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Chemotherapy-induced ovarian toxicity in patients affected by endocrine-responsive early breast cancer

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Abstract

Cytotoxic chemotherapy may variably affect ovarian function depending on age and ovarian reserve at diagnosis, type of chemotherapy and use of tamoxifen.

Ascertaining whether a premenopausal patient with endocrine-responsive early breast cancer and chemotherapy-induced amenorrhea has reached menopause is essential not only in order to provide accurate information on residual fertility, but also to appropriately prescribe

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endocrine therapy. Indeed, aromatase inhibitors are contraindicated in women with residual ovarian reserve. However, the diagnosis of menopause in patients with chemotherapy-induced amenorrhea is challenging, since clinical features, follicle-stimulating hormone and estradiol levels may be inaccurate to this aim. Recent studies demonstrated that the anti-müllerian hormone may improve the assessment of ovarian reserve residual to chemotherapy in women with early breast cancer.

Herein, we review the incidence of amenorrhea and menopause induced by cytotoxic chemotherapy in women affected by early breast cancer and the suggested mechanisms that sustain these side-effects. Furthermore, it has been scrutinized the potential of new markers of ovarian reserve that may facilitate the selection of appropriate endocrine treatment for premenopausal women who develop amenorrhea following adjuvant chemotherapy for early breast cancer.

Keywords: Breast cancer; Chemotherapy-induced amenorrhea; Chemotherapy-induced menopause; Aromatase inhibitors; Ovarian reserve

1. Introduction

Breast cancer (BC) is the second most common cancer in Western Countries and the most common invasive malignancy in reproductive-aged women [1,2]. Approximately 30% of patients are premenopausal and 10% are aged 35–44 at diagnosis [3]. Despite the fact that BC in women under the age of 40 is infrequent (5.5% in the United States) [4], a dramatic increase in the number of BC diagnosed in premenopausal women has been reported in several countries [5]. BC, even in early stages (EBC), presents more aggressive features, and prognosis is poorer in younger compared with older women [6–8]. Therefore, most of these patients receive adjuvant cytotoxic treatments (CT) followed by endocrine therapy (ET) in the case of endocrine-responsive (ER+) disease [9,10].

CT prolongs survival of patients affected by EBC, even in the case of endocrine-responsive disease, particularly in women under 50 [11]. However, in a variable percentage of pre-/perimenopausal patients CT may cause amenorrhea (chemotherapy-related amenorrhea, CRA) or menopause (chemotherapy-related menopause, CRM). These side-effects are predictive of improved clinical outcomes in most clinical trials [12,13], but expose women to a number of physical and socio-psychological distresses regarding residual fertility, sexual dysfunction, bone loss and menopausal symptoms, with a markedly negative effect on quality of life [14].

A number of factors influence the onset of CRA/CRM, including age, type of CT received and use of tamoxifen (Table 1). Estimation of the individual risk to develop CRA or CRM, however, remains approximate.

Nowadays, to ascertain whether a patient with endocrine-responsive EBC and CRA is actually menopausal is of utmost importance not only in order to provide accurate information on residual fertility, but also for prescribing the most suitable ET (i.e., tamoxifen or aromatase inhibitors, AI). Indeed, only in postmenopausal patients are AI recommended as up-front treatment, or sequentially after tamoxifen, since they reduce the risk of recurrence [16]. Instead, AI as single agents are contraindicated in premenopausal patients and in those presenting residual ovarian function [16]. In these patients, the inappropriate use of AI induces a temporary inhibition of estrogen production, leading to a feedback increase in gonadotropin levels, which, in turn, stimulate follicular growth, aromatase activity and restoration of pre-CT estradiol levels [17]. These changes in hormonal levels would be expected to reduce or abolish the efficacy of the anticancer treatment received and expose patients to further unjustified side-effects, including pain from ovarian hyperstimulation and increased risk of unplanned pregnancy [18]. Confirmation of the menopausal status is, therefore, mandatory before prescribing AI [19].

In current clinical practice, menopause in a patient with CRA may be only presumed based on some clinical features, such as age, the likelihood of gonadal toxicity from chemotherapy, use of tamoxifen, menstrual history, vasomotory symptoms, together with serum levels of FSH and estradiol. Information obtained by these parameters, however, may be misleading. In particular, serum levels of FSH and estradiol, widely used to confirm menopausal status, may provide erroneous information in 25–35% of cases [18,20].

This article reviews the incidence and the pathophysiology of gonadal damage induced by CT in women affected by endocrine-responsive EBC. Moreover, practical approaches integrating new markers of ovarian reserve are proposed to distinguish truly menopausal women who may receive an AI as adjuvant ET from those with CRA.

2. Ovarian insufficiency induced by cytotoxic agents

2.1. Definitions

The progressive loss of oocytes from fetal life through menopause is physiological [21]. At approximately the age of 37, however, an accelerated atresia of the oocytes is responsible for the average age of menopause being about 51 years (range 40–60 years) in Western women [14,21,22]. Cessation of menses that occurs before the age of 45 is defined as "early" menopause. When menses cease even earlier (before the age of 40), it is called "premature" menopause or premature ovarian failure (POF). The latter is an arbitrary cut-off point designated by the World Health Organization (WHO) corresponding to menopause occurring at an age two standard deviations below the population mean [23]. Instead, there is no WHO proposed definition for early menopause, which is, however, largely used in several studies.