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Original Research

Prospective evaluation of serum anti-Müllerian hormone dynamics in 250 women of reproductive age treated with chemotherapy for breast cancer

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KEYWORDS
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Abstract ***Aim:*** Women of reproductive age with breast cancer generally receive gonadotoxic chemotherapy. Fertility issues are of great concern for them. However, little is known on ovarian damage during chemotherapy and its evolution during long-term follow-up. The

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Anti-Müllerian hormone;
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aim of this study was to provide a detailed description of serum anti-Müllerian hormone (AMH) evolution during chemotherapy and 24-month follow-up.

Methods: This prospective cohort study was conducted in 250 patients, aged 18–39 years, diagnosed with breast cancer and treated with adjuvant/neoadjuvant chemotherapy. Each patient underwent blood AMH measurement at each chemotherapy cycle, and at 6, 12 and 24 months after chemotherapy. Menses occurrence was also recorded.

Results: Mean basal AMH level was 4.19 ± 4.84 ng/mL, and was negatively correlated with age. Serum AMH level rapidly decreased in all patients after each chemotherapy cycle to undetectable levels in most of them, and slowly increased in 45% of the patients during the 24-month follow-up. AMH decrease was significantly associated with age and basal AMH level, but not with cyclophosphamide dose and tamoxifen use. The prevalence of chemotherapy-related amenorrhoea was 92.4% at the end of chemotherapy; women with amenorrhoea being significantly older and having lower basal AMH than women who resumed menses.

Conclusions: Our study confirms rapid and deep ovarian reserve alteration in young women receiving chemotherapy for breast cancer, and shows moderate AMH recovery in some patients. Although AMH cannot alone predict fertility potential, these new data emphasise the need for post-treatment ovarian insufficiency follow-up, strongly support the use of fertility preservation strategies and may provide new tools for improved counselling.

1. Introduction

Breast cancer is the most common cancer in women worldwide, with a still increasing incidence, especially in developing countries. Fortunately, mortality has declined over the last decade, reaching an average 5-year survival rate of 80% in United States of America or Europe. In women of reproductive age, it is associated with a worse prognosis and higher mortality than in older patients. These young women are usually treated with first-line chemotherapy in adjuvant or neoadjuvant setting including gonadotoxic molecules, such as anthracyclins and cyclophosphamide. The trend towards improved survival rate is now associated with growing concern of patients and oncologists on chemotherapy adverse effects, and particularly fertility issues in women of reproductive age [1–3]. Clinical practice guidelines based on precise biological and clinical data would thus be of great interest for cancer survivors with a high risk of chemotherapy-induced premature-ovarian failure and their oncologists in order to optimise fertility counselling and eventually improve quality of life [4].

Reproductive lifespan, and indirectly female fertility, is associated with ovarian reserve (OR), a pool of non-growing follicles present in the ovarian cortex at a specific time point. These quiescent follicles are progressively recruited into early growing follicles during reproductive lifespan, until exhaustion at menopause, which may occur earlier than expected in case of exposure to gonadotoxic molecules. As these primordial follicles cannot be counted *in vivo*, several indirect clinical and biological OR markers have been developed. Amenorrhoea has long been used as a clinical indicator of impaired ovarian function following chemotherapy. However, this clinical parameter has been shown to be a relatively late and poor marker of residual OR in cancer survivors of reproductive age [5–7]. Among the various biological OR markers, anti-Müllerian hormone (AMH), a peptide synthesised by granulosa cells in preantral ovarian follicles, has been shown recently to be the most relevant endocrine marker of OR, especially in the field of assisted reproductive technology (ART) [8]. In addition to its clinical interest, AMH has the major advantage over other endocrine markers of being relatively stable through the menstrual cycle [8,9]. Its relevance in assessing OR in adult cancer survivors has been reported several times [10,11], although AMH cannot be used alone as a diagnosis marker of premature-ovarian insufficiency (POI) [4]. Some interesting studies reported AMH levels and evolution in women with breast cancer treated with chemotherapy. However, these studies had some limitations, providing an incomplete overview of AMH levels before, during and after chemotherapy for breast cancer [12].

The principal objective of our observational prospective multicentric cohort study was to evaluate the serum AMH level at diagnosis, its evolution throughout chemotherapy and its long-term evolution during a 24-month follow up in women of reproductive age treated with chemotherapy in adjuvant or neoadjuvant setting for breast cancer.

2. Patients characteristics and methods

2.1. Patients

This observational and prospective study (ClinicalTrials.gov identifier NCT01114464) has been approved by the local ethics committee. All patients