ORIGINAL ARTICLE

How Effective is the Treatment of Locally Advanced and Metastatic Breast Cancer in Developing Centres?: A Retrospective Review

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ABSTRACT

BACKGROUND: The use of chemotherapy in advanced metastatic breast cancer remains a subject of controversy. The thought of MicKinnon et al (early 1950s) that the course of breast cancer was unaffected by chemotherapy has been refuted by results of treatment in the developed countries. The poor result of treatment in developing centres still compares with prechemotherapy era. Consequently, The McKinnon's thought may still lurk. We compared the survival of chemotherapy treated with chemotherapy untreated cancer of breast patients.

METHOD: Records of breast cancer patients who presented and died between January 2010 and May 2014 were reviewed. The primary outcome was overall survival. Records of patients that received chemotherapy with or without other tumor directed specific therapy were compared with records of patients who did not receive any tumor directed therapy.

RESULT: Thirty-one patients received chemotherapy while 25 patients did not. All were females, more than 90% were of the patients had advanced or metastatic disease. Treatments were not biologically directed and treatment plans were largely compromised and suboptimal. The overall mean survival was 19.2 ±9.2 months, and the median duration was 17.5 months(range 6-44months). The overall survival was not statistically different between the two groups (p= 0.230, unequal variance assumed). The objective of using neoadjuvant chemotherapy for fungating lesions was not achieved.

CONCLUSION: In advanced and metastatic breast cancer, outcomes of patients who receive suboptimal regimen of cytotoxic chemotherapy do not differ from chemotherapy untreated patients.

KEYWORDS: breast cancer, suboptimal treatment, untreated, chemotherapy

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INTRODUCTION

Controversies trail the use of chemotherapy for advanced and metastatic breast (1-3). In the early 1950s, McKinnon (4) and other spractioners thought that the survival of breast cancer was predetermined (4). Today, in the developed countries where 80% of breast cancer patients present early; there is evidence that optimal chemotherapy prolongs survival in early, advanced and probably metastatic disease (2, 5). Therefore, the thoughts held by the proponentsof McKinnon have abated. In developing countries, 8o% of breast cancer patients present late, and the outcome of management can begenerally described as gloom (6-11). Consequently, it is natural for some clinitians to be worried by the thoughts held by the advocatesof McKinnon more than half a century ago. Reports of cancer survival studies are scanty from developing countries.

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Twenty years ago, Chiedozi (8) in Nigeria noted that the survival of advanced breast cancer was abysmally low. He compared the figures with those obtained in the developed countries about half a century earlier (in the 1940s). Today, figures quoted in Nigeria and some other developing countries are not distinctly different from chiedozi's (5,7,8,11, 12) . Does this mean that despite worldwide improvements in cancer care, our results still remain at par with the results obtained in the developed countries in the late 1940s?

The biology of breast cancer differs between Caucasians and Africans; the pattern of presentation, facilities for diagnosis, treatment and the response to treatment also differ (8,11,12). Despite these facts, many literatures from developing countries commonly appraise the outcomes of their patient management in the light of the results obtained in developed countries. It is rare to find direct comparison with untreated cases because the untreated patients commonly abscond. It is also rare to find comparison of current outcomes with outcomes obtained before the advent of better clinic-pathologic understanding and more effective chemotherapy because of poor records. The implication of always comparing results from developing centres with those from developed countries is that we may be comparing diseases that bear different biology and have received different treatments. This will obscures the true values of our results. For this reasons and for the first time in our centre, we compared the outcome of patients diagnosed of breast carcinoma who did not receive any tumor directed specific treatment with the outcome of those that received chemotherapy with or without other tumor directed specific treatment. This study aimed to obtain information about the effectiveness of chemotherapy treatment of advanced and metastatic breast cancer, directly compared to the "untreated" cases, in a resource poor setting. We also aimed to generate data for subsequent appraisal of outcome of management of this cohort of patients in resource poor centers without recourse to data from developed centers where presentation and facilities differ from developing centres'.

PATIENTS AND METHOD

This is a retrospective study conducted at the University of Ilorin Heaching Hospital in Kwara State, Northcentral Nigeria. The hospital receives breast cancer patients and referrals from the state in which it is located and from neighboring states in Northcentral and Southwestern Nigeria.

We reviewed case notes and pain and palliative unit records of patients diagnosed of cancer of the breast between January 2010 and May 2014. We included all available records of patients who presented and died within the study period because we sought uncensored duration of survival. Information extracted were the demographic characteristic, duration of illness before presentation, duration of illness from time of presentation until demise (i.e. hospital survival) and the stage at presentation. The overall survival was derived as a sum of the duration of illness before presentation and the hospital survival. The responses to treatments were also noted.

The administration of chemotherapy or otherwise was the basis for grouping. We separated the records into those that received tumor directed cytotoxic chemotherapy with or without other specific therapies as group1 and those that did not receive any tumor directed specific therapy as group 2.

The demographic characteristics were presented in descriptive statistics. Time to event (duration of survival) was presented with survival curve. Distribution of the data was checked with Shapiro-Wilk test and visual observation of the Q-Q plot before selection of appropriate inferential statistical method. P-value < 0.05 was considered significant.

Because we included all available complete records, the minimum sample sizes that would generate the. calculatedp-values were determined post hoc by using the R-statistical software. In an attempt to control for the effect of the stage of presentation on the survival, we conducted an exploratory subgroup analysis of stage III and IV disease. The theoretically underpowered subgroup analysis was further explored by conducting simulation resampling generation and comparison of confidence interval of a hundred means using R-statistical software. There was no attempt to control for the performance status, the type/brand of chemotherapy and the complications recorded.

We excluded patients whose diagnoses were not carcinoma, those with recurrent disease and those who died of other causes. Records from which the overall survival could not be calculated were also excluded

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RESULT

Seventy one records were available, but only 56 fit the inclusion criteria. Six case notes could not be traced. Four records were excluded because they were recurrent diseases; 2 were excluded because the final diagnosis was phylloides and stroma tumor; 2 were excluded because the overall survival could not be calculated, and 1 was excluded because the patient died of cardiac failure. All were females. Stages recorded at presentation were II(2,3.6%), III(24,42.9%) and IV(30,53.6%).The overall mean age at presentation was 47.7±11.7 (range 31-80 years). The distribution of the stages and complications clinically recognized in the course of manegement are shown in Table 1.

At the time of this report, in our center, biological profiling was not regular, and staging investigation was not exhaustive. The treatment of diagnosed patients was pre-planned (not biologically directed). The preferred treatment for early breast cancer was modified radical mastectomy followed by adjuvant polychemotherapy. Operable and resectable advanced and metastatic disease were offered simple mastectomy, axillary dissection and postoperative of adjuvant polychemotherapy. Hormonal therapy was prescribed for all patients concurrently with the polychemotherapy. Neoadjuvant chemotherapy was prescribed where necessary. Anthracycline (epirubicin) based polychemotherapy was the first line. Patients who could not afford the appropriate therapy were given cheaper and less effective agents. Patients who could not afford the drugs on schedule were treated as they procured their drugs and those who could not afford the full dose were given suboptimal dose. Brand of drugs and outlet of purchase were uncontrolled.

Patients who refused specific tumor directed therapy or who could not have specific tumor directed therapy were managed symptomatically and followed up by the respective units and pain and palliative unit. Those who discharged against medical advice or absconded from the hospital were traced by the pain and palliative unit.

Table1: Distribution of clinical stage at presentation and recorded complications

Variable	Group 1	Group2
Clinical Stage		
I	0	0
II	2	0
III	16	5
IV	13	20
Local complication		
Ulcerated	3	6
fungated	12	6
Solitary metastasis		
Lung	4	2
Liver	0	3
Long bone	2	0
Brain	1	1
Vertebra	1	1
Multiple metastasis		
Lung and Liver	4	4
Lung and Long bone	1	0
Liver and Brain	1	0

The overall mean survival from time of noticing the first symptom(s) was 19.2 ±9.2 months and the median duration was 17.5 months (range 6-44months). Thirty-one patients had tumor directed specific treatment (group1), while 25 patients had no tumor directed specific treatment (group 2). Shapiro-Wilk normality test for overall survival yielded a p-value of 0.02 (Gaussian distribution) and 0.289 (not Gaussian distribution) for groups 1 and 2 respectively. The visual observation of the Q-Q plot also suggested that group 2 data was not Gaussian distribution (Figures 1).

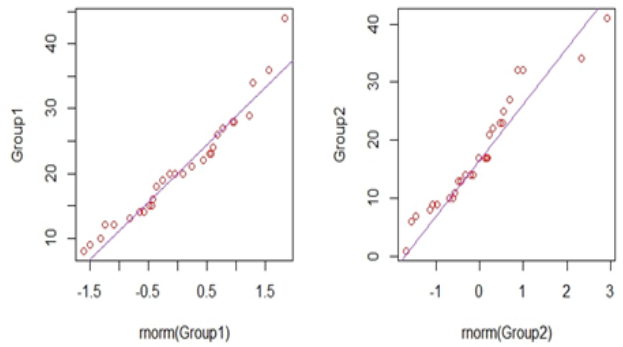

Figure1*: Q-Q Plot for both groups- Group1 shows gaussian distribution; group 2 shows non-gaussian distribution*

In the unsegregated analysis, the overall survival was not statistically different between the two groups (Table 2 and Figure2, p= 0.230, unequal variance assumed). The underpowered stage 3 subgroup exploratory analysis suggested longer survival in the chemotherapy group (Table 2). Further exploratory analysis by simulation resampling method yielded a p value of <0.001 also in favor of better survival in the chemotherapy group. A boxplot and the 95% confidence limit by percentile and the standard error methods were in agreement (Figure 3 and 4) suggesting that there are possibly two separate survival groups. The confidence limits by the standard error method were 10.1, 12.8 and 4.4, 6.6 for groups 1 and 2 respectively (Figure 4).

Table2: Comparison of the demographic characteristics and the unsegregated overall and segregated survival of the two groups

	Group1 (sample size)	Group2 (sample size)	p-value(t)	Minimum sample size on each side required to obtain the p-value
Age at presentation	45.6±10.7(n=28)	49.314. ±1(n=16)	0.366 (t=0.920)	13
Duration of symptom before presentation	9.57. ±1(n=31)	12.4±9.2 (n=25)	0.200 (t=1.289)	14
Hospital survival	11.6±7.1 (n=31)	5.1±5.2(n=25)	<0.001 (t=3.880)	13
Overall survival (stage unsegregated)	20.9±8.4 (31)n=	17.5±9.3 (n=25)	0.166 (t=1.443)	13
Stage III	21± 9.9(n=16)	15 ± 1.6(n=5)	0.047 (t=2.126)	9
Stage IV	19.3±6.9(n=13)	17.0±10.7(n=20)	0.468 (t=0.741)	10

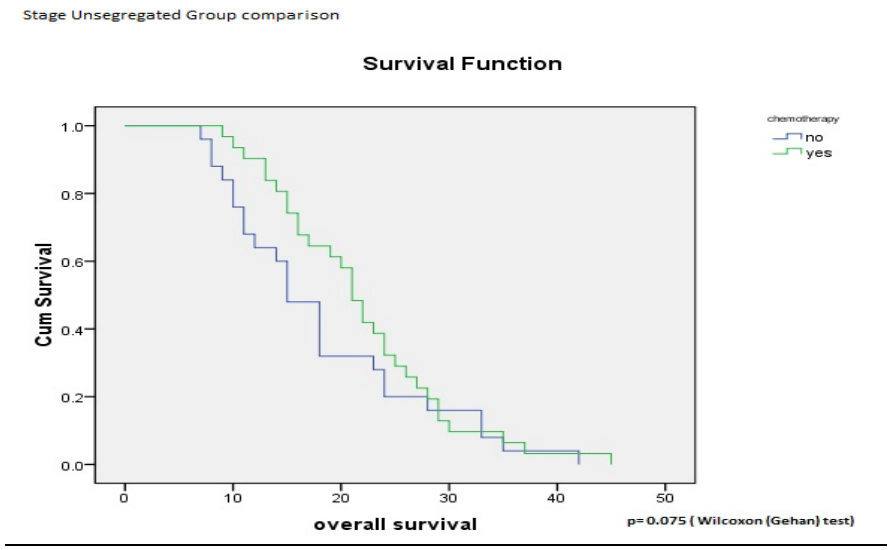

Figure2*: Survival curve comparing the duration of survival of the two groups (stage unsegregated)*

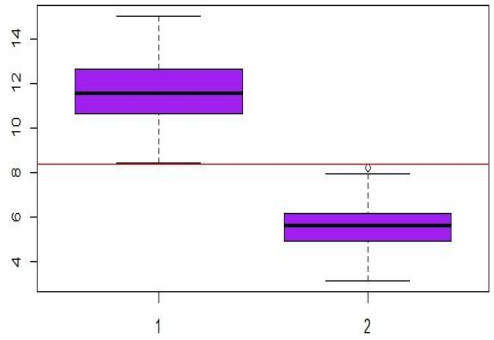

***Figure 3**: Boxplot of 100 bootstrap means of stage3 survival for groups 1 (1) &2 (2)*

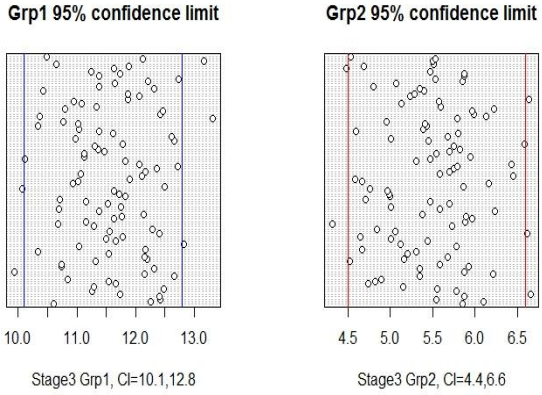

***Figure 4**: Confidence limit (percentile method) of 100 bootstrap means of stage 3 survival for groups 1(Grp1) and 2(Grp2)*

The estimated numerical widest diameter of the breast mass(es) at presentation was documented for 30% of the patients (median 6cm, range 1-20cm). The others were described as a fraction of the size of the breast, as huge, fungation or not at all.

All patients had psychosocial support, analgesics, antibiotic, wound management and blood transfusion as appropriate for their presentation. All patients in group1 had chemotherapy, 8 had mastectomy and axillary dissection. The intention of chemotherapy was neoadjuvant in 16 patients, neoadjuvant and adjuvant in 9 patients and adjuvant in 6 patients. The number of group1 patients that were regular on hormone therapy could not be ascertained from the records. None of the group 2 patients had chemotherapy, hormonal therapy or mastectomy.

Among group 2 patients, the reason for not receiving treatment was explicitly documented in 12 of the 25 the patients. The reasons were cost, poor performance status, absconding, defaulting of clinic visits and refusal to treatment. Of the group1 patients, 18 had anthracycline based treatment, 5 had taxane based treatment, while 2 had taxane and anthracycline at one time or the other. The exact combination of chemotherapy could not be determined from the records in 6 patients. The number of chemotherapy doses received by group1 patient ranged from 1 to 12. The median number of doses was 4. Thirty percent received less than 3 doses because of reasons similar to those who did not receive chemotherapy at all.

The progression of the disease was not explicitly documented for many patients; however, from scrutiny of the records, we found that in group 2, two patients presented with ulceration, while 4 progressed to ulceration. Five presented with fungation, while 1 progressed to fungation. In group1, 12 presented with already fungating lesion, 1 presented with ulcerated lesion and 2 progressed to ulceration while on polychemotherapy. Healing of ulceration was documented for 1 patient and reduction in size of the lesion was also documented for 1 lesion. None of the fungating lesions healed or improved enough to be offered toilet mastectomy before they died.

DISCUSSION

Even though we know that suboptimal therapies are practised in the chemotherapy treatment of breast cancer (5, 7,10,13,14, 15), the aim of this study was not to determine this. Rather, it was aimed to determine the effectiveness of chemotherapy in a poor resource setting compared to untreated patients. The adduced reasons for continuing use of suboptimal therapy are: firstly, it is considered unethical not to offer treatment, secondly the hope that half treatment may be better than no treatment and lastly because of the fear that no tumor directed treatment may be an admittance of defeat (16).

In this article, overall survival was the primary measure of outcome because it is difficult to obtain other measures of outcome in a

retrospective review due to poor records. The mean duration of survival of untreated group 2 patients was about 17months. The unsegregated analysis showed no significant difference in overall survival between the two groups (Table2). This finding is not surprising because more than 90% of the patients in this study were advanced and metastatic. When we compared stages III and IV between the two groups, the stage III who received chemotherapy seemed to show a better survival (see Table 2). Further exploratory analysis by simulation of 100 resampling means also supports this (Figures 3 and 4). Perhaps, this suggests that even with the current suboptimal treatment modalities, the stage III patientsare benefiting from effect of chemotherapy. However, this was just an exploratory result obtained after an underpowered subgroup theoretical analysis supported by a simulation resampling method. Therefore, firm pronouncement cannot be made. There was also a significant difference in the hospital survival which we consider a lead time bias (Table 2).

Considering the objective response rate in fungation and ulceration, we do not think that the patient who had chemotherapy had a better response. This conforms with findings documented elsewhere in Nigeria where tumors are large (10, 17), but contrary to chiedozi's findings where the chemotherapeutic dosing and scheduling were optimal (8,17).

The trio of gloomy outcome, prohibitive cost of therapy and discouraging side effects of the drugs (7) constitute "a lose-lose and lose situation" that may serve as deterrent to orthodox care as reported earlier (7). If the suboptimal treatment is inferior to the standard treatment as previously noted(13, 14) and is not different from results in "untreated" cases as suggested by this study, then we wonder whether it is ethical to recommend an all –or –none treatment protocol where specific tumor directed chemotherapy is reserved for those who will receive the optimal therapy. This triggers a controversial hypothesis stating that "in advanced and metastatic breast cancer, the overall survival of patient who receive suboptimal cytotoxic chemotherapy do not differ from "untreated" patients". Alternatively, we should determine the limits below which the compromised/suboptimal treatment ceases to be better than no tumor directed treatment.

Loibl etal (15) stated that it is not known whether sub-optimal chemotherapy is detrimental to the course of breast cancer, while Hershman etal (13) stated that suboptimal chemotherapy is a predictor of poor survival. The primary results in this study support the later statement thus again question the unreserved deployment of suboptimal chemotherapy treatment. However, the exploratory subgroup analysis indicates that in certain circumstances suboptimal therapy may not be totally futile.

There were several limitations in this study. This is because by necessity studying untreated cancer of the breast patients is typically a retrospective study and retrospective studies have the limitation of missing records. We were able to collect this volume of untreated records because of the home visitations and tracing efforts of the pain and palliative team. Firstly, the overall survival was the only complete measure outcome. The treatment group was heterogeneous. Some of the patients in group1 received other tumor directed specific therapies in addition to chemotherapy. However, the primary focus of this article is on the effect of chemotherapy because it is the advent of chemotherapy in the neoadjuvant or adjuvant context that has revolutionized the treatment of advanced breast cancer (2, 18). Secondly, the overall duration of survival was dependent on the patients' memory. Therefore, there is risk of recall bias. The staging method was not exhaustive; hence; it is possible that most of the patients had metastatic disease ab-initio. Thirdly, we reviewed only records of patients who died of the disease. Thus, it could be argued that we selected patients who had aggressive disease, but we must add that just as there were patients who received chemotherapy that have survived longer than the duration of this study, there were also those that did not receive chemotherapy that were still alive beyond the duration of this study.

And lastly, about 33% of the patients who received chemotherapy received just 1 or 2 cycles; hence; this may be consideredas no chemotherapy. However, because we expect that each dose of chemotherapy should have effects on the symptoms of the disease and should be independent of the effect of subsequent or previous doses, we had to consider any number of dose(s) as received treatment and the analysis had to be based on intention to treat.

Many of the limitations of breast cancer care reported in this study have been previously recognized, but they linger todate. Adisa et al (5) in Southwestern Nigeria noted non-adherence to schedule and the use of less optimal choice of chemotherapy. As mundane as the limitations of breast cancer care in resource poor centres may sound, now we recognize how seriously they may be impacting our care, and this corroborates the statement credited to Loibl (15) et al that the consequences of dose reduction and delays are significant.

In conclusion, this study questions the unreserved suboptimal use of chemotherapy as is currently practised. It suggests that our results are not only inferior to developed centres, they may also in fact just be comparable to the "untreated" probably due to the sub-optimal therapies. Therefore, we suggest the systematic assessment and re-direction of our treatment strategies. We also state that there is the need for insurance schemes to support diagnostic process to fund treatment of breast cancer in developing centers so that we can begin to administer appropriate treatment to the appropriate disease if we want to move forward on a problem recognized more than 20 years ago.

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