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Impact of Relative Dose Intensity (RDI) on Survival in Non-Metastatic Breast Cancer: Nigerian Experience

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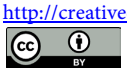

Abstract

Background: This study was initiated to determine practices patterns in adjuvant chemotherapy for non-metastatic breast cancer and to examine the relationship between received dose intensity (RDI) and survival in patients with breast cancer Nigeria. Methods: Our study was a retrospective analysis of patients with breast cancer recruited from 2012 and 2015. A total of 204 patients were initially entered into the study, 102 were lost to follow-up leaving 102 patients who were suitable for the survival analysis. Survival time was calculated from 106 days, the scheduled end of chemotherapy. Results: The total average RDI for patients was 74%. Over the 204 patients that were reviewed, 144 (70.6%) had some reduction of RDI. This subgroup had an average RDI of 63%. On average, 79% of the intended dose of chemotherapy was given. The time to completion of chemotherapy was 1.33 times that specified by the protocol. Dose delays an overall reduction was mainly attributed to intolerability and financial constraints. Survival by RDI showed a significant decrease in survival rate for patients with RDI of >49% (Hazard Ratio = 3.473, 95% CI 1.21 - 9.91, P = 0.020); RDI of 50% - 59% (Hazard Ratio = 3.916, 95% CI 1.01 - 15.18, P = 0.048); RDI of 60% - 69% (Hazard Ratio = 4.462, 95% CI 1.65 - 12.03, P = 0.003) compared with patients who received an RDI of 100%. Although associated with poorer prognosis, there were no significant changes in the survival rate for patients with RDI of 70% - 79% (Hazard Ratio = 1.667, 95% CI 0.56 - 4.96, P = 0.359); RDI of 80% - 89% (Hazard Ratio = 1.620, 95% CI 0.47 - 5.53, P = 0.441); RDI 90% - 99% (Hazard Ratio = 1.590, 95% CI 0.53 - 4.73, P = 0.405) compared with patients who received an RDI of 100%. Conclusion: This study provides evidence that decreased RDI of <70% in

non-metastatic breast cancer patients is strongly associated with decreased overall survival.

Keywords

Breast Cancer, Chemotherapy, RDI, Survival Rate

1. Introduction

Breast cancer represents a growing health concern in Nigeria with a rising incidence rate of 63 for every 100,000 and mortality of 25.5 for every 100,000 [1] [2]. Risk factors associated with breast cancer in Nigeria include lifestyle variables such as physical inability, low breastfeeding practice, high-fat diet and low fruit and vegetables consumption [3] [4]. Additionally, smoking, alcohol consumption and family history of breast cancer are among the causes of cancer that require preventive strategies. The healthcare system in Nigeria needs to address many of its challenges and find solutions to help improve the limited and fragile resources.

Delay in diagnosis plays a crucial role in the excess mortality of breast cancer. Significant disparity in stage of breast cancer at presentation lead to poor outcomes associated with late diagnosis [5] [6]. Importantly, evidence suggests that delays in diagnosis may not be largely associated with patient health education or the stigma associated with the disease but related to adequate access to diagnostic procedures including initial biopsies and subsequent systemic care [7]. Although clinicopathological features including grade, size, nodal status, and receptor status play an important role in determining prognosis [8]-[10], timely access to cancer management and maintaining dose intensity for breast cancer increases the disease free-survival rate and affects the overall survival [11] [12].

Relative dose intensity (RDI) is the relationship of the actual dose and schedule of chemotherapy delivered to the intended dose and schedule of the standard chemotherapy regimen [13]. Decreased RDI comes as a result of dose delays and dose reductions. The relationship between dose intensity of chemotherapy and patient outcomes is well described in the literature [11] [12] [14]-[17]. There have also been reports on the significance of achieving a RDI of more that 85% [12] [14] [18]. Such studies continue to confirm that maintaining dose intensity for certain cancer types increases disease free survival and overall survival. Dose delays and dose reductions can easily result in an overall RDI of less than 85%. For example a collective delay of more than two weeks or a dose reduction of 20% will result in an RDI of less than 85%. Additionally, a 20% dose reduction can compromise cure by 50% and patients receiving less than 65% dose intensity are expected to have a survival similar to that of an untreated control group [19]. Dose delays and dose reductions are a common occurrence amongst the black race as they show lower baseline mean white blood cell count

compared to other ethnic groups [20] making the side effects of the treatment less tolerable.

Chemotherapy compliance in Nigeria is commonly affected by financial constraints due to out-of-pocket financing of treatment. Furthermore, the occurrence of severe to life threatening conditions, including neutropenia often complicates chemotherapy regimens, leading to dose reduction and delays [21]. Therefore, it is important to determine to what extent the reduced RDI might affect survival rates of breast cancer in Nigeria and recommend interventions aimed at improving treatment compliance and reducing the burden of chemotherapy.

2. Patients and Methods

2.1. Patients

Our study was a retrospective analysis of patients with stages I to III breast cancer. The investigations were carried out following the rules of the Declaration of Helsinki of 1975, revised in 2013. We used the diagnosis criteria of breast cancer to create a list of eligible patients within the Cancer Registry at the Lagos State Teaching University Hospital (LASUTH). Inclusion criteria consisted of all females receiving adjuvant chemotherapy for a diagnosis of breast cancer between January, 2015 and June, 2018. Exclusion criteria included patients with metastatic disease and patients not receiving chemotherapy. The total number of eligible patients was 204. Of the patients treated in our data range we determined which subset experienced dose delays and dose reduction during adjuvant chemotherapy treatment by reviewing the patient's medical records. We also identified and quantified the reasons for dose delay and dose reduction.

2.2. Treatment Regimen

The chemotherapy regimen included doxorubicin/cyclophosphamide (A_{80} C_{800}) given as a 1-hour infusion every 21 days for 6 cycles; cyclophosphamide/methotrexate/5-fluorouracil (C_{100} M_{50} F_{750}) given as a 1-hour infusion every 28 days for 6 cycles; and doxorubicin/cyclophosphamide → Paclitaxel (A_{80} C_{800}) given as a 1-hour infusion every 21 days for 4 cycles followed by (P_{100}) given as a 1-hour infusion weekly for 12 weeks.

2.3. Definition of Received Dose Intensity (RDI)

(T), the anticipated time to complete the six cycles was calculated from the day of commencement of chemotherapy and included one day of the final chemotherapy cycle T = T1 + T2 + T3 + T4 + T5 + T6=21 + 21 + 21 + 21 + 21 + 1 = 106 days. For instance, a patient who stopped chemotherapy after cycle four had T = 21 + 21 + 21 + 21 + 1 = 85 days.

(t) is the actual time to complete chemotherapy. This was the time taken from the commencement of cycle 1 to completion of chemotherapy. The date of completion of chemotherapy was day 1 of the last given cycle.

(Γ) is the standardized time for a patients that completed all six cycles of chemotherapy treatment. The standardized ratio (Γ = t/T) compares actual time and anticipated time. For instance, in a patient whom the actual time to complete six cycle of chemotherapy was t = 120 days as compared with 106 days as scheduled, then Γ = 140/106 = 1.32.

The anticipated dose total (Dc), was defined as dose in milligrams, as specifies by the protocol and taking into account that the patient should receive in cycles (c) a maximum of six cycles. The anticipated total dose was therefore D = ΣDc. For instance, if a patient is receiving an anticipated dose = 800 mg, then the anticipated total dose for the six cycles of treatment is D = 133.3 + 133.3 + 133.3 + 1.33 + 133.3 + 133.3 = 800 mg.

The actual dose received (d), this is a sum of the doses received at each cycle, thus d = Σdc. However, if a patient with a d = 800 mg received the first five cycles as anticipated but omitted the six, then d = 133.3 + 133.3 + 133.3 + 1.33 + 133.3 = 666.5 mg.

The standardized received dose Δ. The standardized ratio Δ = d/D comparing the actual dose and the anticipated dose. Therefore Δ = 666.5/800 = 0.83.

RDI is defined by Δ/Γ. If a patient received chemotherapy according to the protocol without any dose reduction or delay, the Δ = 1 and RDI of 1 = 100%. For a patient receiving six cycles this equates 800 mg over a period of 106 days.

2.4. Statistical Analysis

Because RDI can only be calculated after completion of chemotherapy treatment, it is not suitable to evaluate survival from the date of commencement of the first cycle of chemotherapy. Therefore survival was calculated from the scheduled end of the six cycles of chemotherapy. The analysis included all patients who died or experienced disease progression. Survival curves for each RDI group were done using the Kaplan-Meier method and compared using univariate log regression. SPPS software version 26.0 was used for the analysis.

3. Results

3.1. RDI

From the 204 patients with non-metastatic breast cancer recruited in this study, 3 (1.4%) presented with stage I of disease, 23 (11.3%) with stage II, and 178 (87.3%) with stage III.

The average RDI for all patients was 74%. Of the 204 patients reviewed, 144 patients (69.6%) had some reduction in RDI. This subset had an average RDI of 63% (**Figure 1**).

The average RDI by regimen was also calculated including dose-dense doxorubicin/cyclophosphamide (AC); dose-dense doxorubicin/cyclophosphamide (AC) followed by Paclitaxel; and dose-dense cyclophosphamide/methotrexate/5-fluorouracil (CMF). All regimens revealed an average RDI of less that 85% (74%; 67%; and 62%, respectively) (**Figure 2**).

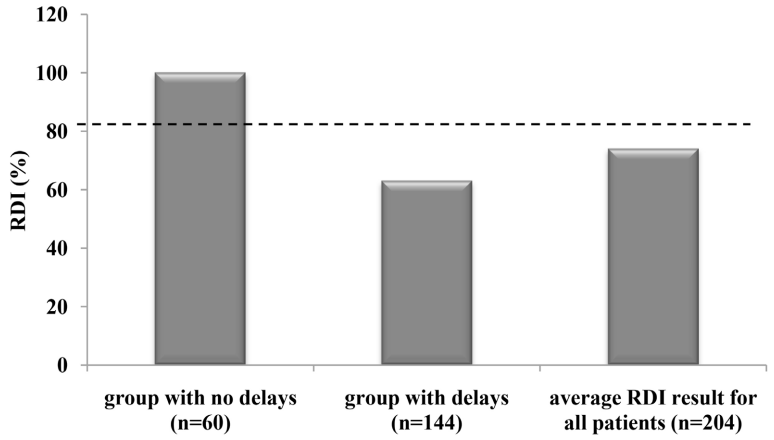

Figure 1. Relative dose intensity (RDI) received by patients in the study. Black line represents optimal RDI of at least 85%.

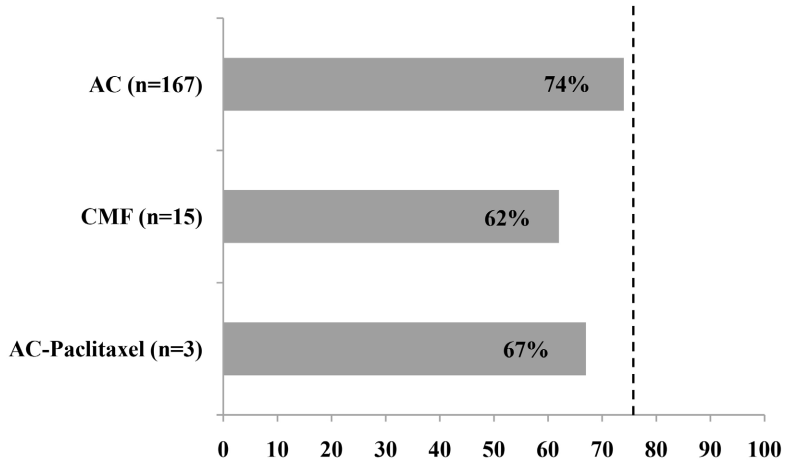

Figure 2. Relative dose intensity (RDI) by chemotherapy regimen. The black line represents optimal RDI of at least 85%.

We also examined the subset that showed RDI reduction so as to identify and quantify the reasons for the dose delays and dose reductions. The most common reasons identified for dose delays was intolerance (57%), followed by financial constraints (30%), scheduling issues from both patient and hospital (8%), and lastly treatment refusal by patient (5%) (**Figure 3**).

3.2. Survival

There was no patient from this study who died before the scheduled end of therapy at 106 days. 102 (50%) patients were excluded from this study because they were lost to follow-up. This study reveals a clear association between RDI and survival outcome in breast cancer. Patients who had RDI of <49% revealed a three-year survival rate of 46%, whereas those who had RDI of 50% - 59% and 60% - 69% showed survival rates of 25% and 33%, respectively. Moreover, patients with RDI of 70% - 79%; 80% - 89%; 90% - 99%; and 100% demonstrated survival rates of 63%; 60%; 69%; and 76%, respectively (**Figure 4**). Survival by

RDI showed a significant decrease in survival rate for patients with RDI of >49% (Hazard Ratio = 3.473, 95% CI 1.21 - 9.91, P = 0.020); RDI of 50% - 59% (Hazard Ratio = 3.916, 95% CI 1.01 - 15.18, P = 0.048); RDI of 60% - 69% (Hazard Ratio = 4.462, 95% CI 1.65 - 12.03, P = 0.003) compared with patients who received an RDI of 100%. Although associated with poorer prognosis, there were no significant changes in the survival rate for patients with RDI of 70% - 79% (Hazard Ratio = 1.667, 95% CI 0.56 - 4.96, P = 0.359); RDI of 80% - 89% (Hazard Ratio = 1.620, 95% CI 0.47 - 5.53, P = 0.441); RDI 90% - 99% (Hazard Ratio = 1.590, 95% CI 0.53 - 4.73, P = 0.405) compared with patients who received a RDI of 100% (Table 1). The death risk for patients who had RDI of >49%; 50% - 59%; and 60% - 69% is approximately four times higher than those who had a RDI of 100%. The death risk for patients who had RDI of 70% - 79%; 80% - 89%; 90% - 99% but not up to 100% is one and half times greater (Table 1).

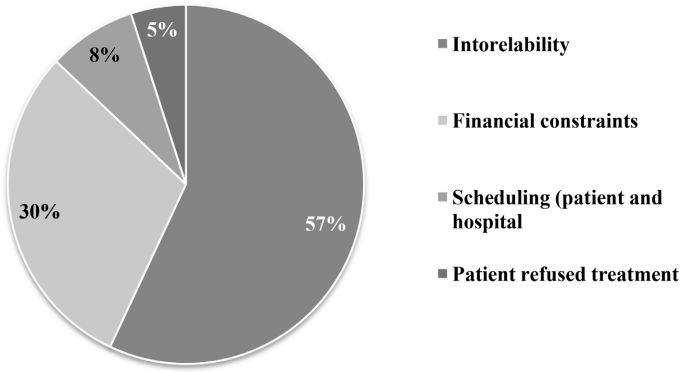

Figure 3. Causes of delayed chemotherapy by percentage of events.

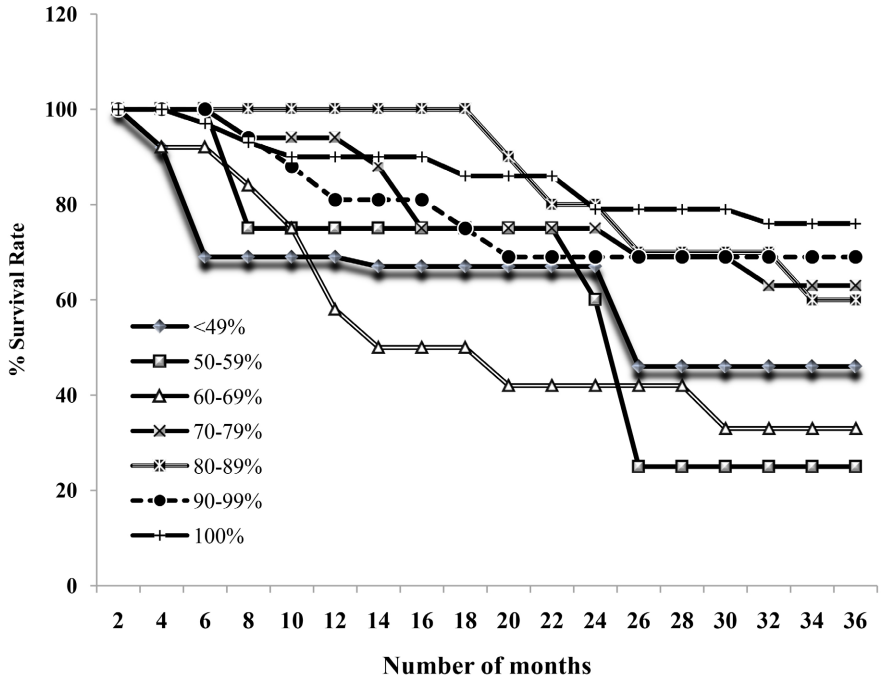

Figure 4. Graph showing three-year breast cancer survival by RDI.

Table 1. Distribution of RDI among breast cancer patients over three-year follow-up.

Univariate Analysis of the Relative dose intensity for 102 patients with breast cancer three-year follow-up, 2015-2018				
RDI	**No. of patients**	**Three-year survival (%)**	**Risk of death ratio (95% CI)**	**P-value**
>49%	13	46	3.473 (1.21 - 9.91)	0.020*
50% - 59%	4	25	3.916 (1.01 - 15.18)	0.048*
60% - 69%	13	33	4.462 (1.65 - 12.03)	0.003*
70% - 79%	16	63	1.667 (0.56 - 4.96)	0.359
80% - 89%	10	60	1.620 (0.47 - 5.53)	0.441
90% - 99%	16	69	1.590 (0.53 - 4.73)	0.405
>100%	30	76	1.00	
Total	102			

4. Discussion

The primary reason we observed for dose delays and overall reduction was intolerability, followed by financial constraints, thirdly scheduling delays initiated by both the hospital and the patient. Breast cancer patients of African origin have been reported to have more problems tolerating the equivalent doses of chemotherapy compared to breast cancer patients from other races [22]. It has been previously reported in an American study that despite controlling for clinical and social-demographic characteristics, blacks with breast cancer had systemic differences in chemotherapy administration compared to whites [23]. Blacks had higher tendency to receive less RDI and more first cycle reductions. The underlying reasons for these discrepancies remained unclear as biological aspects such as lower neutrophil counts or chemotherapy tolerance was not associated with these disparities in the study [23]. However, another study assessing treatment outcome between African Americans and White Americans found that African Americans with breast cancer had significantly lower baseline white blood cell counts compared to white Americans [20]. Racial differences in baseline white blood cell count may contribute to black patients risks of intolerance resulting in dose reductions or delays because low baseline white blood cell count is one of the strongest predictors of an RDI of less than 85% [20]. In the present study chemotherapy intolerance accounted for more than 50% of dose delays and dose reduction, suggesting that low blood count might be one of the major reasons for reduced RDI in Nigerian women. Randomised clinical trials have shown that granulocyte colony-stimulating growth factor (G-CSF), a white blood cell growth factor can reduce the risk of complication associated with intolerance to chemotherapy and also facilitate the delivery of full dose RDI [24] [25]. However, this would come at an additional cost to the patient and further hinder financial constraints commonly observed in cancer treatment. Ultimately, it is rec-

ommended that health insurance in expanded to vast majority of Nigerians so that cancer patients are better covered and chemotherapy compliance is improved.

We also observed that certain regimens were more associated with reductions in RDI than others. For example, patients who received CMF regimen had average RDI of 62% while patients who received AC regimen showed an average RDI 74%. The AC regimen is the primary line therapy for breast cancer chemotherapy in Nigeria. Although, studies have observed that the AC regimen is associated with neutropenia often resulting in dose delay, especially in patients who didn't receive or didn't meet criteria for primary prophylaxis according to National guidelines [26], it is one of the preferred chemotherapy regimen for breast cancer as it is cheaper compared to other preferred regimens [27]. Those on Paclitaxel portion of the AC regimen observed greater reductions in RDI compared to primary prophylaxis, however, combination of AC and Paclitaxel has been associated with improved survival, especially in triple negative breast cancers [28], as it commonly reported in Nigeria [10]. CMF, which recorded the greatest reduction in RDI, is no longer considered the most effective line of treatment in breast cancer due to concerns raised regarding the feasibility of delivering an acceptable dose intensity of this regimen [29]. However, this regimen still retains some significance in the treatment of elderly patients and for the treatment of estrogen receptor negative breast cancer, which are prevalent in the Nigerian population [10].

Although chemotherapy treatment exerts their cytotoxic effect on cancer cells, the favourable impact of adjuvant chemotherapy is minimized when full doses of therapy are not given as planned [23]. Some clinicians seek optimal survival benefits from chemotherapy by either increasing the dose of chemotherapy while others seek to lower dose of chemotherapy to reduced toxicity. However, there is evidence that non-compliance to the schedule can reverse this effect leading to accelerated proliferation of cancer cells and worsening survival outcomes. A randomized trial with 1572 stage II node-positive breast cancer women assigned to either a high or low dose of chemotherapy showed that those treated with the high dose had significantly longer disease free survival compared with low intensity [30]. In this study, the impact of non-compliance on survival rates also showed that patients with non-metastatic breast cancer who had RDI of <49% had significantly reduced disease-free survival at three-years compared to patients with RDI of 100% (46% v 76%). Moreover, patients who had RDI of 50% - 59% and 60% - 69% also showed significantly reduced disease-free survival at three years (25% and 33%, respectively) compared to patients who had RDI of 100%. This is in line with previous reports suggesting that patients receiving less than 65% dose intensity are expected to have a survival rate similar to that of an untreated control group [19]. There was no clear evidence that reduced RDI of 70% - 79%, 80% - 89%, and 90% - 99% reduced disease-free survival at three-years. A significant reduction in disease-free survival for patients with RDI

of <70% is attributed to the extent dose delay or dose reduction. In retrospect, when assessing dose reduction as per the study it is apparent that the omission of one cycle of chemotherapy may not significantly impact on disease-free survival at three-years compared to inclusion of all six cycles at the scheduled time (60% v 76%). However, it shows greater odds in dying from the disease. In addition, not receiving full doses of chemotherapy or significant delays in initiating and completing chemotherapy are associated with lower survival [31] [32]. On the other hand, omission of two cycles of chemotherapy strongly reduces disease-free survival at three-years compared to the administration of six cycles at the scheduled time (33% v 76%) as patient will have RDI of <70%. Equally, dose delay originated from factors such as intolerance, financial constraints or scheduling issues also directly impact on disease outcome. According to the study a patient who received all six cycles of chemotherapy over 106 days (RDI 100%) compared to one that receives all six cycles over a period of 132 days (RDI 81%) should not experience a significant reduction in disease-free survival at three years (60% v 76%). Contrastingly, a patient receiving all six doses over a period of 163 days (RDI 63%) will experience significant reduction in disease-free survival at three-years (33% v 76%).

There are many opportunities to improve RDI of patients with non-metastatic breast cancer in Nigeria. Frequent incidences of hematological toxicity such as neutropenia, anemia and thrombocytopenia can be addressed if primary prophylaxis with granulocyte-colony stimulating factor is readily available and affordable to patients. The implementation of healthcare packages that covers cancer care can tremendously improve the access to care and timely delivery of treatment procedures. It is also important for the Medical professional to provide treatment calendars to the patient with all expected dates of treatment before treatment initiation and provide education on the importance of receiving treatment on time. We are now adding more emphasis on the reasons for delay to help us to better understand the specific causes for delays.

The present study is limited by its retrospective design and small sample size. However, we believe it is a cross-sectional representation of the management of non-metastatic breast cancer in a Nigerian Oncology Centre. Based on this study, we strongly believe that measuring RDI in this setting can help to improve survival of patients with non-metastatic breast cancer, especially when results show a clear correlation in disease-free survival at three years for patients with limited-compliance to treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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