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Endometrial Thickness in Tamoxifen-Treated Patients (About 64 Cases)

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Abstract: *The objective of our work is to determine the impact of tamoxifen on the genesis of endometrial lesions, to discuss the place of screening for endometrial pathologies under tamoxifen, to compare our results with the data of the literature. This is a retrospective analytical study conducted in the department of Gynecology-Obstetrics of CHU Mohammed VI of Oujda in Morocco, over a period of 5 years. Sixty-four cases of endometrial lesions under tamoxifen were recorded. In our series, 64 cases of endometrial lesions under tamoxifen were recorded. All patients received tamoxifen at a daily dose of 20 mg. Postmenopausal metrorrhagia and the discovery of endometrial thickening by surveillance ultrasound were the main circumstances of discovery. 53.1% of cases were discovered during ultrasound surveillance of asymptomatic patients and 46.9% of cases by metrorrhagia. Hysteroscopy with biopsies was used to diagnose the various endometrial lesions under tamoxifen. The risk of endometrial cancer increases significantly with the duration and total cumulative dose of tamoxifen. The majority of endometrial abnormalities found (89%) were benign. 6 cases of atypical hyperplasia (9.4%) and one case of endometrial cancer were diagnosed. These results call into question the place of endometrial cancer screening under tamoxifen. Screening for endometrial cancer on tamoxifen is not systematic in all patients. Surveillance remains justified in women at high risk of developing endometrial carcinoma.*

Keywords: Endometrial thickness, Tamoxifen, metrorrhagia

Introduction:

Tamoxifen (TAM), is used in the adjuvant treatment of breast cancer, is associated with an increased risk of endometrial cancer. However, the overall benefit observed with this drug is no longer in question. The problem of monitoring patients on TAM has always been a matter of debate. There is no consensus on any examination or protocol for endometrial surveillance of patients on TAM.

Methods:

This is a retrospective analysis of a series of patients followed up for breast cancer who received TAM in the adjuvant setting between January 2015 and October 2019 at the Department of Obstetrics and Gynecology of the CHU Mohammed VI of Oujda, Morocco. We included any patient followed for histologically confirmed breast cancer, who received TAM as adjuvant treatment on different periods, and presenting with endometrial thickening on pelvic ultrasound.

Results and discussion:

In our series, the average age of occurrence of an endometrial abnormality under TAM is between 50 and 60 years with an average of 55 years. Indeed, endometrial pathologies under TAM are pathologies of women in menopause, the percentage of menopausal women in our series is 86%, and only 14% are settled.

The first cases of endometrial adenocarcinoma under TAM were reported in 1985 by Killackey et al [1]. Since then, this association has been studied and it is now accepted that treatment with TAM increases the risk of endometrial adenocarcinoma by a factor of 2 to 3 in postmenopausal women [2,3]. This increase in risk seems to depend on several factors: the dose and duration of TAM treatment, and in some cases the prior use of hormone replacement therapy with estrogens [4]. The risk of endometrial lesions with TAM seems to increase with the duration of use. For example, in Bernstein's case-control study, the relative risk is 1.9 for a treatment duration of 2 to 4 years and rises to 4.2 when the duration exceeds 4 years [5]. According to Bergman, the relative risk is estimated to be 2 for 1 or 2 years of TAM, and is in the range of 4 to 7 for longer treatments. [6]. The optimal duration of treatment has not yet been determined. Whether treatment should be extended beyond 5 years is still an open question, although the National Cancer Institute announced in 1995 that 5 years of TAM was the standard adjuvant treatment, anticipating the results of subsequent trials [7]. The American Society of Clinical Oncology recommends that women who are pre- or peri-menopausal and have received 5 years of adjuvant TAM should be offered a total of 10 years of TAM, and that women who are postmenopausal and have received 5 years of adjuvant TAM should have the choice of continuing TAM or switching to an aromatase inhibitor for 10 years of treatment [8].

In the study from the University of Padua in Italy 2013 [9], they objectified no statistically significant correlation between the duration of treatment and endometrial thickening. In particular, thickening was detected in 53.5% of patients during the first year of

treatment, in 51.2% during the second year and in 53.7% after the second year. In comparison with our study, it is noted that endometrial thickening increases with the duration of TAM intake but statistically we did not objectify this correlation.(table.1)

Also in the same study of the University of Padua, there was no significant correlation between the duration of the TAM treatment and the histological diagnosis of atypia. However, it is important to note the following trend linking atypia to duration of treatment:

One case of endometrial atypia in the first year of treatment, one case of endometrial atypia in the second year of treatment, and four cases of endometrial atypia after the second year of therapy. The overall detection rate of atypia was 2.3% during the first year, 2.4% in the second year, and 6% after the second year of treatment.

In comparison with our study, we note:

1 case of atypia during the 1st year of treatment.

5 cases of hyperplasia with atypia after the 2nd year of treatment.

1 case of endometrial cancer after the 2nd year of therapy.

The duration of treatment currently recommended is therefore still limited to 5 years. [10]

Table 1: Comparative table with the study of the University of Padova (from June 2007 to June 2012).

Caractéristiques	Our 2019 study N=64		Padou 2013 N=151	
Average age	55.5 (86-37)		58.3 (35-85)	
Length of time to take TAM (year) <= 1 an <2ans et >1an >= 2ans	12.5% 9.4% 78.1%		28.5% 27.2% 44.3%	
Épaississement endométrial	<5 mm	2%	<5mm	14.6%
			Entre 5 et 10 mm	53%
	>=5mm	98%	>10mm	32.4%
Parity Nulliparous Primiparous	22% 78%		15.2% 84.8%	
Hormonal status Menopausal Non-menopausal	85.9% 14.1%		79.5% 20.05%	
Result of hysteroscopy Suspect Not suspect	20.8% 79.2%		4% 96%	

Histological result		
Negative for neoplasia	70.3%	57%
Hyperplasia without atypia	18.8%	39%
Hyperplasia with atypia	9.4%	4%
Endometrial cancer	1.6%	0%

In our series, the average duration of prescription was 3 years and 2 months with the shortest duration of 9 months and the longest duration of 7 years. 78.1% of the patients took TAM for a period exceeding 2 years. For the group of patients who took the TAM for more than 2 years, endometrial thickening was present in 76.6% of patients and metrorrhagia was present in 80% of cases. However, for those who took it for less than a year, metrorrhagia and thickening represented a relatively comparable rate of 12.5%.

This is consistent with the literature and confirms the effect of increasing the duration of TAM use on the risk of endometrial lesions.

In our study series, one case of endometrial cancer and 3 of the 6 cases (i.e. 50%) of hyperplasia with atypia were manifested by metrorrhagia. All benign lesions: 23 cases of polyps (35.9%), 22 cases of glandular atrophy (34.4%) and 3 cases of hyperplasia without atypia (18.8%); and 3 of the 6 cases (50%) of hyperplasia with atypia were discovered incidentally by surveillance ultrasound in asymptomatic women. The modalities of gynecological surveillance of postmenopausal women taking TAM as hormone therapy for breast cancer are not codified.

In the United States, based on the recommendations of the ACOG (the national college of obstetricians and gynecologists in the United States), practitioners are encouraged to perform an annual gynecological examination, including a Pap smear, in all patients on TAM, and to seek prompt medical attention for breakthrough bleeding or pelvic pain, although the efficacy of such screening in these patients has not been proven. No recommendation has been issued by ACOG regarding the use of ultrasound. [11]

The second and most important recommendation of the ACOG is to perform a thorough evaluation of any loss or bleeding with an endometrial biopsy in women treated with TAM. On this last point (histological sampling in the case of metrorrhagia reported on TAM) all authors agree. [12,13]

Means and rhythm of endometrial surveillance under TAM:

Although there is no clearly established monitoring regimen, several procedures have been proposed for endometrial cancer screening under TAM: pelvic (endovaginal) ultrasound, Doppler ultrasound, hysterosonography, hysteroscopy (HSC), and endometrial biopsy; each with its advantages, disadvantages, and limitations, with no consensus recommendation about their indication, or the order of their implementation. [14]

In 2017, in the annual report of the NCCN (National Comprehensive Cancer Network), have recommended a gynecological examination once a year as well as a prompt assessment of any bleeding in any woman put on TAM. No paraclinical examination has been shown to be useful in screening for endometrial cancer on TAM. [15]

In asymptomatic patients, annual endovaginal ultrasound surveillance can be performed 2 to 3 years after the start of treatment. The finding of endometrial thickening requires hysteroscopy or saline infusion hysterosonography. [16]

In postmenopausal women, the thickness of the endometrium considered normal under TAM is controversial. Indeed, most asymptomatic postmenopausal women treated with TAM have an endometrium greater than 5mm, which is the accepted limit for a normal endometrium in postmenopause [17]. Using this maximum value of 5mm as normal thickness, the risk of missing an endometrial abnormality is low but the false positive rate (46%) is too high, leading to invasive and unnecessary diagnostic procedures[18]. In 2014, the American College of Radiology also specified an endometrial thickness of 5 mm as the cut-off value at which histological exploration of the endometrium is recommended in asymptomatic patients undergoing TAM. [19]

In non-menopausal women, it is difficult to specify endometrial thickness thresholds, even more so in a context of taking TAM containing complex reorganizations of the subendometrial chorion. Therefore, no threshold value for endometrial thickness on ultrasound has been established beyond which investigations are necessary [20]. Arailh et al [21] proposed a threshold of 10 mm without really having provided any justification for it, and without referring to the case of patients in amenorrhoea, although these are two completely different cases. On the other hand, this author puts forward an interval of normality for endometrial thickness in the 1st phase of 4 to 8 mm, and another for the 2nd phase of 10 to 14 mm. The endometrial thickness threshold must therefore be interpreted as a function of non-menopausal status on the one hand, and the period of the cycle on the other.

In France, because of the large number of false-positive ultrasound results, an endometrial biopsy using a Cornier pipelle is always performed as a first-line procedure in patients undergoing TAM. It is only of positive value since its yield is lower under TAM, due to the high frequency of glandulocystic atrophy and polyps. Thus, in case of negative biopsy, diagnostic hysteroscopy with endometrial curettage of the whole uterine cavity is indicated. [22]

In the study by Garuti et al. [23] , evaluation of the performance of hysteroscopy (HSC) to distinguish normal from pathological endometrium, in asymptomatic postmenopausal patients undergoing TAM (66 patients), carrying an endometrium ≥ 4 mm, measured at VEE, and then submitted to HSC associated with histological sampling gave the following results for HSC: Sensitivity:100%, Specificity: 94.1%, PPV(positive predictive value): 100% and NPV(negative predictive value): 97.8%. On this basis, HSC in consultation could be considered a safe, well-tolerated diagnostic test that allows for directed endometrial biopsies because it accurately distinguishes normal from pathological endometrium and has better sensitivity, specificity, PPV and NPV than ultrasound. [24]

Conclusion:

Although tamoxifen use increases the risk of pre-neoplastic and neoplastic endometrial disease, several large-scale randomized clinical trials have shown that the therapeutic benefit of tamoxifen for adjuvant breast cancer treatment outweighs the risks associated with endometrial stimulation. Follow-up of women taking tamoxifen remains a controversial issue. Currently, there is no consensus on a monitoring protocol.

Declarations

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References

[1]. Killackey MA, Hakes TB, Pierce VK. Endometrial adenocarcinoma in breast cancer patients receiving antiestrogens. Cancer Treat Rep 1985;69:237–8
[2]. Van Leeuwen FE, Benraadt J, Coebergh JWW, et al. Risk of endometrial cancer after tamoxifen treatment of breast cancer. Lancet 1994;343:448–52.
[3]. Swerdlow AJ, Jones ME, The British tamoxifen second cancer study group. Tamoxifen treatment for breast cancer and risk of endometrial cancer: a case-control study. J Natl Cancer Inst 2005;97:375–84.
[4]. Bernstein L, Deapen D, Cerhan J, et al. Tamoxifen therapy for breast cancer and endometrial cancer risk. J Natl Cancer Inst 1999;91: 1654–62.
[5]. Bernstein L., Deapen D, Cerhan J.R., Schwartz S.M., Liff J., McGannMaloney E., Perlman J.A. and Ford L. (1999) Tamoxifen therapy for breast cancer and endometrial cancer risk. Journal of the National Cancer Institute, 91, 1654–1662.
[6]. Bergman L., Beelen M.L., Gallee M.P., Hollema H., Benraadt J. and van Leeuwen F.E. (2000) Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen. Lancet, 356, 881–887.
[7]. Rea D, Poole C, Gray R. Adjuvant tamoxifen: how long before we know how long? BMJ. 16 mai 1998;316(7143):1518-9.
[8]. Burstein HJ, Temin S, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, et al. Adjuvant endocrine therapy for women with hormone receptorpositive breast cancer: American society of clinical oncology clinical practice guideline focused update. J Clin Oncol 2014;32:2255–69.
[9]. Van Leuween FE, Benraadt J, Coebergh JW et al. Risk of endometrial cancer after tamoxifen treatment of breast cancer. Lancet 1994 Feb 19; 343(8895):448-52.
[10]. Rose PG Endometrial carcinoma. N Engl J Med 1996; 335:640-649.
[11].ACOG committee opinion. Tamoxifen and endometrial cancer. Number 169, February
1996.Committee on Gynecologic Practice. American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet. mai 1996;53(2):197-9.
[12]. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician Gynecologists: Number 39, October 2002. Selective estrogen receptor modulators. Obstet Gynecol. oct 2002; 100(4):835-43.
[13]. Mourits MJ, De Vries EG, Willemse PH, Hoor KA Ten, Hollema H, Van der Zee AG. Tamoxifen treatment and gynecologic side effects: a review. Obstet Gynecol. mai 2001;97(5 Pt 2):855-66.

[14]. Runowicz CD. Gynecologic surveillance of women on tamoxifen: first do no harm. J Clin Oncol Off J Am Soc Clin Oncol. 15 oct 2000;18(20):3457-8

[15].NCCN Guidelines Insights: Breast Cancer, Version 1.2017 - JNCCN.

[16].https://www.revmed.ch/RMS/2013/RMS-387/Hormonotherapie-dans-le-cancer-du-sein- efficacite-et-effets-adverses.

[17]. Barakat RR. Screening for endometrial cancer in the patient receiving tamoxifen for breast cancer. J Clin Oncol Off J Am Soc Clin Oncol. Juill 1999; 17(7):1967-8.

[18]. Love CD, Muir BB, Scrimgeour JB, Leonard RC, Dillon P, Dixon JM. Investigation of endometrial abnormalities in asymptomatic women treated with tamoxifen and an evaluation of the role of endometrial screening. J Clin Oncol Off J Am Soc Clin Oncol. Juill 1999; 17(7):2050-4.

[19]. Expert panel on women's imaging. American college of radiology ACR appropriateness criteria: vaginal bleeding. 2014;1—13.

[20]. COHEN I , ROSENDJ, SHAPIRA J, CORDOBA M , GILBOA S, ALTARAS MM,
YIGAL D, BEYTH Y. Tamoxifène-treated and nontreated asymptomatic, postmenopausal breast cancer patients. Gynecol Oncol, 1994, 52:190-195.

[21]. Yarnold J.R, Bliss J.M, Earl H. Ovarian ablation in pre-menopausal women with early breast cancer, prescribed 5 years tamoxifen, or tamoxifen plus chemotherapy: Results from the OK NCRI Adjuvant Breast Cancer (ABC) inter - national trial of 2 144 patients. ASCO 2004; Abstract 535.

[22]. Saccardi C, Gizzo S, Patrelli TS, Ancona E, Anis O, Di Gangi S, et al. Endometrial surveillance in tamoxifen users: role, timing and accuracy of hysteroscopic investigation: observational longitudinal cohort study. Endocr Relat Cancer. août 2013;20(4):455-62

[23]. Garuti G, Cellani F, Centinaio G, Sita G, Nalli G, Luerti M. Baseline endometrial assessment before tamoxifen for breast cancer in asymptomatic menopausal women. Gynecol Oncol. Juill 2005;98(1):63-7.

[24]. Giorda G, Crivellari D, Veronesi A, Perin T, Campagnutta E, Carbone A, et al. Comparison of ultrasonography, hysteroscopy, and biopsy in the diagnosis of endometrial lesions in postmenopausal tamoxifen-treated patients. Acta Obstet Gynecol Scand. Oct 2002;81(10):975-80.