Non-adherence to the Use of Tamoxifen in the First year by the Breast Cancer Patients in an African Population

A.S. Oguntola, M.L. Adeoti, O.O. Akanbi,
Department of Surgery, Lautech Teaching Hospital, College of Health Sciences, Osogbo, Osun State, Nigeria.
Correspondence to: Dr. A.S. Oguntola, Email: asoguntola@gmail.com, asoguntola@yahoo.com

Background: Tamoxifen has been in use worldwide in the care of breast cancer over decades. It has been found to significantly reduce disease free survival and also reduce the chance of recurrence. The issue of non-adherence (NA) to its usage has not been reported in the black African setting. The aim of this study was to determine the rate and contributory factors to non adherence rate to tamoxifen during the first year of usage in patients with breast cancer in LAUTECH teaching hospital (LTH) Osogbo , Nigeria .
Methods: One hundred and fourteen patients (108 females and 6 males) were studied during their various first year of tamoxifen usage at LTH Osogbo, South-Western Nigeria between June 2001 and June 2005.The incidence, indications and variables that might contribute to NA e.g. age, sex, disease stage, occupation etc were assessed.
Results; Findings included NA rate of 24.5 % (72% of which occurred in the first 6 months of usage). Adherence tend to worsen with age and higher disease stage (p=0.154 and 0.146 respectively). Non-adherence was commoner in farmers and traders while unbearable side effects and financial constraints are most common reasons.
Conclusion: The 24.5% non-adherence rate, though comparable with results from other reports is unacceptably high These patients could not have been receiving full benefits of hormonal treatment, thus adequate counseling and education on benefit and side effects of tamoxifen is strongly advised.

Introduction

Tamoxifen, a selective estrogen receptor modulator is being widely used either as an adjuvant or as a primary drug in patients with breast cancers. It has been found to significantly improve the overall survival and also the disease free survival when taken over a 5 year period in ER positive breast cancer.[1]. Some reports on rates and indication of discontinuance or non compliance or non persistence are available from the developed world[2-5] but none yet in an African setting.

Adherence can be defined as the extent to which a patient's behavior coincides with medical advice. Lack of consistency in definition of non adherence has not allowed for uniformity in research study relating to it; some define adherence to medication as taking the drug or not, taking a defined minimum proportion or not, or non-taking for a varying period of time. In a poor resource setting as ours tamoxifen is commonly used along with cytotoxic drugs for systemic control since it is still difficult to determine the hormone receptor status of breast tumor tissue, hence higher likelihood of side effects which may affect compliance of this easily available and affordable drug. Observation of non compliance with usage of tamoxifen during follow up clinic attendance in mid-2005 made us to look into the rate and indication for non-compliance.This study was aimed at determining the incidence and factors contributing to the non-adherence to the use of tamoxifen in the first year of usage in an African population at LAUTECH Teaching hospital, a tertiary health centre in south-western Nigeria.

Patients and Methods

The records of all breast cancer patients who had received treatment for a minimum of one year as of mid- June 2005 were assessed for record or documentation of non-compliance. The age, sex, occupation, disease stage, duration of use before stoppage and reasons for stoppage were recorded from case notes. Patients who were freshly enrolled in to the study at the time of observation (mid-

2005) were routinely seen in clinic at 2 – 4 weeks interval during the first year of treatment, they were questioned on adherence and indication for stoppage. Non-use of Tamoxifen for up to a period of one week without consultation with the prescribing doctors was considered as being significant. Tables were drawn and findings were analyzed using simple statistical methods.

Results

A total of 126 patients that were diagnosed as having breast cancer between May 2001 to June 2005 fell into the study group

Table 1. Sociodemographic Data and Disease Stage of Patients on Tamoxifen.

	Total No of Pts	Total No Tamoxifen (TG)	Adherence (TA)	Non-adherence(TD)	Discontinued < 6 months	Discontined 6 - 12months.
SEX M	7	6	5(85.3%)	1(16.7%)	1	**0**
F	122	108	81(75%)	27(25%)	19	**8**
						P =1.00
TOTAL	**129**	**114**	**86**	**28**	**20 (71.42%)**	**8 (28.58%)**
AGE(yr)	……..					
<45	50	44(38.59%)	29(65.9%)	15(34.1) [53.57%]	13 (86.67%)	**2 (13.33%)**
45 – 65	48	44(38.59%)	35(79.5%)	9 (20.5%) [32.14%]	6(66.6%)	**3(33.3%)**
> 65	31	26(22.8%)	22(84.6%)	4(15.4%) [14.28%]	1(25%)	**3(75%)** X^2**=3.74 df=2 p=0.154**
TOTAL	**129**	**114(100%)**	**86**	**28[100%]**	**20(71.42%)**	**8(28.58%)**
AJCC stage						
I	15	12(10.52%)	10(83.3%)	2 (16.7%) [7.14%]	2(100%) (10%)	**0**
II	18	16(14.91%)	14(88.2%)	2 (11.8%) [7.14%]	1 (50%) (5%)	**1 (50%)**
III	38	34(29.82%)	26(76.47%)	8(23.53%) [28.57%]	4 (50%) (20%)	**4 (50%)**
IV	58	52(45.61%)	36(69.23%)	16(30.77 [57.14%]	13(81.25%) (65%)	**3(18.75%)**
						X^2 **=2.76 df=3 p=0.43**
TOTAL	**129**	**114(100%)**	**86**	**28[100%]**	**20(100%)**	**8**
Occup						
Farming		26(22.8%)	16 (61.6%)	10 (38.4% [35.71%]	6 (60%)	**4 (40%)**
Trading		46(40.35%)	35(76.09%)	11(23.91 [39.29%]	9 (81.8%)	**2 (18.2%)**
CS		27(23.6%)	23(85.19%)	4 (14.81% [14.29%]	3 (75%)	**1 (25%)**
PF		7(6.14%)	6(85.19%)	1(14.29%) [3.57%]	1 (100%)	**0**
N/S		8(7.01%)	6(75%)	2 (25%) [7.14%]	1 (50%)	**1 (50%)** X^2**=4.97 df=4 P=0.291**
TOTAL	**129**	**114 (100%)**	**86**	**28[100%]**	**20**	**8**

Key: Occup = Occupation. CS = Civil servants. PF = Professionals. N/S Not stated

Table 2. Reasons for Non-adherence to Tamoxifen therapy

Reason	Frequency	Remarks
Side effects	9	Hot flushes, Nausea/Vomiting, Vaginal Bleeding, Irregular Menstruation
Financial Constraints	6	Mainly farmers and Villagers
Feel the drug is not working	4	Patients with locally advance lesions, ignorance
Co-Morbid Illnesses	3	Diabetes mellitus, Hypertension, Heart failure.
Spiritual	2	Among young patients with early breast cancer
Drug Non-availability	2	Villagers, Poor transportation, ignorance
Not stated	2	Poor record keeping

Only 114 (6 males +108 females) among these were placed on tamoxifen. Of these, 28 (24.5%) failed to use tamoxifen continuously for at least one week within the first year of treatment without prescriber's notice. One of the 6 males (16.7%) and 27of the 108 females (25%) were found not to comply with prescription.

The majority (72%) of the non adherence occurred during the first six months of usage. The non-adherence rate varied with the disease stage and was 16.7%, 11.7%, 23.5% and 30.7% for AJCC stage I, II, III, and IV patients respectively thus non compliance occur more in advanced lesions, although this was not statistically significant (x^2=2.12, df=1, p=0.146). It also varied with the age distribution as follows, less than 45yrs (34%), 45-65yrs (20%) and above 65yrs (15%) thus non adherence rate reduced with age (Table 1). This relationship was also found not to be statistically significant. (x^2=3.74, df=2, p=0.154).

Among patients on Tamoxifen were 46traders (40.36%) 27 Civil Servants (C/S) (23.6%) 26 farmers (22.8%) and 7 professionals (6.14%). Twenty-three percent, 14%, 14% and 38.4% of traders, C/S, professionals and farmers respectively were found to have stopped their medication without notice. Farmers and traders tend to have higher non adherence rate though not statistically significant (x^2=2.6, df=1, p=0.106)

Reasons for discontinuation such as unbearable side effect of the drug, financial constraints, spiritual reasons, non availability and presence of co-morbidity accounted for 9, 6, 2, 2, and 3cases of NA respectively. Four patients with advanced breast cancer stopped because they felt it was not working while two gave no reason for discontinuance. (Table 1) Common side effects noted included hot flushes, nausea and vomiting vaginal bleeding, irregular menstruation and weakness. . Financial constraint was noticed to have taken its toll on villagers and peasant farmers. Only about 31% of our patients were found to be informed about the essence and possible side effects of Tamoxifen usage.

Discussion

Breast Cancer is a major public health problem worldwide and the incidence appears to be on the increase even in the developing world. Tamoxifen is playing a major role in breast cancer management world-wide but more in the developing world where hormonal receptor assay could not be easily achieved. Other drugs e.g. Trastuzumab (anti Her-2), anti-angiogenesis agent, tyrosinase inhibitor, metalloproteinase inhibitor, taxanes and others are undergoing various trials and are not readily available for use[6].

The non adherence rate of 24.5% found in this study fell within the range of previously reported frequency of 15-40%[2-5,7,8].These were mainly from clinical trials but none came from an African setting. Research till date has suggested that the young, elderly, non-white women, previous emotional status, estrogen receptor negative tumor, stage of disease and experiencing of side effects of tamoxifen are likely predisposing factors to non-adherence[8, 9].

Nearly three-quarters (72%) of all non persistence occurred in the first 6 month of commencement; A large proportion of these were in those less than 45 years of age; the age range in which the antiestrogenic side effects of tamoxifen is expected to be more pronounced. About one third of discontinuance was secondary to unbearable side effects. This is comparable with report from other studies[2,9] Common side effects encountered included nausea and vomiting, dizziness, hot flushes, weakness and few with vaginal bleeding, these were found to be more common in young patients. Serkolem et.al[2] found that elderly patients are less likely to report side effects probably because of the lower level of circulating estrogen thus less antiestrogenic effect, and that educated and ER –Negative patients have more side effects.

It may be difficult for us to separate symptoms relating to cytotoxic drugs from that of tamoxifen because these are always used in combination in our centre since we did not possess the facility for hormonal receptor assay. This combined therapy (cytotoxic and hormonal) could have additive benefit[6]. Though it may result in a higher incidence of venous and arterial thrombosis than either treatment alone[10]. Use of tamoxifen is also known to be more likely associated with sexual dysfunction, vaginal symptoms[11], depression and weight gain[10]. Rarely cataract and retinopathy may be consequences of usage[12], however quality of life tend to be preserved in them[11]. Adequate explanation on indication, usefulness and side effects of tamoxifen need be given before commencement of usage i.e. the care should be patient centered[5]. Thrombosis[13] and uterine cancers[14,] the two major complications reported with tamoxifen therapy were not seen in this study. This could be due to short duration of the study; a longer period of usage and life follow up will be required to elucidate this.

Financial constraint was a major reason for discontinuance; about 21% of cases were due to lack of fund to purchase the drug. Poverty has been a well known factor militating against adequate health delivery in the undeveloped world[15]. The average cost of tamoxifen is about #1,200 (Nigeria) (US$10) per month for a dose of 20mg daily. Access to health facilities is important as patients who lived in the rural villages may not be able to find the drug among others within their vicinity or may also find it difficult or cumbersome to attend clinic for follow up and treatment on clinic days.
Four of our patients, all with advance lesions discontinued tamoxifen therapy for belief that the tablet will not work since they have been on various drugs in various peripheral hospitals for a long time to no effect thus discontinuations occur within the first six months. Among the educated, the elites, the patient's perception of risks and possible benefit of tamoxifen was found to be significant by Fink et al [8] as early quitters were less likely to have positive baseline decisional balance scores than the later quitters. The need to have detailed discussion on side effects and benefits of tamoxifen with patients before commencement cannot be over emphasized in reducing the discontinuance rate.

Poor access to specialist centres and inadequate rapport between the Surgeons and patients before commencement of tamoxifen could account for poor adherence in some cases while the poor socio economic and educational status of the farmers who are mainly peasants and the petty traders could account for the rather higher percentage of non-adherence in them.

Availability of social and psychological support for patients with breast cancer will also improve adherence to drug usage among other treatment modalities especially in a poor resource setting.

Limitations

A major limitation to this study was difficulty in follow up of patients under care in the undeveloped world. This was partly obviated by shortening the study period to just the first year of tamoxifen usage. However surveillance for a 5 – year period would be more appropriate as this is likely to produce a more representative non-adherence rate.
Obtaining information from medical records services is usually an uphill task thus militating against accurate result. A more objective way of obtaining information on drug usage e.g. follow up through the family physician (GP) or through record from local Pharmacy (Health Insurance) could have given better result in environment with well organized health service system. The National Health Insurance Scheme (Nigeria) may bring some improvement on this.

The study population in this study was relatively small. A larger study shall allow for easier statistical assessment of the results. The findings in this review however serve as an "eye opener" to practitioners that our cancer patients may not be taking their oral anticancer drugs which could explain the less than expected outcome.

Conclusion and recommendations

The 24.5% non-adherence rate during the first year of tamoxifen usage is high and mostly occurred during the first 6 months especially among the younger patients, those with advanced breast cancers and the farmers. Further studies in form of a prospective nationwide coordinated 5-year study on adherence to use of Tamoxifen among other oral drugs in use in patients with cancers shall go a long way in assisting care givers in oncology in the developing world where poverty, ignorance and rather poorly organized medical services are major problems.

References

1. Fisher B, Bignam J., Bryant J. et al, five versus more than five years of tamoxifen therapy for breast cancer patients with negative Lymph nodes and ER positive tumours. *J.Natl. Cancer Inst*. 88: 1529- 1542, 1996
2. Serkolem D, Sulliman RA, Lash TL. Adjuvant Tamoxifen: Predictors of use, side effects, and discontinuation in older woman. *Journal of Clinical oncology,* Vol. 19 No2 (Jan. 15 200l) P. 322-328.
3. Rowan T, Chlebowski, Michelle L. Geller. Adherence to endocrine therapy of breast-cancer. *Oncology* 2006; 71: 1-9
4. Lash TL, Fox MP, Westrup JL, Fink AK, Sulliman R A. Adherence to Tamoxifen over the five year course. *Breast cancer Res Treat* 2006 Sept; 99(2):215-20.
5. Kahn KL, Schneider EC, Malin JL, Adams JL, Epstein A.M. Patients centered experiences in breast cancer predicting long term adherence to Tamoxifen use. *Medical care*. 2007 May; 45(5): p 431-9.
6. Shapiro CL, Recht A. Side effects of adjuvant treatment 0f breast cancer. *N Engl. J Med*, Vol. 344, No26 p1997-2007.
7. Patridge AH, Wong PS, Winner EP, Avorn J. Non Adherence to adjuvant Tamoxifen Verify in women with primary breast cancer. *Journal of Clinical Oncology* Vol. 21, No4 2003 P602-606.
8. Aliza KF, Gurwitz J, Rakowsky W, Guadagnoli E, Suliman RA. Patient Beliefs and tamoxifen discontinuance in older women with ER_positive cancer. *Journal of Clinical oncology* Vol. 22 No. 16.2004 P. 3209-3315.
9. Barron TI, Connolly RM, Kathleen B, John Feely, M. J Kennedy. Early discontinuation of Tamoxifen. A lesson for oncologists. *CANCER* March 1, 2007.
10. Saphner T, Tormey DC, Gray R. Venous and arterial thrombosis in patient who received adjuvant therapy for breast cancer. *J. Clin. Oncology* 1991; 9: 286-94.
11. Mortimer JE, Boucher L, Baty J, Knapp DL, Ryan E, Rowland JH. Effect of Tamoxifen on sexual functioning in patients with breast cancer. *J. Clin oncology* 1999; 17 1488-92.

12. Nayfield SG, Gorin MB. Tamoxifen Associated eye diseases: a review. J. *Clin oncology* 1996; 14:1018-26.
13. Mc Caskill- Stevens W, Wilson J, By rant J, Mamounas E, Garvey L, James J, Walter Cronin W, Wickerman DL. Contra lateral breast cancer and thrombo-embolic events in African American women treated with Tamoxifen. *Journal of the National Cancer institute* Vol. 96, No. 23 P1762-1769.
14. Fisher B, Constantino JP, Redmond CK, Fisher ER, Wickerham DL, Gronin WM. Endometrial Cancer in Tamoxifen treated breast cancer patient: findings from the National Surgical Adjuvant Breast and Bowel project. (NSABP) B.14. *J Natl. cancer Inst*. 1994; 86: 527-37.
15. Adeoti ML, Oguntola AS, Aderonmu AOA, Agodirin OS. Influence of socio-cultural, political, economic status and environment on the outcome of surgical practice in a developing tropical country using breast cancer as case study. *Surgery Journal* 2008; 3(2): 21-23.