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Review

Position of the Spanish Menopause Society regarding the management of menopausal symptoms in breast cancer patients

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ABSTRACT

Breast cancer is the most common female cancer in Spain. Its high prevalence, its high survival rate, and its incidence are the reasons treatment is increasingly sought for common problems by young women who have survived it. Besides the contraception and fertility issues, many breast cancer survivors develop sexual disorders and menopausal symptoms, whether as a consequence of treatment-induced menopause or side effects of treatment. For such reasons, a panel of experts from the Spanish Menopause Society has met to develop usage recommendations for the relief of vasomotor symptoms and for sexual and reproductive health in patients with breast cancer based on the best evidence available.

Contents

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1. Introduction

More than 20,000 new cases of breast cancer (BC) are diagnosed annually in Spain. BC is the most common type of cancer (28.7% of all cancers) and has the highest mortality of all cancers in women (18.2%). However, survival has also increased in recent years as a result of early detection programmes and advances in treatment; consequently, BC also has the highest survival rate among cancers affecting women [1].

New clinical demands are often difficult to manage and present a challenge because survival and improved quality of life have been interpreted as conflicting interests. In fact, BC patients suffer more hypoestrogenism symptoms than women who reach menopause naturally, in some cases because chemotherapy (CT) has induced early menopause and in others because of the anti-estrogenic effects of adjuvant treatments [2]. This position paper aims to present recommendations for symptomatic patients with BC based on the best scientific evidence available [3,4].

2. Treatment of vasomotor symptoms in patients with BC

2.1. Hormone therapy (HT)

Although hormone therapy (HT) is considered the most effective treatment for the relief of vasomotor symptoms, the suspicion that it could increase the risk of recurrence, especially in oestrogen receptor (ER)-positive tumours, limits its use in patients with BC [5]. We only recommend it for patients with severe symptoms or those who are refractory to other treatments, and we always take into account other favourable factors (e.g., patients with early-stage or ER-negative tumours or with a prolonged disease-free survival) and inform the patient about the risks and benefits. In these cases, the duration and dose of HT should be minimised where possible [6].

The available evidence is limited and of poor quality; although there are many non-randomised observational studies in which prognosis does not worsen (and, in some cases, improvements are described) for women on oestrogen therapy (ET), the selection bias of no-randomisation affects the validity of the conclusions.

While the HABITS (Hormone Replacement Therapy after Breast Cancer: Is It Safe?) [7] trial found an increase in BC recurrences after HT (*hazard ratio* (HR), 3.3; 95% CI, 1.5–7.4), the Stockholm trial did not (HR, 0.82; 95% CI, 0.35–1.9). Possible explanations for these differences are the different doses, the type of progestogen used, or the concomitant use of tamoxifen (TMX) [8]. However, an analysis of the data revealed a slight increase in the risk of recurrence, and the two randomised clinical trials (RCTs) were prematurely ended in 2003[9].

Consequently, HT is not advisable for symptom relief in women with a history of BC.

2.2. Progestogens

High-dose progestogens may be effective for the relief of hot flashes without increasing the recurrence of BC. However, to date, there are no data on their long-term safety in patients with BC.

Megestrol acetate is a synthetic progestogen used to treat BC. In a study with TMX, an oral dose of 20 mg/day of megestrol acetate decreased the frequency of hot flashes by 85%. Weight gain is the main side effect, but glucocorticoid activity and the risk of adrenal insufficiency are also cause for concern [10].

In a trial comparing a single dose of 400 mg of intramuscular medroxyprogesterone acetate (MPA) to venlafaxine, the reduction of hot flashes was higher with venlafaxine than with MPA (80 vs. 55%). Venlafaxine is also associated with more side effects, such as nausea, loss of appetite, dizziness, constipation, dry mouth, and drowsiness [11].

2.3. Tibolone

Tibolone is a drug with complex, tissue-specific action that exhibits a combination of estrogenic, progestogenic and slight androgenic activity. Due to generally positive results regarding the breast [12], the LIBERATE (*Livial Intervention following Breast Cancer; Efficacy, Recurrence, and Tolerability Endpoints*) study was designed to compare the effectiveness and safety of tibolone against the placebo in the treatment of the vasomotor symptoms of 3148 women who had overcome the disease. After an average follow-up of 3 years, 237 of the 1156 women (15%) using tibolone experienced a recurrence of breast cancer, in comparison with 138 of the 1213 (11.4%) in the placebo group (HR 1.40, 95% CI 1.1–1.79), for which reason the study was halted 6 months before the planned date [13].