

## Fertility Preservation in Leukemia

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In this issue of *The Oncologist*, Gazdaru et al. describe a patient with chronic myeloid leukemia (CML) resistant to tyrosine kinase inhibitors (TKIs) who has undergone hematopoietic stem cell transplantation (HSCT), in which treatment by TKI was replaced with interferon- $\alpha$  (INF- $\alpha$ ) before and during ovarian stimulation for fertility preservation. After ovarian stimulation, nine zygotes were cryopreserved [1]. Because of the suggestion that TKIs might have a potential deleterious effect on follicular development during ovarian stimulation, the authors replaced nilotinib with INF- $\alpha$  [1]. After ovarian stimulation, while the patient was on INF- $\alpha$ , using the antagonist protocol, serum estradiol peaked to 9,320 pmol/L on the day of triggering final oocyte maturation with human chorionic gonadotropin (hCG; Ovitrelle, Merck, Kenilworth, NJ), and 12 oocytes were retrieved, generating nine zygotes [1]. The authors are congratulated for the first case report of a patient with CML resistant to TKI with successful ovarian stimulation and cryopreservation of zygotes after switching from TKI to INF- $\alpha$  before HSCT [1].

Fertility preservation despite gonadotoxic chemotherapy is an emerging and rapidly developing procedure for preserving fertility in young women exposed to aggressive gonadotoxic treatment who face a high risk of premature ovarian failure (POF). As the authors correctly declare, fertility preservation options need to be discussed with patients facing gonadotoxic chemo- and/or radiotherapy [1]. The three main avenues for fertility preservation are:

- Ovarian stimulation as for in vitro fertilization (IVF) and assisted reproductive technology and cryopreservation of embryos or fertilized or unfertilized ova;
- Cryopreservation of ovarian tissue for possible future autotransplantation; and
- Temporary endocrine pituitary-ovarian suppression by gonadotropin-releasing hormone agonists (GnRHa).

At present, the only unequivocal, clinically noninvestigational method is cryopreservation of embryos or fertilized or unfertilized ova. The procedure of cryopreservation of ovarian tissue for possible future autotransplantation is gaining popularity and success in fertility preservation in young women and prepubertal girls before gonadotoxic chemo- and/or radiotherapy. Up-to-date autotransplantation of thawed ovarian fragments has generated

almost 140 successful deliveries [2]. However, whereas cryopreservation of embryos and unfertilized metaphase-II oocytes is a clinically accepted procedure in young women, both the American Society of Reproductive Medicine and the American Society of Clinical Oncology consider ovarian tissue cryopreservation (OTC), autotransplantation, and GnRHa cotreatment to be investigational procedures [2–7]. The main concern about the safety of autotransplantation of thawed ovarian fragments is the possible contamination of the graft with malignant cells that may induce disease recurrence [2–5]. This risk is highest in leukemia and lower in lymphoma and early stages of breast cancer [2–6]. Most recently, Shapira et al. [8] have reported the first successful delivery after autotransplantation of thawed ovarian tissue in a patient with lymphoma. The authors made every possible endeavor and meticulously tested the thawed ovarian pieces from their patient for the presence of possible malignant leukemic cells or markers, using histology, immunohistochemistry, fluorescent in situ hybridization, next-generation sequencing, and xenotransplantation in immunodeficient mice [3, 8]. When none of these tests suggested the presence of leukemic cells in the tested ovarian fragments, after informed consent, autotransplantation was carried out, and on the third IVF cycle, the patient successfully conceived. After successful delivery and ceasing breastfeeding, the patient spontaneously conceived again [8].

Despite the successful ovarian stimulation, this case report [1] raises several comments:

- The ovarian stimulation aims at the retrieval of possibly many eggs for generating many embryos to increase the odds of future conception after transfer of thawed embryos. As recently published [2], the cumulative chances of conception after cryopreservation of 10 ova or fewer in women younger than 35 years is about 50%–60%. However, because of the non “soft,” or even more aggressive, ovarian stimulation, the many follicles and high estradiol in the late follicular phase are associated with an increased risk of ovarian hyperstimulation syndrome (OHSS), which may be, rarely, even fatal. Because of the high estradiol concentration on the trigger day—in the reported case, 9,320 picomoles [1]—it might have been safer to trigger final follicular maturation with a GnRHa (such as 0.2 mg Decapeptyl, Ferring, Saint-Prex, Switzerland) and not hCG to minimize the risk of OHSS.

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• The authors suggest that the efficacy of temporary ovarian suppression with GnRH $\alpha$  is equivocal for prevention of gonadotoxicity [1]. Although gonadal suppression with GnRH $\alpha$  is shown to be an effective strategy to reduce the risk of treatment-related POF, its use as a standard procedure is still debatable [3–7]. Two large randomized clinical trials, POEMS-SWOG-S0230 and PROMISE-GIM6; over 12 meta-analyses; and four international expert committees concluded that GnRH $\alpha$  cotreatment reduces chemotherapy-induced POF and increases pregnancy rate, without negatively affecting survival [3–7]. In several case reports, GnRH $\alpha$  cotreatment has been associated with repeated spontaneous pregnancies and deliveries even after stem cell transplantation and after the most gonadotoxic conditioning combination (busulfan and cyclophosphamide [Bu-Cy]) as used in the presented case report [1, 3–7, 9]. Indeed, Remérand et al. [9] described four spontaneous pregnancies and successful deliveries in a patient after prepubertal high-dose Bu-Cy conditioning and bone marrow transplantation (BMT). Similarly, repeated spontaneous pregnancies and two successful deliveries after two autologous BMTs, 10 years apart, and GnRH $\alpha$  cotreatment have been described in a postpubertal patient with lymphoma, suggesting that the prepubertal milieu induced by the GnRH $\alpha$  cotreatment might have contributed to the preserved fertility despite repeated BMTs [7]. After this publication [7], the reported patient experienced a fifth natural conception and third successful delivery. According to an extensive European survey of stem cell transplantation (SCT) involving 37,362 female patients in the European group for blood and marrow transplantation, only 0.6% of patients conceived after one autologous or allogeneic BMT [3–7]. Thus, the calculated odds for pregnancy after two BMTs are negligible (theoretically,  $0.006 \times 0.006 = 0.000036$ ) [7]. Others [3–7] have found a 3% pregnancy rate after BMT. Thus, theoretically, according to the latter, the estimated odds for conceiving after two SCTs are  $0.03 \times 0.03$ , or about 1/900 [3–6, 7]. The GnRH $\alpha$  adjuvant cotreatment in parallel to the gonadotoxic conditioning chemotherapy simulated the prepubertal hormonal milieu

and might have reduced the gonadotoxic effect, enabling ovulation, five spontaneous conceptions, and three successful deliveries of healthy children [3–7].

- Even in centers in which autotransplantation of cryopreserved ovarian tissue in leukemia is not considered, we do recommend OTC because of the possibility that the method of in vitro maturation of primordial follicles to mature fertilizable metaphase-II oocytes will become clinically feasible in a few years [2, 3]. To date, the artificial ovary technology has been successful in laboratory animals but not yet in women. We hope that in a few years, when these children or young patients are disease free and cured from their leukemia, this technology may become clinically successful and applicable; therefore, stored cryopreserved ovarian tissue should be banked, ready for such future developing technology [3].
- Harvesting tissue for OTC in patients with leukemia who are in complete remission after one or two chemotherapy courses decreases the risk of contamination without significantly decreasing the density of primordial follicles within the retrieved ovarian tissue [3, 8]. Therefore, it is safer and preferable to harvest tissue for OTC from patients with leukemia after remission is reached [3, 8]. However, this option is applicable only for OTC, not for cryopreservation of oocytes or embryos. Therefore, the latter option (controlled ovarian stimulation and follicular aspiration for egg retrieval) should be done only before chemotherapy, because exposure of developing follicles to chemotherapy has generated malformed embryos in rodents.
- Because nothing is certain in the still developing and not yet categorically written chapter on oncofertility, it is advisable to offer to these young, postpubertal patients all three avenues of fertility preservation—cryopreservation of embryos or fertilized or unfertilized oocytes; cryopreservation of ovarian tissue; and GnRH $\alpha$  cotreatment—to increase their chances for future fertility and motherhood.

#### DISCLOSURES

The author indicated no financial relationships.

#### REFERENCES

1. Gazdaru S, Perey L, Rosselet A et al. Successful ovarian stimulation for fertility preservation in a patient with chronic myeloid leukemia: Switch from nilotinib to interferon- $\alpha$ . *The Oncologist* 2018;23:716–718.
2. Donnez J, Dolmans MM. Fertility preservation in women. *N Engl J Med* 2017;377:1657–1665.
3. Blumenfeld Z. Ovarian tissue transplantation in leukemia. *Fertil Steril* 2018;109:69–70.
4. Blumenfeld Z, Zur H, Dann EJ. Gonadotropin-releasing hormone agonist cotreatment during chemotherapy may increase pregnancy rate in survivors. *The Oncologist* 2015;20:1283–1289.
5. Blumenfeld Z, Katz G, Evron A. 'An ounce of prevention is worth a pound of cure': The case for and against GnRH-agonist for fertility preservation. *Ann Oncol* 2014;25:1719–1728.
6. Lambertini M, Ceppi M, Poggio F et al. Ovarian suppression using luteinizing hormone releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: A meta-analysis of randomized studies. *Ann Oncol* 2015;26:2408–2419.
7. Blumenfeld Z, Zuckerman T. Repeated spontaneous pregnancies and successful deliveries after repeated autologous stem cell transplantation and GnRH-agonist. *The Oncologist* 2010;15:59–60.
8. Shapira M, Raanani H, Barshack I et al. First delivery in leukemia survivor following transplantation of cryopreserved ovarian tissue, evaluated for leukemia cells contamination. *Ferti Steril* 2018;109:48–53.
9. Remérand G, Merlin E, Froissart R et al. Four successful pregnancies in a patient with mucopolysaccharidosis type I treated by allogeneic bone marrow transplantation. *J Inher Metab Dis* 2009;32(suppl 1):S111–S113.