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Comparative Efficacy of Adjuvant Chemotherapy Regimens for Breast Cancer: A Study on Cyclophosphamide and Doxorubicin (AC) Versus Paclitaxel (T) and the Impact of Biological Characteristics

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Abstract. Background: Cyclophosphamide plus doxorubicin (AC) and single-agent paclitaxel (T) have been shown to be major and effective adjuvant chemotherapy regimens for breast cancer. Personalized treatment plans tailored to individual patient factors have demonstrated significant improvements in curative performance. This study investigated the dataset provided by the CALGB 40101 trial, a phase III randomized study that compared the efficacy of AC and T as adjuvant therapy for breast cancer. **Methods**: The overall survival (OS) and disease-free survival (DFS) distributions grouped by several factors were described by the Kaplan-Meier method. Additionally, the impact of various factors on the OS and DFS was observed by the Cox proportional hazard model. By stratifying data into different subgroups, the model also showed the association between the characteristics and the efficacy of different regimens. **Results**: A significant impact of the agents on OS was observed and the HR was 1.279, while different treatment durations did not show a significant association with OS. Also, the agent significantly affected DFS, while a significant difference grouped by duration was not observed. Furthermore, factors, such as tumor size and age, significantly increased the hazard of mortality and relapse. **Conclusion**: The efficacy of AC and T had significant differences when treating breast cancer as adjuvant therapy, while the treatment duration did not show a significant impact. Also, age, tumor size, receptor status, and histologic grade significantly affect overall or disease-free survival.

Keywords: Paclitaxel, doxorubicin plus cyclophosphamide, personalized treatment, breast cancer, overall survival, disease-free survival, adjuvant chemotherapy.

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1. Introduction

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer-related deaths among women worldwide, causing 670,000 deaths globally and accounting for 11.5% of all new cancer cases and 6.8% of all cancer deaths by 2022 [1]. Effective treatment for breast cancer is considered a combination of different approaches. In addition to the surgery and radiation therapy, adjuvant chemotherapy is also considered an important component [2] of curative treatment for many types of cancers, with the aim to improve the overall survival (OS) and disease-free survival (DFS) for patients undergoing pre-operative and post-operative care. Furthermore, biological characteristics vary from individual to individual, which has a high possibility [3] of influencing the final survival rate and curative effects.

Two common adjuvant chemotherapy regimens for breast cancer are the combination of doxorubicin plus cyclophosphamide (AC) [4, 6, 8], as well as single-agent paclitaxel (T) [4, 5]. While previous studies have examined the AC [6] and single-agent T [7] regimens individually, a direct comparative analysis of these two regimens is currently lacking. Notably, several studies have investigated the difference between the efficacy of AC and paclitaxel plus cyclophosphamide (TC), AC and doxorubicin plus paclitaxel (AT) [8, 9], but these comparisons do not directly show the curative effect of single-agent T since they do not precisely identify the source of the therapeutic effect. Furthermore, previous investigations into the efficacy of various chemotherapy regimens may not incorporate the most recent information and data, as the majority of the studies were based on datasets collected in the 1990s [8, 10].

Unlike earlier research, this study directly evaluates the efficacy of T in comparison to AC, using data from a clinical trial conducted between 2002 and 2010. This specific trial design made it possible to isolate the impact of T alone, avoiding potential confounding factors that could stem from AC treatments.

Previous investigations were typically smaller in scope, with sample sizes under 1000 participants [8, 11, 12], focusing on limited characteristics like the number of positive axillary nodes [11, 13]. Additionally, many studies restricted their analyses to fixed treatment durations [10, 11]. In contrast, the current study utilizes a far larger sample of 3,871 participants with a median follow-up of 6.1 years, allowing a more in-depth examination of treatment lengths—specifically, 4 versus 6 cycles. Furthermore, this dataset included a diverse range of tumor sizes, from less than 2 cm to over 5 cm, enabling a broader examination of patients.

This study also examines AC and single-agent T in terms of OS and DFS as well as how treatment duration (4 cycles vs. 6 cycles) and patient/tumor characteristics (race, dose density, menopause status, receptor status, tumor size, age category, histologic grade, HER2 status) influence the outcomes.

2. Method

2.1. Data Description

This research utilizes the rich dataset from the CALGB 40101 trial, providing a solid foundation to explore the comparative efficacy of different chemotherapy regimens and their interactions with patient factors concerning survival outcomes. CALGB 40101 was a phase III randomized study comparing the standard AC (Cyclophosphamide and Doxorubicin) with experimental Paclitaxel (T) as adjuvant therapies for breast cancer in women with 0-3 positive axillary lymph nodes. While AC served as the control group, T was the experimental treatment. The standard treatment duration comprised 4 cycles, whereas the experimental regimen was extended to 6 cycles.

2.2. Variable Description

Our research examined two primary sections of predictors: chemotherapy regimens(AC or T) and treatment durations (4 or 6 cycles). The primary objective was to assess the efficacy of different chemotherapy regimens while accounting for various patient factors in breast cancer. Thus, we focused on both overall survival (OS) and disease-free survival (DFS) as key outcome measures.

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2.3. Collecting Methods

Patients were randomly assigned by computer to receive either 4 cycles (8 weeks) or 6 cycles (12 weeks) of AC or single-agent T. During the treatment period, patients were regularly monitored for survival status (alive or deceased). Overall survival (OS) was measured from study entry until death, with living patients censored at their last follow-up. Disease-free survival (DFS) was measured from study entry until the first relapse or death, with disease-free patients censored at their last known disease-free date.

2.4. Statistical Analysis

The analysis primarily compared the efficacy of the AC and T regimens, while also considering the role of patient characteristics on outcomes.

The chi-square test was used to explore the relationships between covariates and outcomes calculating 95% confidence intervals. Logistic regression models were employed to examine the effects of treatment on both survival and DFS.

The Kaplan-Meier method was employed to describe the distribution of overall survival time and disease-free survival time. The agent as well as the treatment duration were compared through a two-sided log-rank test with a 5% significance level.

Moreover, the Cox proportional hazards model adjusted for the agent, the length of treatment, age, race, receptor status, histologic grade, tumor size, prior hormonal therapy, and a sentinel node biopsy. Also, the model calculated the 95% confidence intervals and hazard ratio (HR) of the variables. To ensure the validity of the model, the assumption of the proportional hazard hypothesis was tested. At last, the Cox proportional hazards model was fitted to the subset to address the impact of treatment on the specific groups of patients.

3. Result

3871 participants were randomly divided into four groups (AC-4, 1142 patients; AC-6, 789 patients; T-4, 1151 patients; T-6, 789 patients). The characteristics of the patients are summarized in Table 1. The distribution of agent and duration was well balanced. Also, the tumor laterality was evenly distributed (left 50.45%, right 47.79%), with a small percentage having bilateral tumors (1.50%). Regarding menopause status, 39.81% of patients were pre-menopausal, while 60.19% were post-menopausal. 66.29% of patients were receptor-positive, while 33.48% and 66.29% were negative and positive for ER status, respectively. Histologic grade distribution suggested that 45.47% of patients had high-grade tumors, 39.40% intermediate, and 13.54% low-grade tumors. Survival status indicated that 93.13% of patients were alive at the time of data collection, with a mean survival of 68.02 months and a median of 71.1 months. DFS was observed in 88.71% of patients, with a mean of 63.37 months and a median of 64.03 months.

Table 1. Patient and Disease Characteristics at Study Entry

	n	proportion(%)
Menopause status		
Pre-menopause	1541	39.81
Post-menopause	2330	60.19
Receptor status		
Recep+ & Unkown	2628	67.89
Recep-	1243	32.11
Receptor Status ER		
Negative	1296	33.48
Positive	2566	66.29
Histologic grade		
Low	524	13.54
Intermediate	1525	39.40
High	1760	45.47

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Table 1. (continued).

Treatment assigned		
AC-4	1142	29.50
AC-6	789	20.38
T-4	1151	29.73
T-6	789	20.38
Survival Months		
Mean	68.02	
Median	71.1	
Range	0-123.43	
Disease Free Survival Months		
Mean	63.37	
Median	64.03	
Range	0-120.71	

The treatment agent, duration, receptor status, and tumor size significantly impacted OS status by the logistic regression ($p<0.001$). The agent, the treatment duration, menopause status, receptor status, and tumor size also have a significant impact on DFS status ($p<0.001$).

OS and DFS distributions were described by the Kaplan-Meier method in Fig. 1 and grouped by receptor status ER, menopause status, and primary surgery. The log-rank test showed the treatment agent had a significant impact on OS ($p = 0.0455$). This suggests a significant difference in OS between patients treated with different agents. The agent also showed a significant effect ($p = 0.0455$) in the subgroup analysis stratified by treatment duration. Nevertheless, treatment duration and stratification by the agent did not show a significant difference associated with outcomes, as indicated by the log-rank test ($p = 0.5$).

Furthermore, the Cox proportional hazards model, which included both agent and treatment duration as predictors, indicates that the agent has a significant effect on survival (HR = 1.29, $p = 0.047$), while treatment duration did not show a significant influence on OS (HR = 1.089, $p = 0.489$). Additionally, including an interaction term of the agent and treatment duration did not show significant improvement, suggesting no evidence of an interaction effect of these two factors on OS ($p = 0.2048$). For the DFS, the survival difference by the agent ($p = 0.01$) is significant, while the difference by duration ($p = 0.7$) is not.

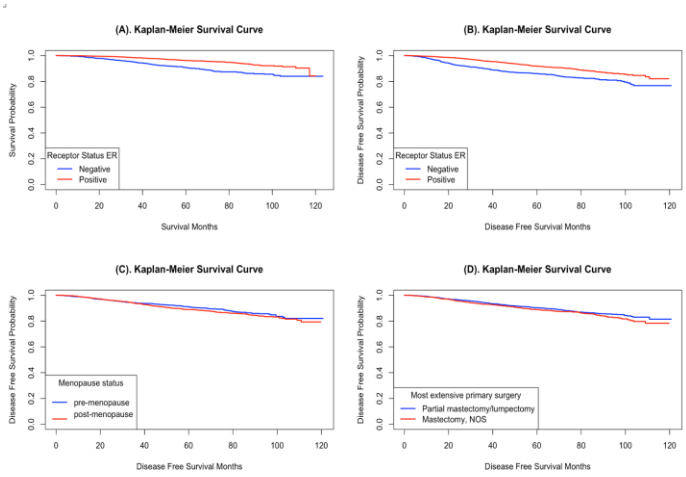

Figure 1. (A) OS for all patients grouped by receptor status ER. (B) DFS for all patients grouped by receptor status ER. (C) DFS for all patients grouped by their menopause status. (D) DFS for all patients grouped by primary surgery.

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The DFS was analyzed by the Cox proportional hazards model, incorporating various factors to evaluate their effect on the hazard (Table 2). The treatment with the agent increased the hazard by approximately 23.2% (HR = 1.2322, p = 0.0332), indicating a statistically significant effect, while the treatment duration did not show a significant impact (p = 0.8291). Tumor size was a significant predictor and larger tumor size increased the hazard (HR: 1.5652 and 2.0282, p: <0.001 and 0.019, respectively). Additionally, high histologic grade (HR = 1.82, p < 0.001) and age (HR = 2.19, p = 0.031) also significantly increased the hazard. Similarly, the agent, tumor size, sentinel node biopsy, age, and receptor status were significant factors influencing OS, and both increased the hazard. While race and ethnicity, as well as several other predictors like prior hormonal therapy, type biopsy, tumor laterality, and menopause status, did not show significant effects. At last, there was no evidence to reject the assumption of the proportional hazard hypothesis, which showed the validity of the models (p = 0.0696; p = 0.0716, respectively).

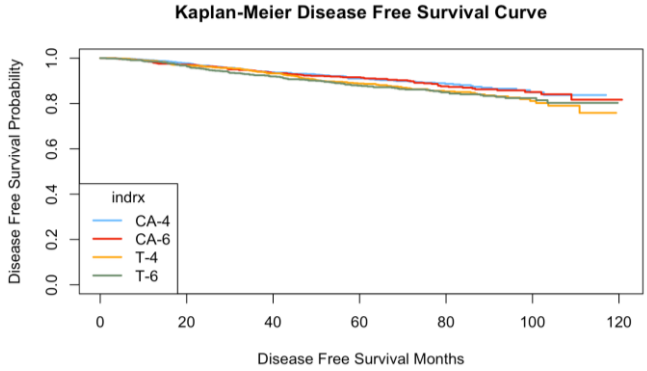

Figure 2. DFS for all patients grouped by the treatments

Table 2. Multivariable Proportional Hazards Models: Observed Effects on DFS and OS (n = 3,862)

Factors	DFS			OS		
	HR	95% CI*	P	HR	95% CI*	P
Agent (AC/T)	1.23	1.02 to 1.49	.033	1.29	1.01 to 1.65	.044
Tumor size was between 2 and 5 cm	1.57	1.29 to 1.91	< .0001	1.58	1.23 to 2.03	.00038
Tumor size was greater than 5cm	2.03	1.12 to 3.66	.019	3.22	1.67 to 6.21	.00047
Native Hawaiian or Pacific Islander or American Indian	2.19	1.07 to 4.45	.031	1.57	0.50 to 4.95	.44
Histologic grade (high)	1.82	1.29 to 2.57	.00068	-	-	-
Sentinel node biopsy	0.80	0.60 to 1.07	.13	0.73	0.55 to 0.97	.029
Age	1.02	1.00 to 1.03	.024	1.04	1.02 to 1.05	< .0001
Receptor status	-	-	-	2.19	1.71 to 2.82	< .0001

* There are two vacuums since the receptor status was not included in the first model and histologic grade (high) was not included in the second model. (1) the Cox proportional hazards model analyzed the DFS, adjusting for the agent, length, tumor size, sentinel node biopsy, age, race, histologic grade, menopause status, number of positive nodes, receptor status, and the primary surgery. (2) the Cox proportional hazards model analyzed the OS, adjusting for agent, length, tumor size, sentinel node biopsy, prior hormonal therapy, type biopsy, tumor laterality, race, ethnicity, age, receptor status, and menopause status.

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Table 3. Comparative Outcomes on OS and DFS in different subgroups

Factor	Subgroup	P value (OS)	P value (DFS)
Menopause Status	Pre-menopause	0.5	0.4
	Post-menopause	0.06	0.01
Hormone Receptor Status	Positive, Unknown	0.2	0.09
	Negative	0.12	0.06
Her2-neu Status	Positive	0.2	0.2
	Negative	0.7	0.6
	Unknown	0.03	0.02
Receptor Status ER	ER-negative	0.03	0.02
	ER-positive	0.5	0.2
Most Extensive Primary Surgery	Mastectomy	0.4	0.3
	Partial mastectomy/lumpectomy	0.06	0.03

Table 3 summarizes the results of log-rank tests comparing OS and DFS between treatment regimens (AC vs. T) across various subgroups. Significant differences are noted for $p < 0.05$.

4. Discussion

The treatment duration did not show significant impact on OS and DFS, which might be contrary to our initial expectations. One critical aspect to consider in this finding is the dose intensity, which refers to the amount of chemotherapy delivered per unit time. Research has shown that dose density plays a critical role in treatment efficacy. Reductions in dose intensity may weaken the effects of chemotherapy agents, leading to poorer survival outcomes. Studies have indicated that maintaining dose intensity, rather than extending the number of cycles, was vital for achieving better clinical outcomes, suggesting that the total dose delivered over a given period may be more important than the actual number of cycles [36]. In our study, the amount of drugs delivered per unit of time was the identical across different treatment durations, maintaining a consistent dose intensity. Consequently, the consistent dose intensity in different treatments could contribute to the lack of significant differences in OS and DFS observed between the 4-cycle and 6-cycle groups. Furthermore, the relatively small difference in treatment length between different cycles made it harder to observe the significant difference.

Age has consistently been a crucial factor when considering different cancer treatments. Aging leads to changes in the immune system known as immunosenescence [15]. With aging, the thymus, a primary lymphoid organ responsible for T-cell development, undergoes progressive atrophy [14, 34]. This results in a decline in the production of T cells [35], which are essential for generating effective immune responses to new antigens, including tumors. Other immune organs and functions, such as telomere shortening, have also undergone certain degrees of senescence and impairment, reducing immune responsiveness and the ability to fight infections and cancer. This would increase the risk of tumor metastasis and recurrence, which is consistent with our finding that one year older increased the hazard of relapse by approximately 2% and an increased hazard of death by approximately 4%.

Larger tumor sizes are consistently associated with poorer DFS and OS in breast cancer patients. Larger tumors typically indicate a greater number of tumor cells and a higher grade of malignancy [16], increasing the risk of metastasis and recurrence, thereby significantly reducing the patient's OS and DFS. Larger tumors generally have more aggressive and metastatic potential [17], as the tumor cells have

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more opportunities to enter the blood vessels and lymphatic system, increasing the likelihood of distant metastasis. Additionally, larger tumors may be more challenging to completely remove through surgery or effectively target with local radiotherapy [18]. The inability to thoroughly eradicate the primary tumor can increase the risk of recurrence, further compromising DFS. Similar to our findings, it was discovered that tumors with a size greater than 5 cm increased the hazard of relapse by approximately 103% and the hazard of death by approximately 222%.

The AC adjuvant chemotherapy agent primarily acts by directly killing tumor cells and inhibiting tumor growth and metastasis [19, 20]. In contrast, T mainly works by modulating the dynamics of microtubules through the regulation of estrogen signaling, thereby inhibiting tumor cell growth [21, 22]. However, in postmenopausal women, the decline in estrogen levels reduces the regulatory effect on microtubule stability [23, 24], which diminishes the efficacy of paclitaxel. This highlights the advantage of AC's direct targeting effect on cancer cells, which is consistent with our finding that patients receiving T had a 31% higher risk of recurrence compared to the AC group. Apart from DFS, the curative effectiveness of the agents has no significant difference on OS. For postmenopausal women, once disease recurrence occurs, OS may be impacted by other factors such as subsequent treatment regimens and comorbidities, such as variable metastasis and lymphedema, which could reduce the differences in DFS between AC and T.

The histologic grade serves as a crucial and practical standard for grading breast cancer, offering a direct, cost-effective, and highly accurate means of assessing tumor biological characteristics [37]. Patients with a high histologic grade face an elevated risk of mortality and are more prone to relapse [38], aligning with our finding that a high histologic grade raises the relapse hazard by approximately 82% compared to a low histologic grade.

Receptor status is an important factor to be considered when treating cancer since the treatments have various effects on different receptor statuses. Receptors, proteins located on the surface of breast cells, transmit signals to the cells to initiate growth and division upon hormone binding. The Hormonal therapy has a better performance when the tumor is ER+ and/or PgR- [28], while dehydroepiandrosterone (DHEA) and its sulfate inhibit the growth of ER- cancer more efficiently [39]. Moreover, according to previous studies, hormone receptor-negative breast cancers are inclined to grow faster than receptor-positive ones. Women with ER- and Pgr- tumors have a higher risk of death [25, 26, 27]. Our research also discovered that the negative receptor status increases the hazard of relapse by about 119%, which strongly affects the DFS.

The Native Hawaiian or Pacific Islander or American Indian had a higher hazard of relapse and their risk of reoccurring breast cancer was 2.19 times of the whites. The relatively high recurrence rate could be attributed to their living conditions and socioeconomic, biological, and behavioral factors. Studies have shown that Native Hawaiian, Pacific Islander, and American Indian populations often face greater socioeconomic disparities [32], including lower incomes, higher poverty rates, and reduced access to quality healthcare [33]. In addition, most native Hawaiian women have low or no participation in routine due to the Hawaiian culture and religious customs. As a result, native Hawaiian women may have poorer health conditions, which leads to a higher hazard of relapse.

5. Conclusion

The efficacy of AC and T had significant differences when treating breast cancer as adjuvant therapy, while the treatment duration did not show a significant impact. Also, age, tumor size, receptor status, and histologic grade significantly affect OS or DFS.

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