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Breast Cancer in Patients on Tamoxifen: Clinico-Pathological Characteristics, Tolerance and Prognostic Factors

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Abstract

The objectify of this work was to report epidemiological, anatomo-clinical and therapeutic aspects, to describe the tolerance of patients to Tamoxifen and to analyze prognostic factors of patients on Tamoxifen. This is a retrospective study involving premenopausal patients with HR+ breast cancer, treated and monitored, from January 2012 to June 2019. A total of 135 patients were included in this study. The most frequent circumstance of discovery was an autopalpated breast nodule in 70.4%. Non-specific invasive carcinoma was found in 91.1%. T2 and T1 tumors were observed in 34.8 and 26,7% of cases. Eighty patients out of 135 underwent Patey-type surgery and 122 received chemotherapy. Adverse effects were experienced by 59.3% of the population. Hot flashes were reported by 37 patients with a cumulative incidence of 27,4% at five years, followed by thickening of the endometrium in 13 patients with a cumulative incidence of 9,6% at five years. Poor compliance was noted in 20% of the population. A relapse was seen in 11.1% of the population and 7 patients died. Overall survival was 94.2% at tree years and 80.9% at five years. TAM improved RH + breast cancer's prognosis and has good clinical tolerance compared to other hormone therapies.

Keywords: Breast cancer, tolerance, Tamoxifen, prognostic factors, Survival

Introduction

Breast cancer (BC) is the most common cancer in women in the world [ ]. The heterogeneity of BC makes it a complex disease with various clinical manifestations, histopathological entities and molecular profiles. For any diagnosed BC, the hormone receptor (HR) status should be systematically investigated to use it as a predictor of response to hormone therapy. BCs with positive HR (HR+) affect 75% of postmenopausal women and 60% of premenopausal women [2]. Approximately70 to 80% of BCs express estrogen receptors (ER) and 60 to 70% are also progesterone receptor (PR)-positive [3]. In premenopausal patients, hormone therapy reference is Tamoxifen (TAM), which is a non-steroidal antiestrogen of the class of Selective Estrogen Receptor Modulators (SERM). This drug has been indicated since 1970 in the treatment of BC which express ER and / or PR either as an adjuvant treatment to prevent recurrence of early BC, or as treatment of advanced or metastatic cancer [4]. Despite its proven effectiveness in the management of patients with BC, this medication has a number of annoying side effects such as (hot flashes, nausea and/or vomiting, weight gain, ovarian cysts...) which may sometimes discourage patients from continuing their treatment [5]. Faced with the scarcity of Tunisian studies focusing on TAM and its tolerance profile, we have carried out this work with the objectives of: Assess the tolerance of TAM and study the evolving status of BC patients treated with TAM.

Material and methods

Study design and participants

This was an observational, retrospective, monocentric study including patients with BC consulting at the department of medical oncology in the University Hospital of Monastir in Tunisia. It was carried out during seven years and six months (from 1 January 2012 to 30 June 2019). All included patients received TAM as an adjuvant treatment at a dose of 20 mg per day. Inclusion criteria were: Histologically proven HR+ BC. Threshold of HR positivity was defined at 10% of stained cells. Pre-menopausal patients at the time of cancer diagnosis, eligible for treatment with TAM in an adjuvant situation. We did not include in this study the patients who received TAM for less than 12 months and patients with metastatic BC.

Results

During the study period, 781 women were treated for BC at the department of medical oncology in the University Hospital of Monastir. Among them, 135 patients were included in the present study. As shown in table 1, the mean age of patients at the time of diagnosis was 43 ± 5.4 years. The mean time of consultation after the first symptom appear was 3 months. Fifty-nine patients (43.7%) consulted within 3 months following symptoms while 24 patients (17.8%) consulted after 6 months. The mean clinical tumor size was 37 ± 22 mm with extremes ranging from zero to 120 mm. The mean radiological size was 24 ± 13 mm, with extremes ranging from four to 70 mm.

Invasive ductal carcinoma is the most common histologic type with a percentage of 91.1%. Among the 135 patients, 70.4% had a high SBR grade (II or III). All of our patients had positive HR. ER and PR were both positive in 88.9%, ER only positive in 9.6% and PR only positive in 1.5%. The Her2 oncogene was overexpressed in 25.9% of patients. The Ki 67 antigen was identified in 71.1% of patients. It was greater than 15% in 60.5% of patients. Patients classified luminal A represented 28.1%, while 43% were classified luminal B. However, the Ki-67 study was not available to the rest of the population. Stage II cancer was the most common with a percentage of 48.9%, 26.7% were classified as having stage III and 24.4% stage I. Radical mastectomy was performed in 59.3% of patients and 40.7% had a breast-conserving surgery. The mean number of lymph nodes removed was 15 ± 6, while the mean positive lymph nodes was 2 ± 4. Fifty-four per cent of patients had at least one positive node. Capsular rupture was observed in 8.9% of the study population. Vascular and lymphatic emboli were found in 10.4% of patients. In our population, 41.5% of patients received neoadjuvant chemotherapy and 51.8% received adjuvant chemotherapy. Radiotherapy was indicated in 91.1% of patients. The 25.9% who over expressed the Her2 oncogene received Trastuzumab. The mean duration of treatment with TAM was 33 ± 16 months, 45.2% were under treatment at the time of the study, 14.1% patients took TAM for 5 years; 2 among them exceeded this duration (one patient for 6 years and the other for 6 years and 4 months). Fifty-five patients (40.7%) did not report any side effects. Hot flashes were the most reported side effect in our population, reported by 27.4% of patients (Table 1). The cumulative incidence of the onset of hot flashes was 24.5% at 2 years and 27.4% at 5 years. Endometrial hyperplasia was found in 9.6% of patients. The cumulative incidence of the onset of endometrial thickening

under TAM was 3% at 2 years and 9.6% at 5 years. The cumulative incidence of the appearance of ovarian cysts under TAM was 7.4% at 5 years (Table 1).

Table 1: The different side effects are summarized in the table

Side effects	N	%
Hoy flashes	37	27.4
Endometrialthickening	13	9.6
Ovariancysts	10	7.4
Metrorrhagia	8	6
Irregular cycle	6	4.5
Genitalitching	5	3.7
Leucorrhoea	3	2.2
Vaginal dryness	2	1.5
Thromboembolic events	1	0.7
Vision disturbance	1	0.7

In our population, 40.7% of patients stopped TAM during the follow-up period. The cumulative incidence of TAM discontinuation was 11% at 2 years and 40.7% at 5 years, the table 2 summarizes the different causes of stopping TAM observed in our population. Twenty per cent of our patients declared that they were non-compliant with their TAM prescription during their follow-ups

Table 2 : Different causes of stopping TAM observed in Tunisian population

Causes of TAM stoppage	N	%
Menopause/Switch	26	47.2
Relapse	14	25.5
Endo metrialthickening	4	7.3
Other side effects*	7	12.8
Desire for pregnancy	1	1.8
Menopauseafter total hysterectomy	1	1.8
Thrombo embolic event	1	1.8
Patient who refused to continue treatment	1	1.8

*Other side effects such as: hot flashes, genital itching and leucorrhoea

Evolution of hormonal status in premenopause under TAM

The explanatory diagram of the change in hormonal status according to exposure or not to chemotherapy is shown in figure 1. In our population, at the start of TAM, 122 patients (90.4%) had chemotherapy, 108 (88.5%) of them had chemotherapy-induced amenorrhea(CIA). Among these patients, 16 (14.8%) resumed their cycles on average of 16.8 months, including 2 after stopping the TAM. Among the 13 patients (9.6%) who did not have chemotherapy, 7 patients (53.9%) stopped cycles after TAM within a mean period of 9.7 months including 2 (28.7%) resumed their cycles within an average of 4 months.

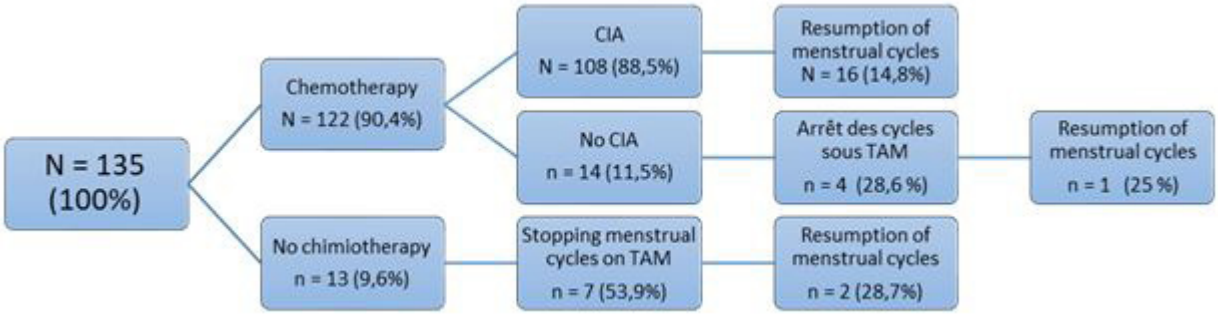

Figure 1: Diagram of the change in hormonal status according to TAM exposure

Evolving status

The relapse rate was 11.1% with an average time to relapse of 34.2 months. A distant relapse was observed in 12 patients and a loco-regional relapse in 3 patients. At the time of data collection, and after contacting all patients, 126 patients were alive, 7 patients dead and 2 were lost to follow-up. The rate of OS at 3 years was 94.2% and 88.9% at 5 years. The median OS was 44 months. The OS curve is shown in the figure 2 .

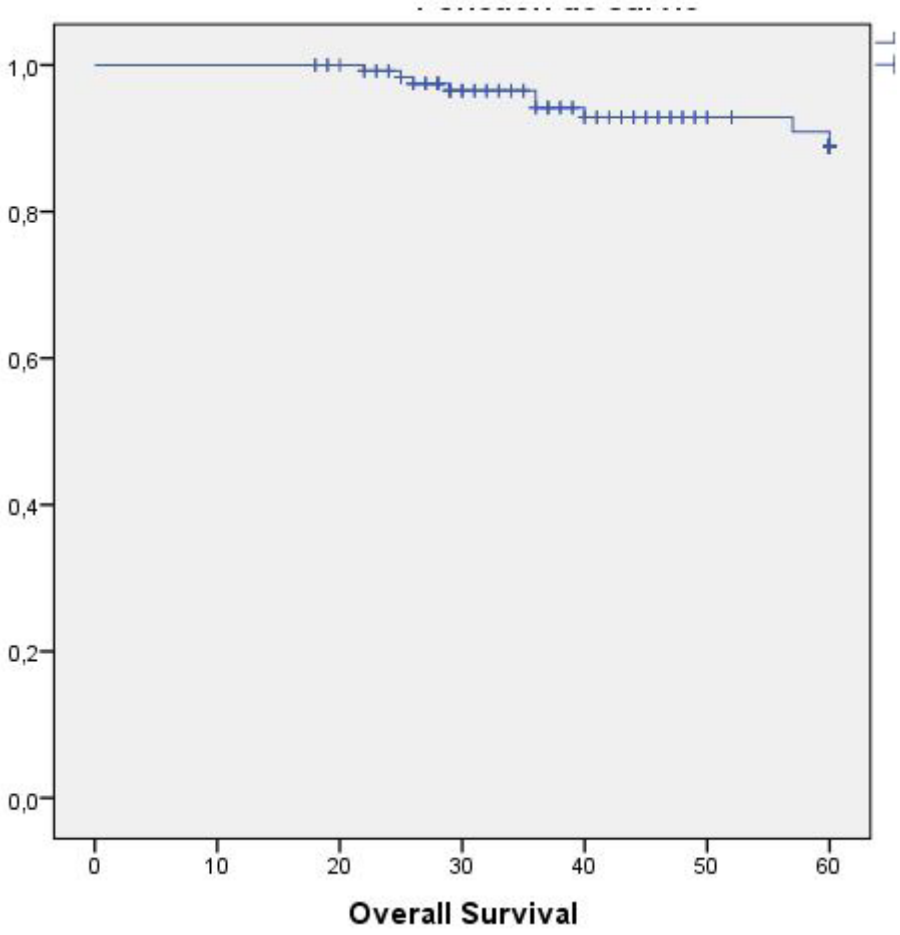

Figure 2: Curve of overall survival

The disease-free survival rate was 91.5% at 3 years and 80.9% at 5 years.

The DFS curve is shown in the figure 3

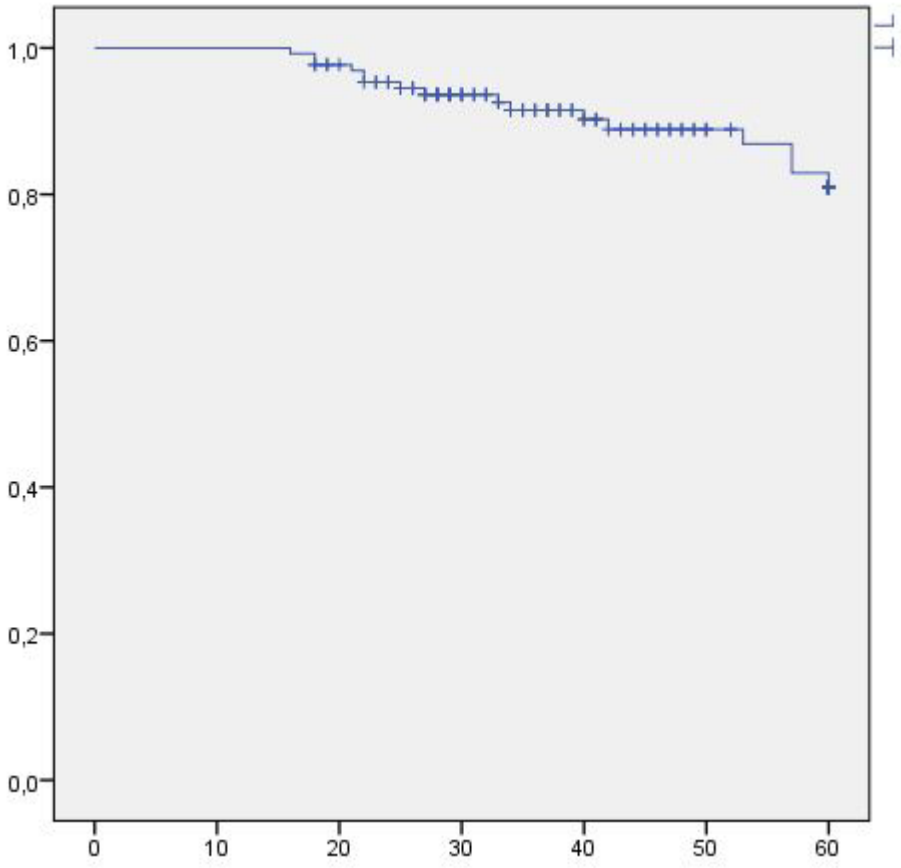

Figure 3: curve of Disease free survival

Discussion

Breast cancer (BC) is the most common cancer in women in the world. In the face of the proven effectiveness of TAM in the management of HR positive breast cancer, this drug has some side effects, which may sometimes cause a non-compliance with the treatment [2]. In this context, the present study is, to our knowledge, one of the first to focus on BC patients treated with TAM by essentially studying their tolerance profile and their prognosis. TAM is considered a revolutionary treatment in Oncology, listed by WHO as an essential drug for the treatment of breast cancer. It is estimated that over 400,000 women are alive today thanks to TAM [6]. In adjuvant situation, after or without chemotherapy, TAM is the gold standard in premenopausal BC women HR + with a daily dosage of 20 mg [7]. Like any treatment, TAM has side effects; in our population, more than half of the patients (59.7%) experienced at least one side effect during their follow-up period. In the literature, hot flashes were the most reported side effect of patients on TAM, affecting more than a third of patients. Hot flashes are correlated with deficit in estrogen action [8].

In the present study, hot flashes were the most observed side effect (n = 37 patients) with a cumulative incidence of occurrence of 27.4% at 5 years. This value was lower than those found in the literature, but given the retrospective nature of our study, this value may be underestimated. In addition, the risk of developing hot flashes under TAM varies in the literature; it goes from 35 to 78% depending on the studies.

In the study of Sebaoun et al., 55.2% of the population presented hot flashes [9]. Another study of Mortimer et al. regarding TAM-induced hot flashes, 78% of patients experienced this side effect [10]. In an analysis of side effects of TAM and

antiaromatases Garreau et al. found that 35% of patients on TAM reported hot flashes [11]. In fact, the most frequent cause of requests for additional treatments during patient follow-ups is for the relief of HF [10].

The pathophysiological mechanism of the occurrence of hot flashesis not fully understood, but several hypotheses have been made on this subject. They may be due to the anti-estrogenic effect of TAM on the central nervous system, which leads to thermoregulatory dysfunction [12]. On the other hand, the decreased biotransformation of TAM to endoxifen due to reduced enzyme activity of CYP2D6 plays a role in the onset of hot flashes [13]. Also, the co-administration of drugs that inhibit CYP2D6 (such as selective serotonin reuptake inhibitors (SSRIs) has been shown to reduce the incidence of hot flushes [12]. Other factors are implicated in the occurrence of HF such as psychological stress, high ambient temperature, alcohol and caffeine [10].

In addition to HF, we found, in our population, ovarian cysts in 10 patients (7.4%) discovered by ultrasounds follow-up. Long known as side effects of TAM, the rate of occurrence of ovarian cystsin the literature could reach 49%. Their onset appears to correlate with hyperestradiolemia caused by TAM [14]. Metindir et al. showed that almost 50% of BC patients developed ovarian cysts on TAM in the premenopausal group. Patients who developed ovarian cysts had a higher level of estradiolemia [15] . A Korean team found that 10.8% of premenopausal BC women on TAM developed ovarian cysts [16]. According to Sebaoun et al., more than two-thirds of patients developed ovarian cysts at 5 years and there was a significant correlation with estradiol levels above 300 pg/ml [9]. Most ovarian cysts developed under TAM were functional and asymptomatic, rarely becoming symptomatic, requiring LHRH analog blockade [17]. The effect of TAM on the endometrium has long been studied due to its ER agonist action [18]. Several lesions of the uterus have been reported in patients on TAM; such as glandular hyperplasia, endometrial polyps, uterine fibroids, and uterine adenocarcinoma or sarcoma. This risk appears to be time dependent [19]. Thirteen of our patients (9.6%) developed endometrial thickening and no endometrial cancer was diagnosed on biopsy curettage. This rate is consistent with the results found in the literature, in fact, a study by Lee et al. [16], out of 92 premenopausal patients on TAM showed that 7.6% of women developed endometrial thickening. In another recent study, carried out by Amer et al [20], focusing on the effect of TAM and AI on the endometrium, the authors reported that in the TAM group the endometrium was thicker compared to the other groups knowing that 17.5% of women on TAM were not menopausal. Other than endometrial thickening, treatment with TAM may put patients at risk of developing endometrial cancer, but this risk is low in patients under 50 years of age [9]. However, this justifies the need for regular monitoring of patients treated with TAM. In our study, only one patient developed deep vein thrombosis on TAM. In the study of Sebaoun et al., only two patients developed thromboembolic events [9]. Also Matthews et al. have shown that this side effect is rare in young women treated with TAM [21]. The risk of developing this side effect with TAM is similar to estrogen-based oral contraceptives and should be looked for during monitoring.

Compliance to treatment

Compliance, which means the level of agreement between doctor's recommendations and patient behavior, is often not considered a problem in cancer patients, due to fear of recurrence and especially the potentially fatal nature of the disease. However, patient adherence to TAM during the 5 years of treatment poses a major problem. Despite the clear benefits of TAM, many patients stop taking their treatment early or do not take it regularly [22].

In the present study, one in five patients (n = 27) reported that she was non-compliant with TAM during the follow-up period and 40.7% (n = 55) stopped it, of which almost 10% did not receive any alternative therapy. These alarming values show the importance of determining the serum concentration of TAM in order to avoid this problem. In the literature, 20% of women under hormone therapy stop their treatment after one year of follow-up [23] and the compliance rate was between 50 and 75% with a particularly high rate of discontinuation during the first year of treatment [22]. Ayres et al. performed a meta-analysis on adherence and discontinuation of hormone therapy; in the 24 included studies, they found that the rates of adherence and/or discontinuation of hormonal therapy forbreast cancer, ranging from 15 to 60% [24]. Another study by Weaver et al, using the medication possession ratio (MPR) to measure medication adherence. MPR is defined as the ratio of the total days covered by the medication divided by the days needing the medication. This study found that the MPR went from 77% the 1st year of treatment to 58% during the 5th year. Only 46% of patients had an adequate MPR after 5 years of treatment [25]. The study of Sebaoun et al. found that 38% of patients stopped TAM before completing the 5 years of treatment with a cumulative incidence of discon-

tinuation of 38.7% at 5 years [9]. The most frequent causes of non adherence or stopping of TAM found in the literature were either the switch to AI or the poor tolerance, which is consistent with the results of our study [9,24,26].

Evolution of hormonal status

In the literature, chemotherapy of breast cancer in premenopausal women induces a transient CIA of 3 to 12 months or permanent, with a rate of CIA which can reach 85%. Age is the main factor influencing the resumption of cycles [27].In 2009, a Korean team concluded that taking TAM and age were significant factors in the persistence of CIA after two years [28]. In 2011, Okanami et al. found that of the 50 patients on TAM, 21% had persistent amenorrhea. They also concluded that TAM significantly increased the persistence of CIA [29].The NSABP B-30 study reported an increase in amenorrhea rates in patients who received TAM after chemotherapy compared to those who did not [30].In order to better understand this effect of TAM on hormonal status, regular dosing of the hormones LH, FSH and estradiol is necessary.Therefore, stopping menstrual cycles under TAM may not always mean true menopause [29], which poses a problem in patients with persistent amenorrhea, of an early switch to an AIwith the real risk of a harmful ovarian recovery [31].

Evolving status

Since the advent of TAM, several clinical trials have considered its use as an adjuvant treatment because of its good tolerability compared to other treatments. Among our patients, 15 (11.1%) had a recurrence (locoregional or distant) and 7 (5.2%) had died. The figures found in our study agree with the data in the literature. The EBCTCG study done in 2011, which included 10 645 HR + BC patients, showed that treatment with TAM for five years reduced the risk of relapse by almost half at 10 years and gave a stable rate of relapse even after 14 years of TAM. Mortality was reduced by a third at 15 years [32]. This suggested that TAM has a protective effect that lasts even for years after stopping treatment. In the study of Sebaoun et al. , among the 55 patients treated with TAM, 14% had a recurrence of the disease and five patients (10%) died [9].A study done in 2012 by Gu et al. found that among the 240 patients treated with TAM, 23 had a recurrence (9.6%) and five patients died (2.1%) [33].

Limitations

This study has several limitations.The first limitation is the retrospective nature of the study involving only 135 patients, which limits the statistical interpretation of the obtained results. Second, testing for the hormones FSH, LH and estradiol was unavailable for most patients, which made it impossible for us to biologically follow the hormonal response of patients under TAM and thus better understand its effect.In addition, the weight of each patient was not measured systematically during the consultations, which represented a limitation in the evaluation of the weight gain that could be induced by the TAM.

Conclusion

Despite its side effects, which vary from patient to patient, TAM remains the important molecule in the treatment of breast cancer in premenopausal women.Predicting changes in hormonal status under TAM is complex, where age and possible chemo-induced amenorrhea at the start of treatment seem to play a major role.The side effects of TAM are mostly well known, some are still discussed until today.At the end of this work and according to our results and those of the literature and in order to improve the management of BC patients treated with TAM, it is necessary to: Improve patient compliance with serum TAM dosing, optimize treatment with TAM by pharmacological monitoring of the endoxifen metabolite and tostudy the genotyping of CYP2D6 in patients on TAM in order to optimize a suitable treatment regimen.

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