Gonadotropin-Releasing Hormone Analog Cotreatment for Preservation of Ovarian Function

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The authors are congratulated for their prospective, phase II study of gonadotropin-releasing hormone analog (GnRH-a) cotreatment for preservation of ovarian function in young women undergoing hematopoietic stem cell transplantation (HSCT). The late effects of cancer treatment have recently attracted interest among a spectrum of health care providers, and protection against the iatrogenic infertility caused by gonadotoxic chemotherapy has assumed a high priority. Whereas several avenues are offered to patients before gonadotoxic chemotherapy, none is ideal and none of them guarantees survivors' future fertility.

The authors enrolled 60 eligible patients; 59 underwent HSCT and 44 were evaluable (median age, 25 years; median follow-up, 355 days) [1]. Only seven of the 44 patients (16%) regained ovarian function. Of the 33 who received myeloablative regimens, six (18%) regained ovarian function, and among the 11 who received nonmyeloablative regimens, only one (9%) regained ovarian function (not significant). The authors concluded that the GnRH-a leuprolide did not preserve ovarian function in patients who underwent HSCT using either myeloablative or nonmyeloablative regimens [1]. However, despite the good intention of the authors, this study falls short of reaching solid conclusions because of several methodological problems.

Whereas in previous studies [2–9], the GnRH-a was administered before the initial chemotherapy, on first exposure to the gonadotoxic treatment, in the present study [1], the agonist was started 2 months before the conditioning chemotherapy preceding HSCT, regardless of previous chemotherapy exposure. Indeed, all patients except two had received at least one prior chemotherapy regimen. The median number of prior chemotherapy regimens before HSCT was two (range, 0–8), and

12 patients also received prior local radiation. Therefore, ovarian reserve was probably affected by previous gonadotoxic exposure, and thus the starting point of the participating patients was suboptimal from the very beginning. Supporting this speculation is the relatively high gonadotropin levels used for eligibility for the study. For follicle-stimulating hormone (FSH) and luteinizing hormone measurements, normal premenopausal levels are 2.6–12.6 IU/L. The inclusion of patients with higher FSH concentrations, up to 20 IU/L, would include subjects with diminished ovarian reserve, as, for example, a result of previous exposure to gonadotoxic chemotherapy and/or radiotherapy. Anecdotal case reports suggest that administration of GnRH-a with every gonadotoxic chemotherapy regimen may be effective in preserving fertility. Such treatment has been associated with multiple spontaneous pregnancies and successful deliveries despite multiple autologous HSCT, 10 years apart [10]. This is the only published case of repeated spontaneous pregnancies and two successful deliveries after repeated autologous HSCTs and GnRH-a treatment. It was reported in this journal and followed the report of similar GnRH-protected multiple pregnancies in a patient who had undergone allogeneic bone marrow transplantation. These cases suggest that the prepubertal milieu induced by the GnRH-a cotreatment might have contributed to the preserved fertility despite repeated bone marrow transplant (BMT) [10, 11]. The odds against repeated pregnancies following one, or several, SCTs are exceedingly high [10–13].

Another methodological problem is the use of a very high dosage of the GnRH-a, twice the used dosage in previous studies [2–9]. Whereas previous studies used a monthly injection of 3.75 mg triptorelin or leuprolide (11.25 mg every 3 months) or 3.6 mg goserelin, the authors of the current study adminis-

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tered 22.5 mg leuprolide in a 3-month depot i.m. injection within 2 months of HSCT. These high doses brought about intolerable side effects, and led nine of the 59 patients to refuse the second dose of leuprolide and leave the study [1]. Administration of the agonist 10–14 days before chemotherapy is sufficient to overcome the flare-up effect of the agonist and establishes the hypogonadotropic milieu before starting chemotherapy. Because >6 months of exposure to a hypogonadotropic milieu may be associated with irreversible bone loss, osteopenia, and osteoporosis, especially in hematologic patients receiving glucocorticoids, it is advisable to keep the hypogonadotropic period as short as possible. Therefore, it is probably unnecessary and potentially undesirable to administer a GnRH-a 2 months before starting chemotherapy [1].

The authors found that five of 15 patients who underwent autologous transplantation (33%) resumed cyclic ovarian activity, compared with only two of the 29 patients who underwent allogeneic transplantation (7%) ($p = .04$) [1]. This is in keeping with our results showing that GnRH-a administration could significantly minimize the rate of premature ovarian failure in young women survivors after autologous HSCT, but not for those who underwent allogeneic HSCT [14].

In order to be able to draw unequivocal conclusions, a similar study should be prospectively randomized comparing reproductive outcomes in patients receiving a GnRH-a in

parallel with every gonadotoxic exposure of chemotherapy with the same outcomes in those receiving the same chemotherapy without a GnRH-a. Such a study should have sufficient power and the GnRH-a should be administered at the least effective dosage to minimize side effects and dropout, and to keep the possible risk for osteopenia as low as possible. Such a prospective randomized controlled trial was recently published on young breast cancer patients, with clear and solid conclusions [3]. The clinical and tumor characteristics of the 133 patients randomized to chemotherapy alone and the 148 patients randomized to chemotherapy plus triptorelin were similar. Twelve months after the last cycle of chemotherapy (last follow-up, August 18, 2009), the rate of early menopause was 25.9% in the chemotherapy-alone group and 8.9% in the chemotherapy plus triptorelin group, an absolute difference of -17% (95% confidence interval, -26% to -7.9% ; $P < .001$). The odds ratio for treatment-related early menopause was 0.28 (95% confidence interval, 0.14 to 0.59; $P < .001$). The use of triptorelin-induced temporary ovarian suppression during chemotherapy in premenopausal patients with early-stage breast cancer reduced the occurrence of chemotherapy-induced early menopause. The publication of similar studies of reproductive efficacy of GnRH protection in SCT patients would be a significant step forward.

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