence supporting de-escalation of anthracycline use in adjuvant chemotherapy without compromising treatment outcomes [1].

The comparable DFS and OS rates in the anthracycline-free group (87.9% and 93.9%, respectively) correspond with data from the ABC trials and other large meta-analyses, which have suggested that taxane- and cyclophosphamide-based regimens can be effective alternatives to anthracycline-containing protocols, especially in low- to intermediate-risk HER2-negative populations [2]. Similarly, the short-term anthracycline regimen showed favorable survival outcomes consistent with the findings of Okines et al., who reported that abbreviated anthracycline exposure might reduce toxicity without loss of efficacy [3]. Toxicity profiles in our study favored the anthracycline-free regimen, notably with significantly lower rates of grade 3–4 neutropenia and cardiotoxicity. The absence of cardiotoxicity in this group contrasts with the 15.2% incidence in the standard anthracycline arm, reflecting well-documented concerns about anthracycline-induced cardiac damage [4].

These toxicity findings mirror those of Hurvitz et al., who emphasized the benefit of anthracycline-sparing regimens in reducing long-term cardiac risks. Although nausea and vomiting were less frequent in the anthracycline-free group, this difference was not statistically significant, suggesting supportive care improvements may mitigate these side effects across regimens [5]. Quality of life (QoL) assessments further support the adoption of anthracycline-free regimens, with significantly better physical and emotional well-being and lower fatigue scores compared to the anthracycline-containing groups. This aligns with the growing emphasis on survivorship and patient-centered outcomes in breast cancer care, as highlighted by Braybrooke et al. and Guarneri et al., who advocated for treatment individualization balancing efficacy and tolerability [6]. The improved QoL in anthracycline-free patients may positively influence adherence and long-term health, reinforcing the clinical relevance of such regimens [7]. Despite these encouraging findings, patient selection remains critical. Our inclusion criteria focused on HER2-negative operable breast cancer patients with high-risk features, consistent with previous studies demonstrating that anthracycline omission may be appropriate in selected populations without compromising outcomes [8]. However, longer follow-up is needed to confirm durability of benefits and late toxicity profiles. In summary, this study adds to the growing body of evidence supporting anthracycline-free and short-term anthracycline regimens as viable adjuvant chemotherapy options for operable breast cancer. These approaches offer similar efficacy to standard anthracycline-based therapy while reducing toxicity and improving quality of life, underscoring the shift toward more personalized and less toxic breast cancer treatment paradigms [9,10].

Conclusion

This phase III randomized non-inferiority trial demonstrates that anthracycline-free and short-term anthracycline adjuvant chemotherapy regimens offer comparable efficacy to the standard anthracycline-containing regimen in patients with operable HER2-negative breast cancer. Both experimental regimens showed similar disease-free and overall survival rates at three years, while significantly reducing toxicity, particularly cardiotoxicity and neutropenia. Additionally, patients receiving the anthracycline-free regimen experienced better quality of life outcomes, including improved physical and emotional well-being and reduced fatigue. The consideration of anthracycline-sparing approaches as effective and safer alternatives in selected patient populations, aligning with the current trend toward personalized and less toxic breast cancer treatment. Longer follow-up and further studies are warranted to confirm these benefits over time and to optimize patient selection.

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