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ARTICLE

Ovarian reserve in breast cancer: assessment with anti-Müllerian hormone

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Abstract Anti-Müllerian hormone (AMH) levels fall during chemotherapy. Treatment-induced amenorrhoea is a reversible phenomenon, but few data are available on long-term AMH changes in breast cancer. The aim of the study was to describe serum AMH levels before, during and in the long term after chemotherapy, and to show a potential AMH recovery. Between May 2010 and June 2011, we selected 134 women aged 18–43 years at the time of breast cancer diagnosis who received chemotherapy between 2005 and 2011, and had not undergone an oophorectomy or had previous cytotoxic treatment. The AMH levels were assessed before, during and 4 months to 5.5 years after the end of chemotherapy. During chemotherapy, AMH was undetectable in 69% of women. After chemotherapy, a significant increase in AMH was found, with an average magnitude of +1.2% per month (95% credibility interval: 0.7 to 1.6). Older age and 12 months of amenorrhoea were found to be associated with a lower AMH recovery rate, whereas baseline AMH

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and number of chemotherapy cycles were not. The process of AMH changes during and after chemotherapy is dynamic, and shows recovery after ovarian injury. Caution should be exercised in interpreting individual AMH assessment in this context.

KEYWORDS: AMH, breast cancer, chemotherapy, ovarian reserve

Introduction

Breast cancer in young women is a growing burden in developing countries. Treatment-induced ovarian damage is a frequent and detrimental adverse effect of chemotherapy, presenting as acute amenorrhoea sometimes followed by irreversible premature ovarian failure. To date, no predictive marker of ovarian function recovery has been validated, and quantification of chemotherapy damage remains a substantial challenge. An accurate and individual assessment of the risk of subfertility or infertility could help in counselling patients and in selecting those women eligible for fertility preservation. Reliable information could alleviate the burden for patients at a low risk for premature ovarian failure by reducing the additional emotional distress induced by the prospect of infertility that accompanies a cancer diagnosis. Amenorrhea and menstrual changes have long been the only variables reported in studies, but have weak predictive value. In recent years, anti-Müllerian hormone (AMH), a glycoprotein and member of the transforming growth factor superfamily of growth factors, has been extensively studied. It is produced exclusively in the somatic cells of the gonads. It plays a variety of roles in reproduction and in the processes of sexual development and differentiation, and it induces testicular differentiation and regression of the Müllerian ducts in men (Münsterberg and Lovell-Badge, 1991). Müllerian ducts evolve into the uterus, fallopian tubes and upper part of the vagina in the absence of AMH. In the human fetus, ovarian AMH expression is observed from 36 weeks' gestation and falls shortly after birth, with concentrations increasing at about 2 years of age and falling between the ages of 8 and 12 years. The relevance of AMH secretion is incompletely understood. After a prepubertal rise, AMH levels peak at 24.5 years and gradually decline throughout the reproductive years, becoming undetectable by menopause (Kelsey et al., 2011). Within the ovary, AMH expression is restricted predominantly to the granulosa cells of growing ovarian follicles (e.g. secondary, pre-antral and small antral follicles less than 4 mm in diameter) (Weenen et al., 2004). Although AMH expression is not observed in primordial follicles, serum AMH concentrations have been shown to be correlated with the size of the non-growing primordial follicle pool (Hansen et al., 2011). It has been reported that AMH reflects a marker of the so-called 'ovarian reserve' (i.e. the number of primordial follicles remaining in the ovaries) (Van Rooij et al., 2002). It has been known for its stability, and its blood concentrations have consistently been shown to have significantly low intra- and inter-cycle variability (Hehenkamp et al., 2006; La Marca et al., 2006; Van Disseldorp et al., 2010).

Several studies (La Marca et al., 2010; Van Rooij et al., 2002) have shown that, in assisted reproductive technology, AMH is a better marker of ovarian reserve than age or basal FSH, oestradiol and inhibin B (La Marca et al., 2010). To quantify chemotherapy-induced ovarian damage, many investigators (Anders et al., 2008; Anderson et al., 2006; Su et al., 2010) have recently measured serum AMH concentrations in women included in oncofertility studies. In women receiving chemotherapy, AMH rapidly declined. Most of the studies lacked long-term data (Anders et al., 2008; Yu et al., 2010), although it is well known that ovarian recovery can occur up to 2 or 3 years after the end of treatment (Sukumvanich et al., 2010). The aim of the present study was to evaluate AMH patterns of changes before, after and in the long term after chemotherapy in a population of women who received chemotherapy for breast cancer. This work is part of the *O.B.A.M.A study* (Ovarian reserve in Breast Cancer: AssessMent with Anti-Müllerian Hormone).

Materials and methods

Study population and participants

From May 1 2005 to January 31 2011, women aged between 18 and 43 years who received chemotherapy in our breast care unit (Saint Louis Hospital, Paris, France) were retrospectively identified from a computerized database. Women with a history of prior cytotoxic treatment or women who had undergone an oophorectomy were excluded from the study. Demographic data, detailed treatment characteristics and dates, type of surgery, chemotherapy doses and regimens, radiation and endocrine therapy were extracted from medical charts. One patient underwent fertility preservation (in vitro maturation). Clinical data (e.g. number of previous pregnancies and children, infertility, menstrual history and smoking habits) were retrieved in a follow-up consultation when possible or by a retrospective review of the medical charts of deceased patients. The study was approved by an institutional review board (IRB) (CPP Ile de France XI, 3 March 2010, study registered as 2009-A01225-52). No ultrasound antral follicle count was available owing to the retrospective design of the study.

Blood collection

Blood samples were systematically retrieved for the monitoring of tumour marker levels on the day of the first chemotherapy (baseline time point, one sample) and during chemotherapy (two to four samples), The blood samples samples were centrifuged at 1000 g for 15 min and stored between –20°C and –30°C in freezers, in agreement with the manufacturer's instructions of the AMH assay, and in accordance with existing literature on the stability of AMH samples (Kumar et al., 2010). One post-treatment measurement was taken at least 4 months and to up to 5.5 years after the end