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Different patterns of ovarian recovery after cancer treatment suggest various individual ovarian susceptibilities to chemotherapy

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KEY MESSAGE

Two patterns of early ovarian recovery are distinguishable in young women who received the same chemotherapy protocol for breast cancer: fast (≤6 months) or slow recovery (>6 months). The increase in blood AMH concentrations precedes or is contemporary with the regain of menstruation.

A B S T R A C T

The relationship between early recovery of menstrual activity and blood anti-Müllerian hormone (AMH) concentrations were investigated within the first year post-chemotherapy in 32 young patients with breast cancer. All were treated by surgery and the same chemotherapy protocol (three cycles of FEC100 plus three cycles of taxanes). Menstrual activity, blood AMH (using picoAMH ELISA) and FSH concentrations were measured longitudinally before, during and up to 12 months after the end of chemotherapy (six samples per patient). Among the cohort, 17 patients recovered spontaneous cycles at +6 months (fast recovery) whereas the remaining 15 patients were still amenorrheic at that time (slow recovery). Blood AMH differed between these two subgroups at each time of the recovery phase starting at 3 months post-chemotherapy. The AMH patterns were also different: rapid and large increase in the fast recovery versus slow and partial increase in the slow recovery subgroup. No difference in ovarian recovery was observed between patients with a hormone positive or negative tumour. In conclusion, studying the post-chemotherapy patterns of menstrual activity and AMH, two paces of early ovarian recovery are distinguishable in young breast cancer patients who received the same chemotherapy protocol. This suggests different individual ovarian susceptibilities to chemotherapy.

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Introduction

Chemotherapy is well known to damage ovarian follicles at any stage of their development. The exact mechanisms of the ovarian toxicity are not yet fully understood (Bedoschi et al., 2016) but it appears that the type of drug, administered dose, patient age and pretreatment ovarian follicular content may play a major role (Morgan et al., 2012). The chemotherapy-induced follicular depletion leads to a loss of menstrual activity that can be transient or permanent. The final recovery of menstrual activity after chemotherapy is a late marker of the resumption of follicle growth, which it should be able to monitor by measuring anti-Müllerian hormone (AMH) concentrations. AMH is produced by granulosa cells of preantral and small antral follicles <8 mm in diameter and represents the ovarian follicular content. Previously published longitudinal studies of AMH variations in patients treated by chemotherapy for breast or haematological malignancies provided crucial information: first, AMH is a real-time indicator of follicular depletion but also renewal (Anderson et al., 2006; Decanter et al., 2010), second, pretreatment AMH concentrations can determine the rate of post-chemotherapy recovery (Anderson and Cameron, 2011; Anderson et al., 2013; Dillon et al., 2013) and third, AMH can discriminate between strong and soft gonadotoxic treatment that allows patients to be given better advice about fertility preservation and future chances of pregnancy (Decanter et al., 2010). In these longitudinal studies, patients received various combinations of chemotherapy regimens (up to nine different ones), and had a wide dispersion in age at tumour onset (from 15 to 52.5 years). Taking into consideration these putative confounding factors it was decided to study individual ovarian susceptibility to a unique chemotherapy regimen in a sample of very young breast cancer patients (<40 years). A hypersensitive AMH assay was used, characterized by a limit of quantification (LoQ) around 0.03 pmol/l, which is able to detect subtle variation in serum concentrations (Decanter et al., 2014).

The study focused on the early ovarian recovery phase, from 0 to 12 months after the end of chemotherapy, to better understand the exact mechanisms of follicular injury and resumption.

Materials and methods

Patients

Thirty-two patients with early breast cancer, mean age (±SD) 31.1 (±3.9) years, were referred to the Fertility Observatory of the Lille University Hospital before the initiation of chemotherapy, to be followed up regarding their menstrual activity and ovarian follicular content. Fertility preservation by mature oocyte or embryo cryopreservation was proposed to each patient, if applicable. All these patients were recruited from the Breast Cancer Unit of the Centre Oscar Lambret, Lille, and signed an informed consent before enrolment (NCT 01614704). Breast cancer cells expressed hormone receptor (HR) in 17 patients, whereas 14 did not. Information was lacking for one patient. Seventeen patients had undergone control ovarian hyperstimulation (COH) for fertility preservation. COH took place during the 6-week free interval between surgery and the start of chemotherapy. All patients reported regular menses in the absence of hormonal contraception. Clinical examination, menstrual activity enquiry and serial blood sampling and AMH measurements were performed before chemotherapy and before COH (if applicable) (AMH0), 15 days before the last chemotherapy cycle (AMH2) and every 3 months during the first year after completion of chemotherapy (AMH+3, AMH+6, AMH+9, AMH+12) according to a protocol previously described in lymphoma patients (Decanter et al., 2010). A total of six blood samples were drawn from each participant. Visits were scheduled to be in the early follicular phase if appropriate. The protocol was approved by the French Research Ministry (Institutional Review Board) on 7 July 2011 (IRB 11.394).

Chemotherapy protocol

All patients were eligible for adjuvant chemotherapy after a complete surgery. All received the same chemotherapy regimen containing a sequential combination of anthracyclins, i.e. three cycles of FEC100 (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 500 mg/m^2) and three cycles of taxanes (docetaxel 100 mg/m^2). Chemotherapy cycles were performed every 3 weeks and the total duration of chemotherapy was around 5 months.

Radiotherapy and adjuvant hormonal treatment

Patients with a HR positive tumour were treated with an adjuvant hormonal therapy by tamoxifen (Tam), 20 mg/day, which was started after completion of radiotherapy, meaning around time +3 months after the end of chemotherapy. Radiotherapy consisted of 50 Gy delivered to the surgical site and on ganglionic areas for node-positive patients. None of the patients received gonadotrophin-releasing hormone (GnRH) agonists in this study population.

Menstrual activity and hormonal follow-up

Amenorrhoea was defined as the absence of any bleeding for at least 3 consecutive months. The duration of amenorrhoea was measured from the last menstrual bleeding the patient experienced before or during chemotherapy and the first menstrual bleeding she experienced after the end of chemotherapy. AMH was measured by a hypersensitive assay (picoAMH; Ansh Labs, Webster, TX, USA) as previously described (Decanter et al., 2014). Intra- and inter-assay reproducibility assessed on a serum with a low concentration (0.16 pmol/l) was 3.7% and 4.5%, respectively. Serum FSH concentrations were measured by an immunometric assay using an automatic analyser (Architect; Abbott Laboratories, USA). Intra- and inter-assay reproducibility assessed on a serum with a 5.0 IU/ml concentration was 3.3% and 4.2%, respectively.

Statistical analysis

For description of populations, results are expressed as mean ± SD, mean ± SEM and also median, 5th and 95th percentiles. Comparison between the two groups was performed by the Mann–Whitney U-test for quantitative variables and by Fisher test or chi-squared test (when appropriate) for qualitative variables. A *P*-value less than 0.05 was considered as significant. Repeated measurements were compared using the Friedmann test with post-hoc analysis using Dunn's test. ROC curves were constructed and areas under the curve (AUC) were calculated to examine the ability of the AMH6-AMH3 index to correctly classify patients into fast or slow recovery groups. Statistical analysis was performed using the GraphPad software (GraphPad Software Inc., USA).

Trial registration number: NCT 01614704.

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