Maturitas xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Treatment of climacteric symptoms in breast cancer patients: A retrospective study from a medication databank

Caroline Antoine[a,*], Lieveke Ameye[b], Marianne Paesmans[b], Serge Rozenberg[a]

[a] Department of Obstetrics and Gynaecology, Free Universities of Brussels (ULB-VUB), CHU Saint-Pierre, Rue Haute 322, 1000 Brussels, Belgium
[b] Data Centre, Free Universities of Brussels (ULB-VUB), Institut Jules Bordet, Boulevard de Waterloo 121, 1000 Brussels, Belgium

ARTICLE INFO

Article history:
Received 16 December 2013
Received in revised form 24 April 2014
Accepted 25 April 2014
Available online xxx

Keywords:
Breast cancer
Breast cancer survivors
Menopause
Climacteric symptoms and treatment

ABSTRACT

Introduction: Women affected by breast cancer (BC) will often go through menopause at an earlier age and display more frequent and severe symptoms than women who have a natural menopause. The safety of hormone replacement therapy (HRT) and vaginal estrogens for BC survivors has been debated over time and remains unclear. Non hormonal therapies such as antidepressants, gabapentine and clonidine may be useful for those patients but there are few data about their safety.
Aim: This retrospective study analyses the use by BC patients of treatments known to alleviate climacteric symptoms.
Material and method: Post-menopausal Estrogen Receptors positive (ER+) BC patients, aged 45–69, were identified as having bought, at least once, an aromatase inhibitor (AI) or tamoxifen between the years 2000 and 2012 through a pharmaceutical databank in Belgium. Among them, we defined users of a climacteric treatment those who bought, at least once, HRT, vaginal topical estrogens, antidepressants, clonidine and gabapentine.
Results: We identified 2530 BC patients. Among them, 45% were buying a treatment known to alleviate menopausal symptoms. The majority of these treatments were non-HRT therapies. HRT and vaginal estrogens were seldom bought (respectively 1.1% and 6%), but 3% bought vaginal estrogens while buying AI. About 9.2% of tamoxifen users patients bought antidepressants implicated in tamoxifen metabolism at the same time as tamoxifen.
Conclusions: Most BC patients follow current guidelines contra-indicating the use of HRT after BC, they use non hormonal therapies. In some cases they use unfortunately antidepressants that may alter the metabolism of tamoxifen.

1. Introduction

Breast cancer (BC) mortality has decreased during the last decades [1–3]. Consequently, quality of life has emerged as an important challenge in the management of BC. Many women affected by BC will, following chemotherapy or hormonal treatment, go through menopause at an earlier age and display more frequent and severe climacteric symptoms than women who go through menopause naturally at a later age [4–7]. Some publications even reported a five times higher prevalence of menopausal symptoms in those patients than in the general population [8].

We hypothesised that nowadays few BC patients would be using HRT and that BC survivors might use more alternative treatments. Indeed, literature about the safety of hormone replacement therapy (HRT) in BC survivors has been fluctuating over time and conclusions remain unclear [9–17].

Between 1994 and 2004, many studies concluded that HRT was not contra indicated in these patients while most randomised trials published since 2004 observed an increased risk of BC recurrence [9,13–16,18–21].

Similarly, safety data regarding vaginal estrogens for the treatment of vaginal atrophy, in BC survivors, were also confusing [22–27].

As a result, non-hormonal treatments to decrease hot flushes, such as new antidepressants, gabapentine, pregabaline and clonidine, have been more often used [26,28,29].

We previously conducted a survey of 169 BC patients treated in our breast cancer clinic, evaluating their climacteric symptoms and treatments used [30]. Over 50% of these women suffered from climacteric symptoms such as hot flushes but very few were using

* Corresponding author. Tel.: +32 2 535 33 02; fax: +32 2 535 34 09.
E-mail address: caroline_antoine@stpierre-bru.be (C. Antoine).

http://dx.doi.org/10.1016/j.maturitas.2014.04.020
0378-5122/

a treatment to alleviate these symptoms. None took HRT and few used vaginal estrogens (6.5%), anti depressant agents (11.2%), phytoestrogens (1.2%), clonidine or black cohosh (7.7%) [30]. Although these results were based on an anonymous survey, we were surprised by the low frequency of use of treatments for climacteric symptoms. The present retrospective study analyses, in a medication databank, the use by BC patients of treatments known to alleviate climacteric symptoms.

2. Material and method

2.1. Setting

We conducted a retrospective longitudinal analysis of pharmaceutical data provided by EPC-Familia (i.e. a group of 100 pharmacies in Brussels and Wallonia) covering the period between 2000 and 2012.

2.2. Inclusion criteria

It was restricted to women who are regular clients, defined as having bought at least 4 times whatever medication per year in one of their pharmacies, i.e. 364 518 women of whom 83 870 were between the age of 45 and 69, in the year 2000. Each patient has a unique identifier and all the medications are registered by their national code (CNK).

2.3. Cases

Users of a specific treatment were defined as patients who bought this treatment at least once.

Post-menopausal Estrogen Receptor positive (ER+) BC patients, aged 45–69, were identified through their purchase of AI or tamoxifen, since in Belgium these medications are currently restricted to this indication. The use of tamoxifen and AI for BC prevention, in Belgium, is expected to be small since they are not reimbursed in this indication. ER+ tumours represent approximately 80% of all BC. We had no way to identify Estrogen Receptor negative (ER−) BC patients, as there is no specific medication for.

2.4. Outcomes

(1) Use of HRT:

In those ER+ BC patients, we analysed, retrospectively, whether therapies alleviating menopausal symptoms were bought concomitantly with or after having bought AI or tamoxifen. These therapies included: HRT and tibolone.

HRT included oral estrogens (Aacifémine®, Estrofem®, Progynova®, Zumenon®), transdermal estrogens (Climara®, Dermestril®, Estraderm®, Estradiol Hexal Patch®, Estreva®, Feminova®, Oestrogel®, Systen®, Vivelle Dot®), oral combined HRT (Activelle®, Angeliq®, Climen®, Climodien®, Cyclocur®, Diviplus®, Diviva®, Femoston®, Kliogest®, Novofem®, Trisequens®), transdermal combined HRT (Estalis®, Estracombi®, Feminova Plus®), estrogens only combined with progestins prescribed separately (Duphaston®, Lutenyl®, Nogest®, Orgamétril®, Utrogestan®) and others (Meno-implant®, Progynon®).

Tibolone is sold in Belgium as Livial® or Heria®.

We also analysed whether the purchase of these therapies varied before or after the publication of the results of trials on this topic such as the HABITS, Stockholm and LIBERATE trials [13–15]. The results of the HABITS trial have been first published in a short version in 2004 and in an extended version in 2008 [13,31].

(2) Use of vaginal estrogens.

Vaginal estrogens included Ortho-gynest® and Aacifémine® (both estriol). Data on Vagifem® were unfortunately missing and were estimated to represent between 4.6% and 9.6% of vaginal estrogen use, based on the general Belgian population IMS Health sales data (1997–2008). The use of Vagifem® in BC survivors is expected to be smaller than in the general population since it is estradiol and estriol is often preferred in these patients.

(3) Use of other medications known to alleviate menopausal symptoms but also prescribed for other indications (anti depressant agents, pregabalin, gabapentine and clonidine).

Anti-depressant agents included tricyclic and related antidepressants first and second group (such as venlafaxine (serotonin, norepinephrine and dopamine reuptake inhibitor)), SSRI (such as citalopram, paroxetine and fluoxetine) and monoamine oxidase inhibitors.

Some antidepressants are strong inhibitors of the cytochrome p450 enzyme CYP2D6 (paroxetine and fluoxetine used for depression and climacteric symptoms and bupropione and duloxetine used for depression only).

We mostly analysed antidepressants recognised to alleviate climacteric symptoms (venlafaxine, fluoxetine, paroxetine and citalopram) and antidepressants that may interact with the tamoxifen metabolism (bupropione and to a lesser extent duloxetine).

Gabapentin is sold in Belgium as Gabapentine® or Neurontin®, pregabalin as Lyrica® and clonidine as Dixarit®.

2.5. Statistical analyses

In the patients identified as having ER+ BC (bought AI or tamoxifen), we looked at the use of medication in the years following the year of 1st use of AI or tamoxifen. We determined the number of women who used the above list of medications and calculated the relative rate of users in all ER+ BC patients.

We also assessed the relative rate of users who used medication in the same year as they were using AI or tamoxifen. The 95% CI intervals were calculated based on the Wilson score method without continuity correction. No further statistical analyses were done as this is a mainly descriptive study and the only hypothesis was that we expected very few patients who used HRT after ER+ BC. We considered that there was no missing data since when a woman bought a medication at one of the pharmacies it is recorded.

3. Results

The EPC-Familia data bank included 83 870 women aged 45–69, in the year 2000. We identified 2530 patients as having bought either tamoxifen or AI between the years 2000 and 2012 and we therefore considered them as BC patients with ER+ tumours (Fig. 1).

Among these patients, 1143 (45%) filled at least one prescription of HRT, tibolone, vaginal estrogens, antidepressants, gabapentin, pregabalin or clonidine after the initiation of either tamoxifen or AI (Table 1). Some women bought more than one medication.

Twenty-seven women (1.07%) filled a prescription for HRT: nine (0.36%) used low potency estrogens, estriol (E3) (Aacifémine®), nine (0.36%) used tibolone, five (0.2%) used transdermal 17β estradiol (E2) (Oestrogel®, Demestril®), three (0.12%) with micronized progesterone (Utrogestan®), two (0.08%) used E2 combined with dydrogesterone (Femoston®), two (0.08%) used E2 combined with drospirenone (Angeliq®), one (0.04%) used E2 combined with medroxyprogesterone acetate (MPA) (Diviva®), one (0.04%) used

Please cite this article in press as: Antoine C, et al. Treatment of climacteric symptoms in breast cancer patients: A retrospective study from a medication databank. Maturitas (2014), http://dx.doi.org/10.1016/j.maturitas.2014.04.020