ORIGINAL ARTICLE

Default from neoadjuvant chemotherapy in premenopausal female breast cancer patients: What is to blame?

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Abstract

Background: Breast cancer is the most frequent cancer among women in most parts of the world including Nigeria. Neoadjuvant chemotherapy has been demonstrated to be a helpful strategy in the context of locally advanced breast cancer.

Aims: The purpose of this study was to investigate some factors that may contribute to low rate of acceptance and adherence to neoadjuvant chemotherapy.

Materials and Methods: A 1-year prospective study of premenopausal women with locally advanced breast cancer recommended for neoadjuvant chemotherapy from June 2009 to May 2010.

Results: Forty-four patients gave consent to be part of the study. The ages ranged from 26 to 51 years with a mean age of 42.1 years ± 7.7 years. Only 31 patients completed the four courses of NAC. Seventeen (38.6%) patients dropped out of treatment, before, during or after completing NAC. Ten of these defaulted due to inadequate funds to procure chemotherapy, three patients because they insisted on immediate mastectomy, and four of these patients refused surgery when they achieved complete clinical response, probably due to fear of mastectomy which is common among women in our environment. Twenty patients had dose deferment.

Conclusion: Lack of funds to procure chemotherapy and refusal of additional modality of treatment are the two major factors responsible for default of NAC and its goal in patients with LABC.

Key words: Default, neoadjuvant chemotherapy, premenopausal

Introduction

Breast cancer continues to be a significant problem worldwide. It is the most frequent cancer among women in most parts of the world including Nigeria.[1,2] Breast cancer in African and Nigerian women is characterized by young age of presentation; they present about a decade earlier than patients in western countries.[3,4] Breast cancers in Nigerian women present at advanced stage of the disease[5-7] with poor survival compared to their white counterpart.[5,8] Achieving local and distant disease control in locally advanced breast cancer [LABC], which may improve survival, remains a challenge. Neoadjuvant chemotherapy [NAC] has been demonstrated

to be a helpful strategy in the context of LABC, because of its tumor down staging benefits.[9-11] Our earlier study[12] revealed a low rate of adherence to NAC in our patients; however the reason for nonadherence was not clearly demonstrated.

The purpose of this study was to investigate some factors that may contribute to low rate of acceptance and adherence to NAC before, during, and at the end of the NAC regimen so as to proffer suggestion on how to overcome these factors so

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as to maximize the benefit of NAC as part of the multimodal treatment of breast cancer with hope of improving survival in our patients who present mostly with LABC.

Materials and Methods

A 1-year prospective study of premenopausal women with locally advanced breast cancer recommended for NAC was conducted.

Patients presenting with LABC, AJCC stage III, with a histopathology or a cytology diagnosis at the specialty breast clinic of Nnamdi Azikiwe University Teaching, Nnewi, Nigeria were counseled on the need for NAC with the hope of down staging the primary tumor before mastectomy or possible breast conserving surgery. The NAC regimen was four courses of cyclophosphamide 500 mg/m², Doxorubicin 50 mg/m² and 5-Fluorouracil 500 mg/m² all given on day 1 (CAF). Fluorouracil and cyclophosphamide were given as bolus injection in a free flowing intravenous line and doxorubicin was given as an infusion. The courses of the CAF were repeated at 3 weekly intervals. The drugs were procured by the patients who also bore the cost of any additional laboratory investigation.

On the visit before each course of CAF chemotherapy, hematological indices and BSA were assessed. The hematological indices included the hemoglobin concentration [Hb], white blood cell [WBC], and platelet count. To qualify to receive chemotherapy, patients were expected to have Hb of 10 g/dl, WBC of ≥2500/mm³ with absolute neutrophil count of ≥1000/mm³ and platelet count of ≥100,000/mm³. At the visit before the next course of NAC the patients were asked about adverse effects like nausea, vomiting, alopecia or any other adverse effect they might have experienced. The hematologic indices were also repeated three weekly and the presence of anemia, leucopenia, or thrombocytopenia noted and NAC deferred until parameters were adequate. Also any reason for failure to receive the NAC was also documented. The data were recorded and analyzed using the SPSS Statistical software (Statistical Package for Social Sciences) version 15.0.

Results

During the study period from June 2009 to May 2010, 857 new patients were seen at the General Surgery Out-Patient clinics of Nnamdi Azikiwe University Teaching Hospital Nnewi. One hundred and fourteen patients presented with breast cancer of which 65 patients had LABC, of these 44 patients gave consent to be part of the study. The remaining 21 patients were not included because they were postmenopausal women. The ages ranged from 26 to 51 years with a mean age of 42.1 years ± 7.7 years. Most patients, 27 (61.4%) had at least some high school education, 9 (20.4%) had only primary school education, and 8(18.2%) had no formal education.

Out of the 44 patients who consented to be part of this study, three women did not receive any chemotherapy because of lack of enough funds to procure the drugs. Seven patients defaulted after the first course, three of these because they preferred to proceed with mastectomy and the remaining four patients due to lack of adequate fund. Three patients dropped out after the second course also due to lack of fund [Table 1]. Only 31 patients completed the four courses of NAC. Four patients discontinued further treatment after neoadjuvant chemotherapy on achieving complete clinical response when they were expected to have mastectomy.

Of the 31 patients who received NAC, 10 (32.3%) patients had leucopoenia, 4 (12.9%) thrombocytopenia, and 8 (25.8%) had anemia. Leucopoenia was considered as white cell count below 2,500/mm³, thrombocytopenia as platelet count below 100,000/mm³, and anemia as hemoglobin concentration below 10 g/dl [Table 2]. Three of the patients with hematologic side effects required more than hematinics and deferment of the course of NAC to

Table 1: Reasons for default

Reason for defaulting	Frequency
Finance	10
Opted for mastectomy	3
Complete clinical response	4
Total	17

Table 2: Reasons for deferment/hematologic side effects defaulting

Reason for deferment	Frequency
Anemia	3
Leucopenia	5
Thrombocytopenia	2
Finance	2
Feeling unwell	1
Pancytopenia	2
Anemia + leucopenia	3
To attend funeral	1
No reason	1
Total	20

Table 3: Nonheamatologic side effects

Side effect	Frequency	Percent
Nausea	5	16.1
Vomiting	12	38.7
Diarrhea	1	3.2
Mucositis	4	12.9
Alopecia	16	51.6
Hyperpigmentation	7	22.6

Nb: [Some patients had more than one side effect]

correct the deranged hematologic profile. The three patients had anemia and were treated initially with hematinics, then erythropoietin, but were later admitted for blood transfusion following failure to correct the anemia. The most common reason for deferring NAC was hematologic toxicity seen in 15 patients. No patient dropped out of the study because of myelosuppression.

NAC was deferred in 20 patients (64.5%). The reasons for deferring NAC are shown in Table 2. The most common reason for deferring NAC was hematologic toxicity seen in 15 patients (75%), with leucopoenia being the most common. One patient had chemotherapy deferred due to feeling unwell. Fourteen patients deferred one course while six patients deferred two courses. Twelve patients deferred it for ≤2 weeks. Only six patients deferred for >1 month.

The nonhematologic side effects are shown in Table 3. None of those reporting to have vomited required hospital admission and only four patients took antiemetic for the vomiting. However, none of these patients deferred NAC or dropped out of the study because of any of the nonhematologic side effects.

Discussion

The mean age of the study population was 42.1 years with age ranging from 26 to 51 years. This is slightly lower than the 45.2 years reported in our previous study because the study population in this study were premenopausal women while we studied premenopausal and postmenopausal patients in the previous study.

Of the 44 patients that gave consent to be part of this study, 17 (38.6%) patients dropped out of treatment, before, during or after completing NAC. Ten of these defaulted due to inadequate funds to procure chemotherapy, three patients because they insisted on immediate mastectomy, and four of these patients refused surgery when they achieved complete clinical response, probably due to fear of mastectomy which is common among women in our environment. Twenty patients had dose deferment.

The above findings are similar to what Clegg-Lamptey[13] and colleagues observed in Ghana. They reported a 34.8% default rate, where 12.7% defaulted before treatment, 9.5% during or after NAC either when there is improvement or when mastectomy was due. They suggested that for the latter groups the fear or misconception about mastectomy was probably the main reasons for defaulting.

The most common reason for default is inadequate fund to procure chemotherapy. Another important reason for default on the goal of NAC is refusal of surgery after achieving complete clinical response.

Inadequate fund and refusal of surgery on achieving complete clinical response are two major factors negatively affecting the use of NAC in our patients which would no doubt result in poor outcome for our breast cancer patients.

Leucopoenia has not been observed to be a frequently encountered chemotherapy side effect with commonly used regimen in most studies.[14-16] However, leucopoenia occurred in 10 (38.5%) of patients in this study. This is quite high when compared to 10% reported by Chintamani *et al*.[14] who used similar NAC protocol as in this study. But, in the report of Moon *et al*.[17] leucopoenia [Leucocytes count < 2000/mm^3] occurred in 36.0% with one episode of pneumonia with septic shock. They used the granulocyte colony stimulating factor (G-CSF) to manage the bone marrow suppression. The rate reported by Moon *et al*.[17] is equivalent to what is observed in this study. However, none of the patients in this study received G-CSF or developed septic complication. Nine of the 10 patients were qualified to receive their next course of NAC after 2 weeks of deferring the course. This is an advantage considering that G-CSF is not readily available and the cost would be inimical to patients in our low resource area. Also, the absence of febrile neutropenia may support the observation that acute hematologic toxicities are less in Africans.[18]

In a previous study on the effect of adjuvant chemotherapy on myelosuppression in the same environment Anyanwu[15] noted dose deferment in for 1-2 weeks in 24% of patients with low white cell count in 5/42; low hemoglobin concentration in six of 42 and low platelet count in 7/42 patients. There were no infective crises or bleeding dyscrasia. This study collaborates with that that hematologic side effects of chemotherapy were generally mild and acceptable with very few requiring any active intervention except the three patients who had blood transfusion for anemia. Even the dreaded leucopoenia was manageable in 90% by just deferring the NAC for ≤2 weeks.

Kirshner *et al*.[19] reported that 88.3% of patients with normal prechemotherapy hemoglobin concentration (Hb ≥12 g/dl) treated with adjuvant AC developed some degree of anemia. However, rate of intervention with erythropoietin or blood transfusion was low. Low rates of intervention have been reported by other workers.[15,20,21] Generally these patients are allowed dose deferment or reduction in the dose given to 75-50% of the prescribed dose depending on the level of the hematologic parameters below normal values. However, Bonadonna *et al*.[22] found that breast cancer chemotherapy was more useful when given in a full dose (that is ≥85% of the planned dose). In our study we allowed deferment, erythropoietin, and transfusion was given when hemoglobin was not corrected after 1-2 weeks.

Nausea and vomiting was observed in 12 patients (38.7%) at first course, this decreased to two patients (5.7%) by the fourth course. Five (16.1%) patients had nausea at first

course and none at fourth course. None of these patients required hospital admission because the vomiting was readily managed with antiemetic. This agrees with the observation made by Fisher *et al.*[23] that vomiting is readily managed with antiemetics. Chintamani *et al.*[14] working in India observed acute vomiting in 63.3%. This is quite higher than observed in this study. They did not, however, state if the vomiting was readily managed with antiemetic or if hospital admission was required for any of their patients. In Ghana, Clegg-Lamptey and his colleagues[13] reported that nausea and vomiting was present to a degree in all their patients receiving CAF neoadjuvant chemotherapy while in Nigeria Anyanwu[15] noted that the cases of nausea among premenopausal women receiving adjuvant chemotherapy was easily controlled with metoclopramide. In this study not up to 50% had nausea and vomiting. These findings in Ghana and Nigeria may suggest that patients in our environment tolerate chemotherapy in terms of nausea and vomiting.

Alopecia was noted in 16 (51.6%) patients with most occurring by the third week of commencing NAC. This is consistent with the finding of alopecia in 60% of patients by Chintamani *et al.*[14] but does not agree with the report of Fisher and co-workers[23] that alopecia is almost universal following use of doxorubicin and cyclophosphamide (AC) as the NAC. The NAC protocol used by Chintamani *et al.* [14] is similar to the one used in this present study. Hence it may appear that alopecia is not almost a universal finding following CAF but may be so when AC is used. Nonetheless, in Ghana Clegg-Lamptey[13] and colleagues reported alopecia in all patients receiving doxorubicin.

Other observed nonhematologic side effects were hyperpigmentation of the hands and feet in seven (22.6%) patients, mucositis in four (12.9%) and diarrhea in 1 (3.2%). Except for the hyperpigmentation that the patients find distressing for cosmetic reasons, the other side effects were mild and not bothersome. Chintamani *et al.*[14] did not document this other side effect while Moon *et al.*[20] reported oral mucositis and diarrhea which were mild, but did not state the number who developed these side effects. Therefore, the finding of Moon *et al.*[17] agrees with this study in that mucositis and diarrhea when they occur are mild.

None of the above hematologic or nonhematologic side effects was a reason for discontinuing NAC in our breast cancer patients. However, the hematologic side effects were enough to defer chemotherapy until the hematologic parameter returned to normal or was corrected as with blood components.

Since the major reason for default is lack of adequate funds to procure the chemotherapy, provision of free medication by the government or nongovernmental organization to low/middle income countries like Nigeria could go a long way to eliminate default while the patient is getting NAC. The value of such an effort was seen in Ethiopia when a fairly limited investment program that included free Tamoxifen and public awareness on benefit of early breast cancer treatment resulted in improvement in cancer care.[24] The National Health Insurance scheme should be made to cover treatment for at least some selected malignancies like breast cancer in the female because it had been reported that lack of health insurance was one of the barriers to treatment.[25]

Additionally, a culturally sensitive public awareness[26] effort that emphasize the potential benefits of the therapeutic efforts of NAC for downstaging breast cancer and that complete clinical response is not synonymous with cure and those not obviate the need for additional treatment modalities.

Conclusion

Though breast oncologists in Nigeria generally accept that lack of fund militates against adherence to the use of chemotherapy in breast cancer patients, this study may be the first that has demonstrated clearly that lack of funds to procure chemotherapy and refusal of additional modality of treatment are the two major factors responsible for default of NAC and its goal in patients with LABC. Therefore, provision of free chemotherapeutic drugs for breast cancer patients as is done for HIV/AIDS patients or incorporation of treatment of breast cancer into the National Health Insurance Scheme may go a long way to improve the benefit NAC contributes to breast cancer treatment in our low resource environment where most patients present with advanced disease.

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