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Editorial

Use of GnRH Agonists in Fertility Preservation in Female Patients with Hematological Malignancy

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Editorial

In the past 20 years there has been a significant improvement in the success of cancer treatment, particularly in the treatment of hematologic malignancies. Exceptionally impressive is the success in the treatment of Hodgkin's disease and some forms of non-Hodgkin lymphoma [1-3]. Improved survival resulted in increased number of cancer survivors, who are unfortunately struggling with chronic effects of their treatment. Besides the known difficulties with cardiovascular and pulmonary toxicity and an increased risk of other malignant diseases, loss of reproductive function is another consequence of chemotherapy treatments, in particular hematopoietic stem cell transplantation, in which high, myeloablative doses of chemotherapy are used. Fertility loss in men and women treated with chemotherapy may be transient or permanent, and it is particularly important to note that fertility in women may be compromised despite normal return of cyclic ovarian function after treatment is completed. The use of chemotherapy reduces the ovulatory reserve, resulting in weakened prospects for later pregnancy and an increased chance of premature menopause. Thus, although women after treatment regained cyclic ovarian function and are able to conceive, the duration of their child-bearing age can be reduced by developing premature menopause. Two-thirds of the adult women who receive chemotherapy will develop premature loss of ovary function [4]. In the treatment of hematological malignancies chemotherapeutic agents that are particularly toxic to the gonads are frequently used, such as cyclophosphamide and busulfan, with the majority of patients receiving drug combinations, which further contributes to the damage of gonads. Results of a study that examined the reproductive status of patients who are treated for Hodgkin's lymphoma in the frame of the German Oncology Group showed that after a follow-up period of 3.2 years 51.4 % of patients treated with BEACOPP protocol had a permanent amenorrhea. Furthermore, the study showed that amenorrhea is significantly more common in patients who were treated with escalated doses of BEACOPP protocol for advanced disease and in patients who were older than 30 years at the time of diagnosis [5].

Loss of fertility is an important factor in reducing the quality of life of cancer survivors. It is shown that most cancer survivors feel healthy enough and want to have children [6]. Since the options to preserve ovarian function after the treatment of chemotherapy are limited, physicians today are rarely speak of them and those options are rarely applied.

There are available procedures that can be administered to preserve women's childbearing function such as ovarian stimulation and oocyte collection, cryopreservation of oocytes or embryos before the start of chemotherapy, as well as cryopreservation of ovarian tissue, ovarian tissue transposition in cases when it is necessary to radiate the pelvic area and the use of gonadotropin-releasing hormone agonist (GnRH-a). Evidence in favor of the urgent stimulation followed by cryopreservation of embryos show it is a good option for preserving fertility [7,8], while cryopreservation of oocytes is still problematic and fairly inefficient [9]. Some authors prefer cryopreservation of oocytes / embryos / ovarian tissue to application of GnRH agonists since the results of the GnRH-a studies are contradictory, but the fact is that there are no published randomized trials with a significant number of patients assessing the above methods of stimulation and cryopreservation. It should be noted that each of these manipulations are demanding not only financially and logistically, but also time consuming and require delaying the onset of treatment, which in most cases of patients with malignant hematological disease is not possible. It is particularly important to emphasize that cryopreservation and re-transplantation of ovarian tissue is not recommended in patients with leukemia since it has been shown that ovarian tissue may contain malignant cells [10,11] and also there is evidence that Hodgkin's disease can infiltrate tissue of the ovary and that prior to re-transplantation histological verification of ovarian tissue is required [12].

But what is the rationale for using GnRH for fertility preservation? As it was elegantly described by Blumenfeld Z. and von Wolf M, chemotherapy destroys the astral follicles, causing decrease in estrogen and inhibit production, and in turn increasing FSH concentration due to negative feedback. The increased FSH concentration induces an enhanced recruitment of follicles which are further destroyed by the next cycle of chemotherapy. The administration of GnRH-a may prevent the increased FSH concentration, therefore rescuing the follicles from accelerated atresia (Figure 1) [13].

So far, to the best of our knowledge, there are 29 published studies that included a total of 1430 patients which have assessed the efficacy of GnRH-a in preserving ovarian function in patients treated with chemotherapy; 20 studies (5 of them are randomized controlled trials) showed a reduction in premature ovarian failure with the use of GnRH-a, while the results of nine studies (6 of which were randomized controlled trials) did not show efficacy of GnRH-a use. Of these, a total of 12 studies carried out taking into account patients suffering from hematological diseases, and most, though not all have demonstrated the effectiveness of preserving ovarian function by administering the GnRH-a [14-25]. For hematologists particularly

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interesting is a study that showed the value of this approach in preserving ovarian function in patients undergoing hematopoietic stem cell transplantation [21]. In 95 included patients, of whom data were available for 83 of them, Cyclic Ovarian Function (COF) was regained in 38.3% of patients receiving GnRH-a, and 11.1% of those who did not receive the therapy. The difference was even more pronounced when investigators analyzed only patients transplanted for lymphoma; in that subgroup the return of COF occurred in 66.7% of patients receiving GnRH-a, and 18.2% of those who did not, while the difference was less pronounced in patients receiving treatment for leukemia (10% vs. 8.3%).

The differences in the results of studies conducted so far in our opinion does not diminish the importance of the application of GnRH-a with chemotherapy, but give motivation to better elucidate the effect of GnRH-a on the ovarian tissue and hormonal status. Even the study from studies Demister and colleagues [25], although not giving evidence for efficacy of GnRH agonists in preserving ovarian function, argues in favor of preserving ovarian reserve after chemotherapy treatment; it showed that after one year of follow up the level of anti-Mullerian hormone (AMH) is higher in the group treated with agonists as compared to the control group (1.40 ± 0:35 vs.0:56 ± 0,15 ng/ml, P <0.04). An interesting view on the subject matter provides the only study that was conducted prospectively and randomized that evaluated the effect of GnRH-a on ovarian tissue, where the data was obtained from the analysis of histological preparations. The study was conducted in rhesus monkeys, and loss of follicles was assessed after administration of cyclophosphamide, with or without GnRH-a concomitant therapy. It was found that in the group not receiving a GnRH-a during gonadotoxic drug exposure 64.6% ± 2.8% of primordial follicles were lost, as compared to 28.9% ± 9.1% in the group treated with GnRH-a(P <0.05) [26].

And although the issue is of growing importance, clear and unambiguous recommendation to preservation of childbearing function is lacking, and randomized studies with sufficient number of patients and appropriate follow-up period are warranted. There is a consensus however that every woman of childbearing age suffering from malignant disease should be advised about the opportunities that we have at our disposal [27,28].

Taking into account all the aforementioned literature and current findings we can conclude that, although the current results somewhat contradictory, there are reasons to believe that the use of GnRH-a may contribute to better preservation of ovarian function in patients treated with chemotherapy. In contrary to oocyte stimulation and cryopreservation, and also cryopreservation of ovarian tissue and its transposition, the use of GnRH-a is safe, simple and inexpensive. It also does not delay the start of chemotherapy, which is of importance when treating certain hematological malignancies. Therefore this approach should definitely be mentioned as one option when informing patients of options to preserve fertility prior to chemotherapy.

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