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Mechanisms of chemotherapy-induced ovarian damage in breast cancer patients

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ABSTRACT

Fertility preservation in breast cancer patients is an increasingly relevant topic. In the present paper we review available data on the mechanism of ovarian damage caused by anticancer agents currently used for the treatment of breast cancer. We also describe current methods to preserve fertility including oocytes or ovarian tissue freezing and administration of LH-RHa during chemotherapy.

Abbreviations: 5FU, 5-fluorouracil; AMH, Anti-Mullerian Hormone; CI, Confidence Interval; CIA, Chemotherapy-Induced Amenorrhea; CPA, Cyclophosphamide; FSH, Follicle Stimulating Hormone; LH, Luteinising Hormone; LH-RH, Luteinising Hormone Releasing Hormone; LH-RHa, analogues of Luteinising Hormone Releasing Hormone; MTX, Methotrexate; OTC, Ovarian tissue cryopreservation; POF, Premature Ovarian Failure; SLE, Systemic Lupus Erythematosus.

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The aim of the paper is to provide clinical oncologists with an adequate knowledge of the subject to enable them to give a correct counselling to young women that must receive chemotherapy and want to increase their possibilities of maintaining fertility.

1. Introduction

Improvement of diagnostic and therapeutic procedures has allowed prolonged survival also for breast cancer patients diagnosed before the age of 40. Nonetheless, cure comes with a price for many women. Among young breast cancer patients, the loss of future fertility is considered among the most dreadful long-term side effects of treatments (Partridge et al., 2004; Ruddy et al., 2014; Howard-Anderson et al., 2012), and many women do not start effective therapies for the fear of treatment-derived infertility (Llarena et al., 2015).

Oncofertility is a new and rapidly growing topic in oncology: several techniques have being developed to protect women fertility, but the understanding of the mechanisms of ovarian damage caused by medical treatment still remain elusive (Table 1).

Our aim is to provide medical oncologists who treat young women with breast cancer with a basic knowledge of the subject so that they can provide sound information based on scientific data (Del Pup et al., 2014a; Del Pup et al., 2014b; Del Pup et al., 2014c). Nonetheless, no accurate information will ever compensate for the lack of sympathy and respect towards women's priorities and attention to individual values and projects (Del Pup et al., 2014a; Del Pup et al., 2014b; Del Pup et al., 2014c).

2. Ovarian structure and physiology, cell types

Oocytes reach their maximum number in the embryonal ovary during foetal life. After birth, oocytes remain in the prophase state of first meiotic division surrounded by a single cellular layer (primordial follicles). At puberty, primordial follicles are recruited in cohorts of 10–20 and start growing: the surrounding cells undergo modifications and the primary follicle is formed. At each menstrual cycle follicles undergo further growth and maturation, granulosa cells evolve and stratify and at the end one oocyte is usually extruded: it is now in the metaphase of the second meiotic division and ready to be fertilized (Reichman and Green, 1994).

One of the reasons of the special fragility of oocytes lies in the extremely long time spent in the prophase of first meiotic division (Carroll and Marangos, 2013) during which DNA damage may accumulate especially when DNA repair mechanisms are altered (Titus et al., 2013; Amelio et al., 2014). Oocytes appear to be exquisitely sensitive to genetic damage caused by toxic agents (Morgan et al., 2013; Chun et al., 2014) and are able to activate DNA verification also at a later time (Jurisicova et al., 2006). On the other hand, when a oocyte is damaged apoptosis rather than repair may happen (Amelio et al., 2014; Feng et al., 2011; Carroll and Marangos, 2013) and response to damage differs between fertilized and non-fertilized oocytes (Perez et al., 1997).

3. Experimental systems

Studies of ovarian damage by chemotherapy largely rely on experiments performed in vitro or in animals. However, results are often difficult to interpret and it may not be easy to transfer preclinical observations to the clinical setting. The most widely used animals, rats and mice, have a different reproductive physiology and oocyte response to damage may differ (Desmeules, 2006). On the other hand, drug doses and schedules are in some cases different from what are used in patients (Chang et al., 2015) despite some attempts to translate drug doses from clinical to experimental settings (Chun et al., 2014).

A more sophisticated approach is based on the transplantation in immunodeficient mice of fragments of human ovarian tissue, generally obtained from women undergoing ovarian tissue cryopreservation. This allows a quasi-physiological environment to study cell maturation, but the effect of drug treatment may not be as accurate as desired (Oktem and Oktay, 2007a, 2007b).

In vitro analysis is a fast, cheap and clear-cut technique to evaluate cell damage. Cell lines derived from granulosa or from stroma cells are widely available. It is also possible to keep fragments of ovarian tissue in culture, but only for a relatively short time, and to observe cell development and the effect of drugs.

All these systems are especially important in the evaluation of protecting agents that may reduce ovarian damage caused by toxic agents.

4. Ovarian damage from chemotherapy

The exact mechanisms of ovarian toxicity have not been fully understood (Ben-Aharon et al., 2015) and depend on the type of drug and on the type of cell studied (Yuksel et al., 2015). Stroma and granulosa cells are generally more affected, but a direct toxicity of anticancer drugs (especially alkylating agents) on oocytes has also been described (Oktem and Oktay, 2007a, 2007b; Morgan et al., 2012).

The first observations focussed on the consequences of radiation treatment (reviewed in Stroud et al., 2009), as irradiation was actually used to induce menopause as a form of endocrine treatment of breast cancer. Similar data were later obtained from the analysis of women included in trials of adjuvant treatment for breast cancer using alkylating agents (Fisher et al., 1979) and Cyclophosphamide (CPA).

CPA is at present one of the most widely used agents in the adjuvant treatment of breast cancer: it is therefore not surprising that this probably is the most extensively studied agent. Its mechanism of action, after liver activation, consists in the formation double strand breaks in DNA. Actively proliferating cells are most sensitive to this agent, but this type of damage also affects oocytes (Ben-Aharon and Shalgi, 2012; Oktem and Oktay, 2007a, 2007b; Chun et al., 2014). DNA damage results in apoptosis mediated by complex molecular mechanisms (Desmeules, 2006; Chang et al., 2015) which may in part be reversed by protecting agents (Gonfloni et al., 2009; Chun et al., 2014). Protection may be obtained when low doses are employed, but it may become insufficient with high doses (Chun et al., 2014).

Even if CPA is generally used in combination with other anticancer agents, its importance is prominent since antimetabolites such as Methotrexate (MTX) and 5-Fluorouracil (5FU) have a very limited ovarian toxicity (see below).

Ovarian damage has also been described in patients with autoimmune disorders treated with CPA, such as Systemic Lupus Erythematosus (SLE) (Slater et al., 1999; Warne et al., 1973). In these patients disease itself may affect ovarian function and fertility so