EUROPEAN HEMATOLOGY ASSOCIATION

Fertility preservation in patients with hematological malignancies - Section 2

Fertility preservation in female patients

Marie-Madeleine Dolmans[1,2]

[1]Cliniques Universitaires Saint Luc, Brussels, Belgium; [2]Gynecology Research Laboratory, Institut de Recherche Expérimentale et Clinique (IREC), Université Catholique de Louvain (UCL), Belgium

Take-home messages

- Fertility preservation options should be discussed with all young women having to face gonadotoxic treatment.
- Oocyte cryopreservation can be proposed to post-pubertal patient who can afford a delay in the onset of chemotherapy (at least 10-12 days are necessary to allow time for ovarian stimulation and oocyte collection).
- Ovarian tissue cryopreservation can be proposed to prepubertal patients and all patients younger than 35 years of age, who cannot afford a delay in the onset of cancer treatment.

Introduction

The advances in cancer therapy over the past two decades have led to remarkable improvements in survival rates,[1] but treatments such as chemotherapy (especially alkylating agents), radiotherapy and/or surgery can induce premature ovarian insufficiency (POI) in some circumstances.[2] Fertility preservation (FP) is therefore a key challenge for these women. At diagnosis, all women affected by cancer should benefit from an informed consultation on the threat of compromising their fertility with planned cancer treatment. In case of total body irradiation, pelvic irradiation, bone marrow transplantation and aggressive chemotherapy with high dose of alkylating agents,[2-5] the risk is considered to be very high. However, only a small fraction of patients are actually referred to specialists to discuss FP prior to cancer treatments. The decision-making process is especially problematic since the long-term effects of cancer treatment have not been fully elucidated.[2-4] The prevalence of subfertility is nevertheless known to be increased, even when ovarian function is maintained.[5] The main issue is that health care workers are unfamiliar with the rapid advances taking place in FP research and their implementation in clinical practice.[2,6] Selection criteria need to be available not only to endocrinologists and gynecologists in reproductive medicine, but also pediatricians and oncologists. Moreover, informed discussion on a patient's fertility prognosis can be a positive experience, even if an FP procedure is not indicated (low risk) or possible.

Current state of the art

GnRH agonists for fertility preservation

According to ASCO[7] and ASRM[8] recommendations, evidence supporting the effectiveness of gonadotropin-releasing hormone (GnRH) agonists for FP is currently insufficient, although it is recognized that these agents might yield other medical benefits, such as reduced vaginal bleeding when patients have low platelet counts as a result of chemotherapy.
Reviews on the topic remain contentious, even if a randomized controlled trial (RCT) found that the ovaries are protected from depletion by administration of GnRH agonist in young women receiving cyclophosphamide.[9] As stressed by the authors themselves, the markers of ovarian reserve [like anti-Müllerian hormone (AMH) and antral follicle count (AFC)] were not evaluated. Moreover, the real benefits should not only be evaluated in terms of recovery of menses, but in terms of ongoing pregnancy and live birth rates.
A very recent RCT, clearly demonstrated the absence of any beneficial effect of GnRH agonists on future pregnancy rates.[10] Until definitive proof of efficacy has been clearly established, other FP approaches should be offered alongside GnRH agonist therapy.

Oocyte or embryo cryopreservation

Embryo cryopreservation is generally offered as the primary method of FP if the woman is postpubertal and if sperm is available. Nevertheless, we have to keep in mind that cryopreserved embryos are the joint property of the woman and her male partner.[2] Therefore, some centers propose oocyte cryopreservation instead of embryo cryopreservation, at least in the

context of FP. This was possible thanks to the excellent survival rates of oocytes after vitrification and warming. In the field of FP, oocyte cryopreservation gives women the possibility of reproductive autonomy. It should nevertheless be pointed out that, in young women, 15 vitrified oocytes are required to achieve a cumulative live birth rate of 85%, and this live birth rate decreases dramatically if the patient is over 36 years of age.[11] For oocyte vitrification in the case of cancer women, chemotherapy usually needs to be delayed by at least 10-12 days[6,11] to allow time for ovarian stimulation and oocyte collection. Also, specific ovarian stimulation protocols are used according to the steroid sensitivity of the cancer.[2] Importantly, the patient should be informed that there is no guarantee that good-quality oocytes will be collected.

Ovarian tissue cryopreservation

Ovarian tissue cryopreservation (OTC) is the only fertility preservation option available for prepubertal girls and women who cannot delay the start of chemotherapy.[2-4,12] Indications for OTC in our department are shown in Figure 1 (series of 600 patients). Hematologic malignancies represent the most frequent indication for OTC, as these represent 36% of all indications, and 48% in the subgroup of patients younger than 18 years of age**.** An age less than 35 years, a realistic chance of surviving for 5 years, and at least a 50% risk of POI are established selection criteria.[2,12] This risk of POI is directly related to the intensity of treatment received. The real concern is that it is impossible to predict exactly who will develop POI after aggressive chemotherapy.[2,4] Moreover, treatment protocols sometimes need to be adapted or become more aggressive, e.g. in case of relapse, and patient may change risk category of POI.[4,12]

Ovarian tissue reimplantation in an orthotopic site (namely inside the pelvic cavity, either to the ovarian medulla or inside a peritoneal window)[13] leads to restoration of ovarian endocrine activity with occurring of menses in more than 95% of cases after transplantation. The mean duration of ovarian function is 4-5 years, but this can vary according to follicular density at the time of cryopreservation, which depends on the patient's age at the time of cryopreservation and if she received or not already some chemotherapy before.

Taking into account all published series to date, the number of live births has now (January 2017) reached more than 110. An evaluation including patients from 5 renowned centers (n=111), yielded a pregnancy rate of 29% and live birth rate of 23%.[14] These rates were subsequently confirmed by other series with live birth rates of at least 30%.[15,16]

Transplanting ovarian tissue to heterotopic sites remains rather questionable, however, and only one pregnancy has been reported following this procedure.[17]

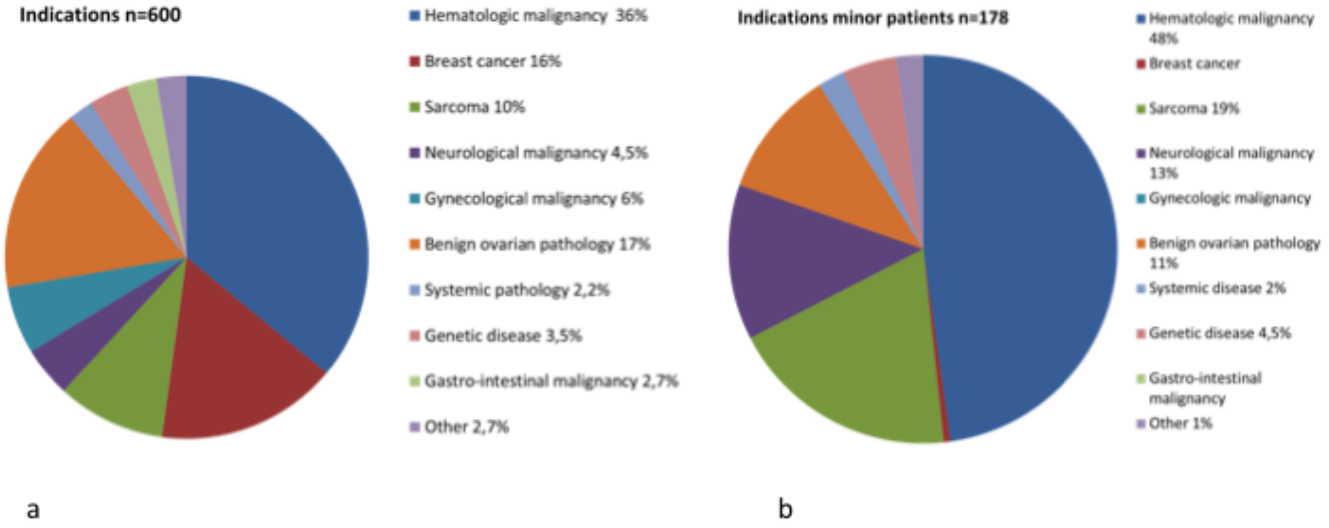

Figure 1. Indications for ovarian tissue cryopreservation in 600 women in our ovarian tissue cryobank (a) and in the subgroup of patients younger than 18 years of age (b).

Combined technique: a way to improve FP chances

A combination of OTC followed immediately by ovarian stimulation and ovum pick-up (with a view to vitrifying mature oocytes) does not impair oocyte number or quality, and could actually increase the efficacy of the procedure by giving young patients with cancer more chances of success.[18]

Future perspectives

A serious concern that must be addressed is the risk of reimplanting malignant cells together with the grafted tissue, especially in patients with leukemia,[19] which is the most common hematological cancer in women under 20 years of age. The risk is particularly high in women with acute leukemia and cannot be completely eliminated, even if the biopsy destined for cryopreservation is taken from patients in complete remission.[20]

One alternative to avoid reimplanting malignant cells is to obtain mature oocytes by means of the so-called transplantable artificial ovary. Isolation of primordial follicles from cryopreserved ovarian tissue and their transfer onto a scaffold to create this artificial organ will serve to eliminate the risk of transmission of malignant cells.[21] This option is also applicable to leukemic patients.[22] Another option is to obtain *in vitro* follicular growth through a dynamic multistep culture system[23] before fertilizing the oocytes *in vitro*. Both options are still experimental.

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