Analysis of the Benefit of Gonadotropin-Releasing Hormone Agonist in Premenopausal Women undergoing Hematopoietic Cell Transplantation

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Article

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Abstract

Objective: The purpose of this study was to analyze the benefits of gonadotropin-releasing hormone agonist (GnRHa) in premenopausal women undergoing hematopoietic cell transplantation (HSCT).

Methods: Candidates for myeloablative chemotherapy HSCT requiring fertility preservation in the Gynecological Endocrinology Clinic of Peking University People's Hospital from December 2011 to December 2021 were retrospectively analyzed. The patients were consecutively included. Patients who chose to receive GnRHa treatment were given at least 2 courses of 3.75-mg dose of GnRHa treatment before myeloablative chemotherapy, and patients who chose not to receive GnRHa treatment were included in the control group. All patients were monitored for menstruation return, menopause-related symptoms, and ovarian function tests (follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol) were done 6-12 months after HSCT. In addition, we counted the vaginal bleeding of patients in the laminar air-flow room (LAFR).

Results: A total of 234 cases were included in this study, 77 cases in the treatment group and 157 cases in the control group. Compared with the control group, the incidence of vaginal bleeding in LAFR in the treatment group was significantly lower than that in the control group (24.68% vs. 79.62%, P<0.001). The menopausal symptoms of the patients in the treatment group were reduced after transplantation (46.75% vs. 19.75%, P<0.001). There was no difference in visible follicles by the follow-up ultrasound in the two groups after HSCT (16.88% vs. 13.38%, P=0.474). The level of FSH at 6-12 months after transplantation was lower (98.00 mLU/ml vs. 117.53 mLU/ml, P=0.001). The proportion of patients with FSH <40 mLU/ml did not differ between the two groups. One patient in the treatment group recovered spontaneous menstruation while none in the control group (1.30% vs. 0%, P=0.329).

Conclusion: The use of GnRHa may relieve menopause-related symptoms, reduce vaginal bleeding in LAFR and breakthrough bleeding after transplantation. GnRHa treatment can reduce the level of FSH after myeloablative chemotherapy, but it cannot reduce the incidence of premature ovarian failure in women of reproductive age following myeloablative HSCT.

1. Introduction

Hematopoietic stem cell transplantation (HSCT) is a well-established treatment for many congenital or acquired diseases of the hematopoietic system and several other life-threatening conditions(1), which can effectively improve the survival rate of patients. The number of HSCTs in China is increasing year by year. The annual number of HSCTs in 2019 exceeded 10,000 for the first time(2). With the advancement of medical technology, the long-term survival rate of such patients has increased significantly. In China, population-based data indicated that women who underwent HSCT had a 5-year survival rate of 74.8% to 79.4%(3). More and more people are pursuing quality of life on the basis of surviving, and have the need to establish a family or fertility needs. Huang and colleagues at Peking University established “Beijing Protocol” for haplo-SCT using myeloablative conditioning (MAC) regimen(4), solving the problem of
insufficient hematopoietic stem cell donors. The commonly used fully MAC regimens are high-dose chemotherapy and total-body irradiation. The chemotherapy dosages used in these combinations are very gonadotoxic. It has been reported that the prevalence rate of ovarian insufficiency exceeds 90%-100% of female patients who have received HSCT following MAC (5-7), and studies have shown that HSCT is an independent risk factor for premature ovarian failure (POF)(8).

Although impaired ovarian function after HSCT is a clinically recognized phenomenon, there are few studies on the protection of ovarian function, and most studies focus on cryopreservation of oocytes, embryos, and ovarian tissues(9, 10). These studies partially address fertility issues associated with ovarian failure, but do not apply to patients who must undergo transplants in the short term or who are physically or financially disadvantaged.

Due to iatrogenic POF, patients also face the early onset of menopausal symptoms, which always affects the quality of life. What’s more, patients with hematologic disorders often face more severe abnormal uterine bleeding in the laminar air-flow room (LAFR). In the event of uncontrollable severe vaginal bleeding, the patient’s life may be in danger, eventually leads to the failure of the treatment. Currently, the commonly used treatment to stop bleeding in the LAFR is mainly through high doses of hormone-based drugs, such as norethindrone, combined oral contraception(COC). But there is relatively little awareness of the prevention of bleeding in the LAFR.

Gonadotropin-releasing hormone agonist (GnRHa) in gynecological endocrine therapy can put patients into a pseudo-menopausal state. In recent years, the protective effect of GnRHa on ovary during chemotherapy has attracted attention. Several meta-analyses and prospective randomized studies(11, 12) have shown that GnRHa significantly reduces the risk of POF in women undergoing gonadal toxic chemotherapy. Although these results seem promising, a paucity of data exists on similar use of GnRHa in the HSCT population, especially in China. Several small studies suggested inconclusive benefit of using a GnRHa to preserve ovarian function in the HSCT patients. If GnRHa works for HSCT patients, it will serve as an economical, non-invasive and simple method to protect ovarian function. This study was to analyze the benefits of GnRHa in premenopausal women undergoing HSCT, including the reduction of vaginal bleeding in LAFR, protection of ovarian function, and improvement in perimenopausal symptoms.

2. Methods

This is a retrospective cohort study. We confirm: (i) the study was approved by the Ethics Committee of Peking University People’s Hospital (No. 2015PHB087-01), including any relevant details; (ii) all experiments were performed in accordance with relevant guidelines and regulations. And we confirm that all research was performed in accordance with relevant regulations, and every consent was obtained from all participants and/or their legal guardians and signed by the patients or their families. The patients were consecutively included. Patients with hematological diseases at Peking University People’s Hospital routinely undergo gynecological physical examination before HSCT, such as the collection of menstrual history, pelvic examination and cervical cancer screening. Patients with fertility protection
desire will be triaged to the gynecological endocrinology clinic for consultation on fertility protection methods. The research subjects of this study were all from the gynecological endocrinology clinic. The study population was women of childbearing age under 40 years of age who were going to undergo myeloablative chemotherapy before HSCT from December 2011 to December 2021. After consulting about ovarian function protection methods, they chose whether to inject GnRHa by themselves. The inclusion criteria were: (1) women undergoing myeloablative chemotherapy HSCT for hematological diseases; (2) age <40 years; (3) patients with normal hormone levels or without laboratory data but with regular menstruation before HSCT. The exclusion criteria were: (1) patients whose ovarian function was found to have declined before HSCT with myeloablative chemotherapy through menstruation, B-ultrasound monitoring and hormone examination; (2) patients who were unable to survive after HSCT after myeloablative chemotherapy; (3) patients with incomplete clinical data; (4) patients who received less than 2 courses of GnRHa treatment before myeloablative chemotherapy.

Each patient requiring fertility preservation in the gynecological endocrinology clinic was informed by gynecologists about methods of ovarian protection, and was fully informed that the efficacy of GnRHa was not clear. Patients who voluntarily chose to inject GnRHa and signed informed consent were included in the treatment group. Patients in the treatment group injected GnRHa (leuprolide acetate) 3.75 mg subcutaneously before the start of myeloablative chemotherapy, once every 28 days as a course of treatment. Considering the onset time and safety of GnRHa, all patients in treatment group were given at least 2 courses of GnRHa treatment before they entered LAFR. And patients who chose not to receive GnRHa treatment were included in the control group.

The clinical data of all patients were collected for analysis when they went back to the gynecological endocrinology clinic 6-12 months after HSCT. The patients were followed up by vaginal bleeding in the LAFR, menstruation return, menopause-related symptoms, and ovarian function tests (follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol) were done.

POF was defined as age <40 years old, FSH ≥40 mIU/ml. Patients with ovarian insufficiency underwent hormone-replacement therapy (HRT) after diagnosis of POF. Recovery of ovarian function was defined as resumption of menstrual cycles (at least two consecutive episodes) without HRT after HSCT, and a normal FSH level without HRT. The following conditioning regimens were used and were considered myeloablative: busulfan plus cyclophosphamide; busulfan plus fludarabine; cyclophosphamide plus total-body irradiation (>10 Gy); carmustine, etoposide, cytarabine, and melphalan; and a single melphalan dose >140 mg/m².

All data were statistically processed using SPSS 25.0 (SPSS Inc., Chicago, IL) statistical software package. Continuous variables were described using medians, ranges and ranges; categorical variables were described using frequencies and proportions. Comparisons were performed using chi-square test, Fisher’s exact test, and Mann-Whitney U test. P<0.05 means the difference is statistically significant.

3. Results
From December 2011 to December 2021, 391 patients visited Peking University People's Hospital Gynecology Clinic for fertility protection counseling before undergoing myeloablative chemotherapy HSCT. A total of 234 cases were included in this study, followed up for a median of 28 months. There were 77 cases in the treatment group and 157 cases in the control group (Figure 1). The general conditions and clinical data of the study population are shown in Table 1. All patients underwent allogeneic transplantation. There were statistical differences between the two groups in terms of hematologic diseases type and whether they received Cyclic chemotherapy before myeloablative chemotherapy and HSCT. Compared with the control group, the treatment group was less likely to receive courses of chemotherapy before myeloablative chemotherapy and HSCT (67.53% vs 85.35%, P=0.002). There were no statistically significant differences between the two groups in terms of age, HLA-matched situation, and whether had graft vs host disease (GVHD).

The median follow-up times for the treatment and control groups were 28 and 29 months, respectively. Hormone levels were measured before HSCT in 35 of 77 patients in the GnRHa group while 20 of 157 in the control group. From this part of the data, there was no difference between FSH levels and LH levels between the two groups before HSCT (5.69 mIU/ml vs. 5.93mIU/ml, P=0.582, 5.15 mIU/ml vs. 4.96 mIU/ml, P=0.564). The medians of E₂ are 36.32 pg/ml and 26.38 pg/ml. Observation indexes between the treatment group and control group 6-12 months after HSCT are shown in Table 1. The incidence of vaginal bleeding in LAFR, in the treatment group was significantly lower than that in the control group (24.68% vs. 79.62%, P<0.001). Compared with the control group, the menopausal symptoms of the patients in the treatment group were reduced after transplantation (46.75% vs. 19.75%, P<0.001). There was no difference in visible follicles by the follow-up ultrasound in the two groups of patients after HSCT (16.88% vs. 13.38%, P=0.474). The level of FSH at 6-12 months after transplantation was lower (98.00 mIU/ml vs. 117.53 mIU/ml, P=0.001), though both had reached the POF standard. While there was no significant difference in LH levels after transplantation (65.07 mIU/ml vs. 61.38 mIU/ml, P=0.127). Because the sensitivity of the E₂ assay was 20 pg/ml, most of these levels were not detectable as they were 20 pg/ml or lower. But the median E₂ level after HSCT in both groups was less than 20 pg/ml. The proportion of patients with FSH <40mIU/ml did not differ between the two groups. Only one patient in the treatment group recovered spontaneous menstruation while none in the control group (1.30% vs. 0%, P=0.329). Only one 25-year-old acute lymphocytic leukemia patient returned to a regular menstrual cycle with normal hormone levels (Table 2).

Whether or not to perform pre-transplant cyclic chemotherapy was associated with the type of hematological disease, and the conclusion remained unchanged after we stratified the main outcome indicators according to the type of disease (supplementary material).

4. Discussion

Our study showed that the use of GnRHa before transplantation did not preserve ovarian function in patients who underwent HSCT using myeloablative regimens.
Chemotherapy-induced POF was first reported in the late 1950s(13). Subsequent studies suggested that the effect of ovarian damage may be age dependent and dose dependent(14). The "Beijing Protocol" using the MAC regimen improves the success rate of allogeneic haplo-SCT, which also means high-dose chemotherapy and total-body irradiation were used. As the treatment of hematological disorders has progressed, the majority of patients receiving such treatments are expected to survive for many years. Women of childbearing age are confronted with the risk of compromising their fertility by therapy-induced temporary or permanent amenorrhea. In addition, abnormal hormone levels and the early onset of menopausal symptoms cause great distress to patients with POF. Nakayama et al.(15) conducted a survey and reported that most patients believe that a discussion of fertility-related or menopausal-related issues was as important as a discussion of their cancer issues and suggested that healthcare providers should provide information on fertility and menopause repeatedly throughout the treatment period, and that menopause-related information should be reemphasized after HSCT. The American Society of Clinical Oncology guideline recommends the discussion of ovarian preservation as early as possible in treatment planning(16).

GnRHa are synthetic peptide drugs modelled on GnRH that are designed to interact with the GnRH receptors and modify the release of gonadotropins. The protective mechanisms of GnRHa on ovarian function remains unclear. Several proposed mechanisms for how GnRHa work have been proposed, such as GnRHa can suppress gonadotropin levels to stimulate the prepubertal hormonal milieu, which subsequently prevents primordial follicle maturation, reducing the number of follicles susceptible to chemotherapy(17). Or GnRHa can reduce utero-ovarian perfusion, resulting in less exposure of the ovaries to chemotherapeutic agents(18). Or it can directly activate GnRH receptors on the ovary and regulate the expression of anti-apoptotic molecules in the gonads(19). GnRHa have been shown to preserve ovarian function in chemotherapy-treated patients outside of the HSCT setting in meta-analyses and prospective randomized studies(11, 12, 20). In 2014, Z Blumenfeld et al.(21) presented their meta-analysis of 20 studies (15 retrospective and 5 randomized, controlled trials) have reported on 1837 patients treated with GnRHa in parallel to chemotherapy, showing a significant decrease in POF rate in survivors. In 2015, Moore et al.(22) published the results of a prospective RCT trial, in which 257 premenopausal breast cancer patients received chemotherapy with or without GnRHa, showing that GnRHa-treated patients had better-preserved ovarian function across multiple endpoints than the controls. However, there are few data on the protection of ovarian function with GnRHa in the HSCT population. In 2012, Cheng YC et al.(5) conducted a prospective phase II study to evaluate the efficacy of a GnRHa in reducing the incidence of POF in the setting of HSCT. The result was 7 of 44 patients (16%) regained ovarian function and showed that the use of GnRHa before transplantation did not preserve ovarian function in HSCT patients either myeloablative or nonmyeloablative regimens.

Our study showed that the application of GnRHa before myeloablative chemotherapy may be able to reduce FSH level of patients after HSCT, but it still reaches the standard of premature ovarian failure, which showed GnRHa cannot reduce the incidence of premature ovarian failure in patients with myeloablative chemotherapy HSCT. Only one case maintained spontaneous menstruation and hormone levels suggested normal ovarian function while none in the control group. In conclusion, GnRHa could not
reduce the incidence of premature ovarian failure. Combined with previous studies to analyze this study, the following aspects deserve attention. In terms of diagnosis, the diagnostic criteria for premature ovarian failure in this study were age <40 years old, FSH $\geq$ 40 mU/ml. But cyclic HRT was given when the hormone levels reached the POF standard 6-12 months after HSCT, especially the patients with perimenopausal symptoms. Therefore, there may be patients who have regained ovarian function after using HRT. In terms of timing of medication, all patients in this study were given GnRHa before the initiation of MAC, but considering that a part of patients with hematological malignancies in the study population received unprotected, gonadotoxic chemotherapy before GnRHa was administered, a stratified analysis was performed, and the results showed that the application of GnRHa did not significantly reduce the incidence of premature ovarian failure, regardless of whether the group was based on disease type or whether or not there was chemotherapy before MAC.

Although GnRHa does not reduce the incidence of premature ovarian failure, there are other benefits for the female patients before HSCT to use GnRHa. The results showed that injection of GnRHa at least 2 weeks before transplantation was effective in reducing vaginal bleeding during transplantation. Other studies have also shown that GnRHa may prevent post-transplantation of breakthrough bleeding(23). Once a donor is identified, the recipient completes a pretransplant evaluation and then undergoes a conditioning regimen (1–2 weeks), receives the graft infusion, and then must await the initial signs of engraftment (10–28 days) and repopulation of bone marrow (60–90 days)(24). Myeloablative conditioning typically results in severe pancytopenia within 1-3 weeks of initiation, and thrombocytopenia increases the risk of heavy menstrual bleeding, potentially life-threatening heavy menstrual bleeding, and may delay treatment leading to suboptimal outcomes. Therefore, the menstrual management of patients in the LAFR cannot be ignored. Even without regarding to ovarian protection, GnRHa only requires a simple one-time injection and has few side effects when given regularly over 2 weeks before pancytopenia, which makes it the first choice of many transplant physicians. Therefore, GnRHa injection before HSCT can be recommended for women of childbearing age to prevent vaginal bleeding during bone marrow transplantation and breakthrough bleeding after transplantation.

Menopause-related symptoms are also important reference indicators for evaluating the ovarian protective function of GnRHa. Previous studies have shown that women with premature ovarian failure who underwent HSCT showed less symptomatic menopause rating scale and the modified Kupperman index scores compared with naturally postmenopausal women of the same number of years after menopause(25). The five most frequently reported perimenopausal symptoms were recorded by the gynecological clinician at the patient's follow-up visit after transplantation. Although GnRHa did not show the benefit of ovarian protection based on the diagnostic criteria based on hormone levels, GnRHa can significantly reduce the incidence of perimenopausal symptoms, and its role in ovarian protection is difficult to deny, and further research is needed to prove it.

This study has limitations. First of all, it was not a randomized controlled trial (RCT). The patients' exposure history could only be reviewed through medical records, and laboratory examination records were incomplete. This also leads to a high dropout rate of patients due to the loss of follow-up and
incomplete clinical data. Secondly, the final sample size available for analysis in this study is relatively small. Differences in the number of patients with different diseases and the treatment plan and length of treatment before HSCT all would increase the possible bias.

5. Conclusion

In conclusion, the benefits of GnRHa can be seen in reducing vaginal bleeding and menopausal symptoms in women of childbearing age with myeloablative HSCT. GnRHa may decrease FSH levels after myeloablative chemotherapy, which may suggest that GnRHa have certain ovarian protection effect, but did not reduce the incidence of POF. The clinical application value of GnRHa in fertility-sparing treatment of female patients of reproductive age undergoing myeloablative HSCT still needs to be validated by more standardized and rigorously designed RCT with a larger number of included study populations. However, standardized injection of GnRHa can be considered as a way to prevent vaginal bleeding in the LAFR and improve menopausal symptoms after iatrogenic POI.

Declarations

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

Ruxue Han: Data curation, Formal analysis, Investigation, Writing- Original draft preparation

Ziyi Song: Validation, Investigation, Writing- Original draft preparation

Huiling Li: Data curation

Chaohua Wang: Methodology, Data curation, Supervision

Xin Yang: Methodology, Writing- Reviewing and Editing, Funding acquisition

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Data Availability
The datasets used and analysed during the current study available from the corresponding author on reasonable request.

References


18. Blumenfeld Z. How to preserve fertility in young women exposed to chemotherapy? The role of GnRH agonist cotreatment in addition to cryopreservation of embryo, oocytes, or ovaries. Oncologist. 2007;12(9):1044-54.


Tables

Table 1. Patient characteristics according to whether GnRHa was injected
### Table 2. Observation indexes between the treatment group and control group 6-12 months after HSCT.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Treatment Group, n=77(%)</th>
<th>Control Group, n=157(%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(mean±SD),yrs</td>
<td>23.83±6.66</td>
<td>24.51±6.79</td>
<td>0.180</td>
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<tr>
<td>Hematologic diseases type</td>
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<td></td>
<td>0.017</td>
</tr>
<tr>
<td>ALL</td>
<td>25</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>25</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>16</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>MDS</td>
<td>9</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Other</td>
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<td>6</td>
<td></td>
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<tr>
<td>HLA-matched situation</td>
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<td>HLA-matched</td>
<td>13</td>
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<td></td>
</tr>
<tr>
<td>HLA-haploidentical</td>
<td>64</td>
<td>126</td>
<td></td>
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<tr>
<td>Cyclic chemotherapy before HSCT</td>
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<td>0.002</td>
</tr>
<tr>
<td>Yes</td>
<td>52 67.53</td>
<td>134 85.35</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>25</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>GVHD</td>
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<td></td>
<td>0.623</td>
</tr>
<tr>
<td>Yes</td>
<td>50</td>
<td>107</td>
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<tr>
<td>No</td>
<td>27</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

P value indicates the differences between the two groups.

ALL, Acute lymphocytic leukemia; AML, Acute myelogenous leukemia; AA, Aplastic anemia; MDS, myelodysplastic syndrome; GVHD, graft vs host disease.
<table>
<thead>
<tr>
<th>Treatment Group, n=77(%)</th>
<th>Control Group, n=157(%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaginal bleeding in LAFR</strong></td>
<td>19 24.68</td>
<td>125 79.62</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hot flushes</strong></td>
<td>32 41.56</td>
<td>74 47.13</td>
</tr>
<tr>
<td><strong>Sweating</strong></td>
<td>24 31.17</td>
<td>64 40.76</td>
</tr>
<tr>
<td><strong>Nervousness</strong></td>
<td>30 38.96</td>
<td>35 22.29</td>
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<tr>
<td><strong>Insomnia</strong></td>
<td>21 27.27</td>
<td>74 47.13</td>
</tr>
<tr>
<td><strong>Sexual problems</strong></td>
<td>10 12.99</td>
<td>40 25.78</td>
</tr>
<tr>
<td><strong>None</strong></td>
<td>36 46.75</td>
<td>31 19.75</td>
</tr>
<tr>
<td><strong>Follicles visible on gynecological ultrasound</strong></td>
<td>13 16.88</td>
<td>21 13.38</td>
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<tr>
<td><strong>FSH mIU/ml</strong></td>
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<td>117.53</td>
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<tr>
<td><strong>LH mIU/ml</strong></td>
<td>65.07</td>
<td>61.38</td>
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<td><strong>FSH 40 mIU/ml</strong></td>
<td>5 6.49</td>
<td>4 2.55</td>
</tr>
<tr>
<td><strong>Recovering menstrual Cycles</strong></td>
<td>1 1.30</td>
<td>0 0</td>
</tr>
</tbody>
</table>
P value indicates the differences between the two groups

LAFR, laminar air-flow room; HSCT, hematopoietic stem cell transplantation; GnRHa,
Gonadotropin-Releasing Hormone Agonist; FSH, follicle-stimulating hormone; LH, luteinizing hormone

Figures
Figure 1

Flow sheet explaining patient dropout.

HSCT, hematopoietic stem cell transplantation; GnRHa, Gonadotropin-Releasing Hormone Agonist

Supplementary Files

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