Adherence to Newly Implemented Tamoxifen Therapy for Breast Cancer Patients in Rural Western Ethiopia

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Abstract

Introduction: Endocrine therapy for breast cancer (BC) patients is highly underutilized in rural Ethiopia and other African countries. ***Objective:*** This study aims to assess the feasibility of and adherence to tamoxifen therapy in rural Ethiopia. ***Methods:*** We ascertained the hormone receptor (HR) status in 101 women diagnosed with BC from January 2010 to December 2015 and who had surgery in Aira Hospital, in rural Ethiopia. From 2013, tamoxifen was offered to patients with HR-positive (HR+) tumors. Prescription refill records and a structured questionnaire were used to assess receipt of and adherence to tamoxifen. ***Results:*** Of the 101 BC patients tested for HR status during the study period, 66 (65%) patients were HR+ and were eligible for tamoxifen treatment. However, 15 of the HR+ patients died before tamoxifen became available in 2013. Of the remaining 51 HR+ patients, 26 (51%) initiated tamoxifen but only 9 of them (35%) adhered to therapy (medication possession rate ≥80%, median observation 16.2 months). After 1 year, 52% of the patients were still adherent, and 9 patients had discontinued therapy. The reasons for non-initiation of tamoxifen included patient factors (*n* = 5), including financial hardship or lack of transportation, and health care provider factors (*n* = 12). ***Conclusions:*** Endocrine therapy for BC patients seems feasible in rural Western Ethiopia, although non-adherence due to financial hardship and a less developed health care infrastructure remains a major challenge. We postulate that the implementation of breast nurses could reduce patient and health system barriers and improve initiation of and adherence to endocrine treatment.

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Introduction

Breast cancer (BC) is the most common cancer and leading cause of cancer death in sub-Saharan Africa [1, 2], including in Ethiopia, where the estimated incidence in 2018 was 15,244 [3, 4]. The estimated 2-year survival rate in a rural hospital in Western Ethiopia was only 53% [5] compared to 5-year survival rates of >81% in Europe [6].

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Fig. 1. Patients eligible for analysis from those enrolled in our study over the period January 26, 2010 to December 31, 2015. Tamoxifen treatment was initiated on March 18, 2013 and the adherence assessment period was March 18, 2013 to December 31, 2015. HR, hormone receptor; TAM, tamoxifen.
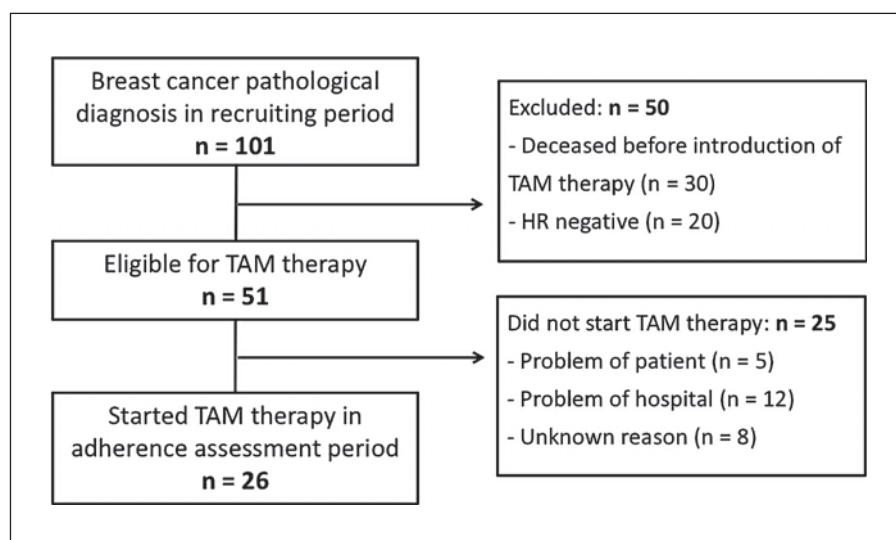
Reasons for these disparities in outcome include differences in stage at first presentation [7], availability of therapy [8], and underlying levels of investment in health care [9]. Like in many sub-Saharan African countries, only basic surgical treatment services are available at regional hospitals in Ethiopia [10]. Hospitals offering adjuvant systemic therapy and the only radiotherapy center are located in urban Addis Ababa. The majority of patients with BC face serious challenges in accessing these facilities [11] since 80% of the Ethiopian population reside in rural areas [12].

Tamoxifen is an effective treatment option for patients with hormone receptor-positive (HR+) and unknown receptor status BC [13, 14]. It is easy to administer (oral), inexpensive, and has few serious side effects [15, 16]. In women with HR+ non-metastatic BC, the absolute reduction in the risk of recurrence after 15 years with 20 mg of tamoxifen daily over 5 years is 13.2%, and the reduction in the mortality rate is 9.2% [17]. Although the majority (65%) of BC patients in Ethiopia are HR+ [18] and tamoxifen is on the essential drug list of Ethiopia [19], it is not widely used in rural Western Ethiopia.

The Breast Cancer Initiative 2.5 developed resource-stratified guidelines for BC control in sub-Saharan Africa [20]. In line with these guidelines the National Cancer Control Plan (NCCP) of Ethiopia aims to "strengthen cancer control capacities," including de-centralization of oncology care [21].

In this pilot project, funded by the German Gynecologic Oncology Working Group (AGO), Aira Hospital in rural Western Ethiopia offered pathology workup including immunohistochemistry for the detection of HR expression and provision of tamoxifen treatment. Extreme poverty in addition to a high rate of illiteracy are thought to pose significant challenges for women to adhere to long-term tamoxifen treatment.

Materials and Methods

Study Design

This is an explorative, prospective, hospital-based cohort study to assess the feasibility of administering tamoxifen to patients with BC in rural Western Ethiopia. Feasibility was investigated by focusing on the adherence to therapy, defined as "the extent to which a person's behavior – taking medication [...] corresponds with agreed recommendations from a health care provider" [22].

Setting

Ethiopia has a three-tier health care system, with 1st regional Primary Health Care Units, 2nd General Regional Hospitals in zones, and 3rd Specialized Referral Hospitals. Aira Hospital in Oromia State, Western Wollega District, officially provides primary health care to 68,000 people, but unofficially serves 500,000 inhabitants due to the presence of a specialist surgeon.

The international collaboration between Aira Hospital and the Department of Gynecology, Martin Luther University (MLU) Halle-Wittenberg, Germany began in 2010. In March 2013, free endocrine treatment with tamoxifen (20 mg/day) was provided for BC patients. Patients received tamoxifen in packages containing 30 tablets each, usually three packages (range 1–4).

Participants

All BC patients operated at Aira Hospital between January 2010 and December 2015 were included (*n* = 101), 66 (65%) were HR+ or receptor status unknown. Of these, 15 had passed away before the initiation of treatment and 51 were eligible for tamoxifen therapy (Fig. 1). C.F.R. and a local nurse visited all HR+ BC patients in their homes in February 2016.

Data Sources/Measurement

A questionnaire obtained clinical, social, and reproductive factors. A structured interview including open questions assessed: (i) difficulties in the provision of the medication, (ii) patients' perception about the beneficial effects, and (iii) reasons for adherence or non-adherence. The questionnaire was developed by a panel of experts (W.T., C.T., E.J.K., S.U., C.F.R.) based on the MARS (Medication Adherence Rating Scale) questionnaire and considering the sociocultural context, comments from local health workers, and previous experiences [5].

Table 1. Patient characteristics (*n* = 51)

Age at diagnosis, years	45 [35–51]
Number of children	4 (0–11)
Walking time to health center, h	1.1 (0.1–3)
Travel time to hospital, h	6.1 (0.1–24)
Age group	
<35 years	11 (22)
35–50 years	25 (49)
>50 years	15 (29)
Premenopausal	24 (47)
Postmenopausal	27 (53)
Place of residence (*n* = 48)	
Rural	38 (79)
Urban	10 (21)
Religion (*n* = 48)	
Christian	38 (79)
Muslim	9 (19)
Other	1 (2)
Literate (*n* = 38)	
No	31 (77)
Yes	9 (23)
Profession (*n* = 49)	
Housewife	28 (57)
Farmer	17 (35)
Student	1 (2)
Other	3 (6)
Marital status (*n* = 41)	
Married	38 (93)
Not married	3 (7)
Survival status	
Deceased	21 (46)
Alive	21 (35)
Unknown	9 (18)
AJCC stage (*n* = 33)	
1	2 (6)
2	10 (30)
3	20 (61)
4	1 (3)
Clinical tumor size (*n* = 38)	
T1	3 (6)
T2	22 (46)
T3	18 (38)
T4	5 (10)
Pathological diagnosis	
NST	47 (92)
Other	4 (8)
Grading	
Grade 1	3 (6)
Grade 2	14 (27)
Grade 3	34 (67)
HR status	
ER+PgR+	28 (55)
ER+PgR–	9 (18)
ER–PgR+	12 (23)
Unknown	2 (4)
HER2	
Negative (0 to 2+)	39 (76)
Positive (3+)	10 (20)
Unknown	2 (4)
Ki-67	
Negative (<14%)	16 (31)
Positive	33 (65)
Unknown	2 (4)
Surgical treatment (*n* = 44)	
Modified radical mastectomy	15 (34)
Simple mastectomy	4 (9)
Radical mastectomy	1 (2)
Lumpectomy[1]	7 (16)
Quadrantectomy[1]	6 (14)
Mastectomy (not specified)	11 (25)

Data are presented as the mean [IQR], mean (range), or *n* (%). AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PgR, progesterone receptor; NST, non-specific type of BC.
[1] No irradiation in breast-conserving therapy.

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The questionnaire was translated from English into local Oromifa then proofread and revised. A local nurse with experience in qualitative research read the questions to the patients and they answered in their local language. Patient perception was only assessed for a total of 22 patients alive. Computer-based prescription refill records were also used to assess implementation, initiation, and treatment persistence (adherence). Clinical and pathological information was obtained from the patient files.

Definitions

Adherence is defined by initiation, implementation, and discontinuation [23]. Initiation is the date of the first handover of tamoxifen. Implementation equates to the medication possession ratio (MPR), which describes the patient's medication intake compared to the prescribed drug dosing regimen [24]. An MPR of ≥80% was defined as an acceptable adherence [25]. Discontinuation occurred when the patient stopped taking tamoxifen and did not present for a refill. In this study, discontinuation was defined as a refill gap of more than 6 months [26]. Adherence was defined as the length of time between initiation and last dose before discontinuation. Descriptive statistical analyses were performed using SPSS version 22.0 (IBM, Armonk, NY, USA).

Results

Of the study population of 101 patients, due to predefined criteria, a total of 51 patients were eligible for tamoxifen therapy. Table 1 shows characteristics of eligible women. The mean age at diagnosis was 45 years (IQR 35–51). Almost 80% were residents outside Aira. Most women were illiterate (77%). The mean walking time to the next health center (nurse available) was about 1.1 h (range 0.1–3) and travel to Aira hospital (physicians available) required 6.1 h (range 0.1–24). At the time of diagnosis, the vast majority of the patients had stage 2 or 3 disease (*n* = 30/33; 91%). One third (*n* = 15/44; 34%) underwent modified radical mastectomy; due to lack of consent, lumpectomy (*n* = 7; 16%) and quadrantectomy (*n* = 6; 14%) were also performed. Of 51 patients eligible for tamoxifen therapy, 25 (49%) did not initiate endocrine treatment. The reasons for non-initiation included problems on the health care provider side (12; 48%) where patients had not been given an appointment (*n* = 9), the physician was absent (*n* = 2), and other (*n* = 1). Reasons on the patient side (13; 52%) included lack of money (*n* = 2), too weak to travel (*n* = 1), fear of treatment (*n* = 1), and private reasons (*n* = 1). No information was available for 8 patients. One patient explained: "I went to the hospital, and the surgeon was not at the hospital, or maybe didn't know about my presence."

During the observed March 2013 to December 2015 treatment adherence assessment period, of the 26 patients who initiated tamoxifen therapy (Fig. 1), 9 discontinued treatment (Table 2). One patient recounted, "I took two tablets a day and then waited for the appointment," although she had already finished her medication. Another

Table 2. Patient perception of tamoxifen

Symptom duration, months	22.4 (6–24)
Time to treatment of those patients operated in the adherence assessment period, months	5.7 (0.1–10.8)

Questionnaire	
What is the most important medical problem for women in this area? (*n* = 22)	
"No idea"	14 (64)
Back pain	3 (14)
Cervical cancer	3 (14)
Mastitis	1 (4)
Gastritis	1 (4)
What is cancer? (*n* = 22)	
"No idea"	11 (50)
Disease	5 (23)
Deadly disease	6 (27)
Do you have cancer? (*n* = 20)	
No	10 (50)
Yes	10 (50)
Is tamoxifen necessary? (*n* = 19)	
No	0 (0)
Yes	19 (100)
Would you pay for tamoxifen? (*n* = 14)	
No	11 (79)
Yes	3 (21)
Wherefore do you take tamoxifen? (*n* = 17)	
"No idea"	6 (35)
Prevents cancer	9 (53)
Is helpful	1 (6)
Minders the power of cancer	1 (6)
Why did you stop taking tamoxifen? (*n* = 9)	
Terminal illness	2 (22)
Difficult circumstances	2 (22)
Lack of money	2 (22)
Side effects of therapy	2 (22)
Unknown	1 (11)
Describe complaints on your health (*n* = 20; more than one answer possible)	
None	14 (41)
Nausea	3 (9)
Hot flushes	3 (9)
Sweating	6 (18)
Vaginal discharge	1 (3)
Diarrhea	1 (3)
Changes in mood	2 (5)
Other	4 (12)
Describe discomforts with the taking of tamoxifen (*n* = 21; more than one answer possible)	
"No problems"	14 (59)
Difficult to swallow	7 (29)
Interrupts daily work	2 (8)
Reminds of the disease	1 (4)

Data are presented as the mean (IQR) or number of answering patients (%). *n* = 22 of 26 who initiated tamoxifen; families of 3 deceased patients were not found, and 1 husband was unable to answer the questionnaire

woman said, "I missed one appointment because my child was sick and I was afraid of presenting too late." One woman described tamoxifen as "hard medicine" causing epigastric burning and vomiting. Another shared she "had to borrow money from neighbors for traveling."

Figure 2 provides the patients' refill and possession data for tamoxifen with a resolution of 10 days for the 26 patients who initiated tamoxifen treatment. All except 2 patients had at least one refill delay of 10 days. Of the

women who received surgery and initiated adjuvant tamoxifen, most (7; 58%) of the 12 patients experienced a long delay from the time of operation to the initiation of tamoxifen (median 5.7 months; IQR 0.1–10.8).

The mean MPR was 54% (IQR 28–89). During a median observation time of 16.2 months (range 1–35.7), 17 patients (65.4%) took less than 80% of the prescribed dose and were declared non-adherent, while 9 patients (34.6%) were adherent to therapy. After 1 year the Kaplan-Meier estimated proportion of persistence to therapy was 52%; 6 patients took tamoxifen for more than 1 year (Fig. 3).

Table 2 shows the results of open questions on the patient self-reported perception of health and treatment. The mean time between the first breast symptoms and the patient's presentation at the hospital was 22.4 months (IQR 6–24). Half of the patients had "no idea" what cancer is. At least a few identified cancer as a disease or as a "killer disease." Tamoxifen was considered necessary to all patients, but only 3 were willing to pay for it. Two thirds identified tamoxifen as an anti-cancer drug. For some patients, tamoxifen was difficult to swallow, interrupted daily work, or reminded them of the disease.

Discussion

About half the patients in rural Ethiopia initiated the therapy and of those, half still used the medication after 1 year. Limited data are available concerning the adherence to tamoxifen therapy in Africa. A study from Nigeria reported very high adherence rates of 75.5% after 1 year in an urban setting [27]. Data from Europe and the USA show that 90 and 74.6% of BC patients take up adjuvant endocrine therapy [28, 29]. Generally, reviews on endocrine treatment reveal a great range of adherence of between 41 and 93.4% after 1 year (including non-initiation and discontinuation) [30, 31].

Challenges on the Health Care Provider Side
According to the incidence rates of BC in Ethiopia, and a population coverage of 500,000, 488 BC patients were expected at Aira Hospital within 5 years compared to the actual cohort of 101 patients, revealing significant underutilization of the service. The non-initiation and delay of initiation of tamoxifen treatment in this study reflects common shortcomings in rural settings in sub-Saharan Africa of inadequate pathology capacity and infrastructure [32, 33] and a small number of overburdened physicians [34]. Additional staff including dedicated cancer nurses to track and navigate patients may enhance initiation and adherence and avoid ineffective discontinuation of chronic tamoxifen treatment. A step forward would be the implementation of local pathology and better referral services to increase initiation and adherence.

Fig. 2. Summary of 3-year adherence assessments for the 26 patients who initiated tamoxifen treatment and were censored for prescription refill between March 26, 2013 and March 10, 2016. TAM, tamoxifen; Int., interrupted; OP, operation.

Fig. 3. Kaplan-Meier estimates of the duration of tamoxifen therapy. Discontinuation: no patient contact for more than 6 months, 9 events in 26 patients.

Challenges on the Patient Side

A review showed that high out-of-pocket costs are associated with poor adherence to chronic cancer treatment [30] and remain a barrier to adequate health care access [35]. A Nigerian study listed costs for the drugs, laboratory expenses, and transportation to the hospital as the most common reasons for non-adherence [36]. Although this study minimized financial efforts, they were still the main reason for discontinuation or non-initiation on the patient side. Tamoxifen has been available in Addis Ababa since 1999 in private pharmacies [37]. As most people in rural parts of Ethiopia are farmers with a low income, the average cost of living of about USD 70/month makes tamoxifen (USD 9/month) inaccessible in remote areas (personal inquiry).

Being convinced of the necessity of medication seems to be an important factor in adherence [38]. Patients who understand their disease are more likely to adhere to therapy [25, 39]. Although most patients in this study were convinced of the necessity of tamoxifen, half of the patients in this study had "no idea" what cancer is and they stopped therapy at some time. Reminders and encouragement by SMS or phone calls has improved adherence to HIV medication in South Africa [40]. Patient education and pharmacotherapeutic follow up by health professionals such as breast nurses could be helpful in improving adherence to endocrine treatment [31]. A study in Ghana suggested that women are more likely to complete treatment (71.4%) if they know a person who survived cancer [41]. Therefore, long-term survivors should be included in awareness campaigns to demonstrate the effect of continuous treatment.

Limitations

First, the sample size of our study is small. There could be selection bias since wealthy patients would be more able to access the hospital and very poor patients were probably among the estimated 80% who never arrived at the hospital. Second, the adherence (continuation after initiation) of those patients who initiated therapy and who already understood the necessity of treatment was assessed. These patients could have a better adherence than those who did not initiate any therapy. It follows that even if the adherence rate in this study was low, findings may still overestimate the adherence rate of all patients. Third, a potential bias of the qualitative data could be the suggestive character of the questionnaire and imprecise answers about adherence by relatives of deceased patients. Such an influence was minimized by performing the structured interviews in the local language with a nurse experienced in qualitative research and home visits. We have shown that most BCs in Ethiopia are HR+ [5, 42]; therefore, implementation of endocrine treatment is a promising approach in Ethiopia. The administration of endocrine ther-

apy in rural Ethiopia was implemented, but major challenges remained. Histopathological reports including diagnosis and immunohistochemical services were fully supplied from outside the system; tamoxifen was given by donation. Patient education and navigation was identified as a major shortcoming. Comprehensive interventions to improve system-wide issues in health institutions and to improve patient engagement are needed. One potential health care provider intervention is training and allocating time for breast nurses. We agree with the *Lancet* series on health, equity, and women's cancers in suggesting a persuasive opportunity for breast nurses to educate patients, administer tamoxifen, and relieve the burden of cancer patients [43]. In alignment with the NCCP, we state that treatment for cancer patients must be subsidized by government in low-income rural settings [21].

Statement of Ethics

This study was approved by the institutional review boards at Addis Ababa University, Ethiopia (study approval's reference No. 050/2013 protocol 124/10/IM), and MLU Halle-Wittenberg, Germany (vote on August 23, 2010 of the "Medizinische Ethikkommission"). Informed consent was obtained from all patients when the pathology specimens were sent to Germany for analysis. Additional consent was obtained when tamoxifen therapy was started.

Conflict of Interest Statement

The authors declare no conflicts of interest related to this paper.

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Author Contributions

C.F.R., W.T., E.J.K., and C.T. designed the study. C.F.R., P.E.-S., and W.T. acquired the data. S.G. and A.A. organized the project. C.F.R., S.U., and A.W. performed the statistical analysis. S.H., C.W., and M.V. performed the pathological services. E.J.K. and C.W. obtained the funding. C.F.R. and E.J.K. drafted the manuscript. A.J. critically read and revised the manuscript. All authors substantially contributed to the interpretation of data for the work, critically revised the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

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