Case Series

Feasibility of ovarian stimulation for fertility preservation during and after blinatumomab treatment for Ph-negative B-cell acute lymphoblastic leukemia

Yusuke Tashiro[1)], Junya Kanda[1) †], Tomoki Iemura[1)], Tadakazu Kondo[1)], Kouhei Yamashita[1)], Masumi Sunada[2)], Akihito Horie[2)], Akifumi Takaori-Kondo[1)]

1) Department of Hematology, Kyoto University Hospital

2) Department of Gynecology & Obstetrics, Kyoto University Hospital

†Correspondence: Junya Kanda, M.D, Ph.D.

Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan, 54 Shogoin-kawahara-cho, Kyoto, Kyoto, Japan, 606-8507.

Tel: +81-75-751-3152; Fax: +81-75-751-3153; e-mail: jkanda16@kuhp.kyoto-u.ac.jp

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Abstract

It is challenging to preserve the fertility of female patients with B-cell acute lymphoblastic leukemia (B-ALL) before allogeneic hematopoietic stem cell transplantation (allo-HSCT) while maintaining treatment intensity. We report two cases of female patients with Philadelphia chromosome-negative (Ph -) B-ALL whose oocytes were retrieved after controlled ovarian stimulation during and after blinatumomab treatment.

The first patient was a 30-year-old woman with relapsed Ph - B-ALL who received prednisolone (PSL) and cytoreductive chemotherapy with cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), followed by three courses of blinatumomab bridging to allo-HSCT. Ovarian stimulation was performed twice during blinatumomab administration, and two oocytes were retrieved during each course. The second patient was a 26-year-old woman with newly diagnosed Ph - B-ALL who received PSL, one course of conventional chemotherapy, and one course of high-dose methotrexate and cytarabine followed by two courses of blinatumomab bridging to allo-HSCT. Immediately after completion of the first course of blinatumomab, ovarian stimulation was performed, and three oocytes were retrieved.

Use of a two-week rest period enabled ovarian stimulation and oocyte retrieval to be performed without delaying treatment. Blinatumomab may be an option for preserving fertility while maintaining treatment intensity.

Introduction

As the survival rates of acute lymphoblastic leukemia (ALL) patients have increased significantly over the past three decades [1], fertility preservation has become an important concern for women with ALL, especially in the adolescent and young adult (AYA) generation [2,3,4]. Chemoradiotherapy often impairs fertility; especially, allogeneic hematopoietic stem cell transplantation (allo-HSCT) inevitably causes irreversible infertility [5,6,7,8,9,10]. Fertility preservation should be considered and planned before allo-HSCT. However, it is difficult to preserve fertility in ALL patients before allo-HSCT because patients with hematologic malignancies often cannot delay treatment to collect oocytes. Blinatumomab is a bi-specific T-cell engager that targets CD19+ lymphocytes [11]. It has previously been reported to be highly effective for relapsed/refractory B-ALL [12,13,14]. However, the feasibility of fertility preservation during blinatumomab treatment remains unknown. We report two cases of AYA patients with Philadelphia chromosome-negative (Ph^-) B-ALL whose oocytes were retrieved after controlled ovarian stimulation during and after blinatumomab treatment.

Case 1

A 20-year-old woman was diagnosed with Ph^-B-ALL. The white blood cell count at the onset was 16.1×10^9 /L with a lymphoblast ratio of 90%. The lymphoblast karyotype was normal. After the first course of Hyperfractionated cyclophosphamide (CY), vincristine (VCR), doxorubicin (DXR), and dexamethasone (DEX) (Hyper-CVAD), she achieved cytogenetic complete remission (CRc). We administered a total of eight courses of rituximab plus Hyper-CVAD (considered one course) alternating every 21 days with rituximab plus high-dose methotrexate-cytarabine (considered one course). Triple intrathecal therapy (TIT; consisting of MTX, Ara-C, and DEX) was administered in every course. Thereafter, POMP

(mercaptopurine, 50 mg, day 1; VCR, 2 mg, day 1; MTX, 20 mg/m^2, weekly for 4 weeks; prednisolone (PSL), 60 mg/m^2, days 1-5) therapy was started as maintenance therapy. However, since pancytopenia (neutrophil count $<0.2 \times 10^9$ /L and platelet count <20,000 mm^3) persisted for over a month, we switched to a combination of rituximab plus Hyper-CVAD and conventional chemotherapy (MTX, 100 mg/m^2 on day 1 and L-asparaginase [20000 KU] weekly for 4 weeks). A total of four courses of the above combination therapy were administered as maintenance therapy. The patient was considered to have a relatively low risk of relapse and had no human leukocyte antigen (HLA)-matched sibling donor; thus, allo-HSCT in the first CR was not performed.

The patient relapsed when she was 30 years old. The immunophenotype of lymphoblasts was the same as that in the first onset; therefore, she was diagnosed as ALL recurrence. Five days of PSL (60 mg/m^2) and one course of Hyper-CVAD were performed for cytoreduction. The patient immediately achieved CRc. A total of three courses of blinatumomab (started at 9 μg/day and continued at 28 μg/day from day 8 until day 28 in the first course, 28 μg/day from day 1 until day 28 in the second course, and 28 μg/day from day 1 until day 9 in the third course) were administered as bridging therapy to allo-HSCT. She achieved molecular complete remission (CRm) after the first course of blinatumomab.

Although the influence of CVAD therapy and blinatumomab treatment on embryo development and chromosomal abnormalities was unknown, oocyte cryopreservation was planned since allo-HSCT inevitably causes irreversible infertility [15,16,17]. Ovarian tissue cryopreservation was not considered because there was a risk of contamination by tumor cells [18,19,20,21]. Treatment with gonadotropin-releasing hormone (GnRH) agonist (buserelin 1.8 mg every 28 days) was started to protect the ovaries from chemotherapy-induced toxicity and to control menstrual bleeding, from the day Hyper-CVAD therapy was initiated [17,22]. With a thorough explanation and her consent, the first ovarian stimulation (human

menopausal gonadotropin [HMG], 300 U, days 17-28; human chorionic gonadotropin [hCG], 10,000 U, day 28) was performed, using the random start method [23]. Two oocytes were retrieved the day after the first course of blinatumomab administration was completed. The second ovarian stimulation (HMG 300 U, days 16-32; cetrorelix, 0.25 mg, days 28-32; hCG 10,000 U, day 32) was started on day 16 of the second course of blinatumomab treatment, and two oocytes were retrieved five days after the second course of blinatumomab was completed. The treatment of ALL and the schedule of ovarian stimulation in Case 1 are shown in Figure 1. Since she was married, fertilization of the oocytes was attempted, but failed. In the first oocyte retrieval, one oocyte was in the germinal vesicle stage and did not mature enough thereafter. Therefore, intracytoplasmic sperm injection (ICSI) was performed on only one metaphase II (MII) oocyte. Its fertilization ended in failure. In second oocyte retrieval, one oocyte was degenerated, thus ICSI was performed on only one MII oocyte. Its fertilization also ended in failure.

No adverse events, including cytokine release syndrome (CRS) and neurologic adverse events (NEs), or other notable events were observed during blinatumomab treatment [24]. No adverse events associated with fertility preservation were also observed, including symptoms indicating ovarian hyperstimulation syndrome (OHSS).

Case 2

A 26-year-old woman was diagnosed with Ph^-B-ALL. The white blood cell count at the onset was 253.6×10^9 /L with a lymphoblast ratio of 94%. The lymphoblast karyotype was 49, XX, +X, +5, +9 [6/12] / 46, XX [6/12] at diagnosis. PSL (started at 15 mg/m^2 and titrated up to 60 mg/m^2) was administered for 5 days as pre-induction therapy. One course of conventional chemotherapy (CY, 1,200 mg/m^2, day 1; daunorubicin, 45 mg/m^2, days 1-3; VCR, 1.3 mg/m^2, days 1,8,15, and 22; L-asparaginase, 5,000 KU/m^2, days 8,10,12,14,16,18,20, and 22;

PSL, 60 mg/m^2, days 3-23) was administered, however, she did not achieve complete remission (CR). Following this, HD-MA and TIT (MTX, 15 mg; Ara-C, 40 mg; PSL, 20 mg) were administered, but CR was still not achieved. Thereafter, a course of blinatumomab (started at 9 μg/day and continued at 28 μg/day from day 8 until day 28) was administered, and she achieved CRc. A total of two courses of blinatumomab were administered as bridging therapy to allo-HSCT.

Treatment with GnRH agonist (buserelin 1.8 mg every 28 days) was initiated in conjunction with conventional chemotherapy [17,22]. As in Case 1, ovarian tissue cryopreservation was not performed. With a thorough explanation and her consent, ovarian stimulation (HMG, 300 U, days 29-37; cetrorelix, 0.25 mg, days 33-37; hCG, 10,000 U, day 37) was started from the day the first course of blinatumomab was completed. Three oocytes were retrieved 10 days after the start of stimulation. The treatment of ALL and the schedule of ovarian stimulation in Case 2 are shown in Figure 2.

On day 18 of the second course of blinatumomab, the neutrophil count dropped to 0.32×10^9 /L. This decrease was considered to be an adverse event of blinatumomab treatment, and the second course was discontinued on that day. After blinatumomab administration was discontinued, the neutrophil count quickly recovered to the normal range. No other notable adverse events were observed during blinatumomab administration. No adverse events associated with fertility preservation were also observed, including symptoms indicating OHSS.

Discussion

We experienced two cases of oocyte retrieval followed by ovarian stimulation during and after blinatumomab treatment. During the two-week rest period of blinatumomab treatment, we were able to collect oocytes without delaying treatment, thus retaining high therapeutic

efficacy while collecting oocytes. This is the first report of ovarian stimulation and oocyte retrieval during and after blinatumomab treatment.

Chemoradiotherapy often impairs fertility. Especially, in the treatment of hematologic malignancy, alkylating agents and total body irradiation subject the patient to high risk for infertility because of direct ovarian toxicity and indirect ovarian toxicity mediated by an acute vascular insult and oxidative stress. These conditions cause a decrease in the number of primordial follicles and hormone production [10,25]. Alkylating agents also have a mechanism of burning out primordial follicles [26].

However, the effect of blinatumomab on fertility remains unclear. Considering its functional mechanism, blinatumomab may exert less ovarian toxicity than conventional cytotoxic chemotherapy. B cells are reported to be sparse among the leukocytes in the ovary [27,28]. Since blinatumomab is an antibody agent that targets B cells, it may have less impact on follicles wherein B cells are sparse.

There are no reports on the impact of blinatumomab on fertility, however, there are some reports on rituximab, another antibody agent that targets B cells. In a previous report, 78 of 102 pregnancies were delivered within 6 months of, or during rituximab use, and no major complications such as fetal malformation or premature birth were observed [29]. These reports indicate that pregnancy is possible under B-cell suppression.

The number of oocytes retrieved in our cases was not sufficient. Furthermore, attempted fertilization in the first case ended in failure. Fertility has been shown to be decreased among female childhood cancer survivors compared with their siblings, especially in patients treated with an alkylating agent [8]. In our case, the total dose of CY before oocyte stimulation in Case 1 was high, amounting to 16,200 mg/m^2, and the total dose of DXR was 450 mg/m^2. The anti-Mullerian hormone (AMH) level was 1.14 ng/mL at diagnosis of relapse in Case 1 and 2.83 ng/mL just before ovarian stimulation in Case 2. These levels were lower than those

expected in women of the same age, suggesting that ovarian damage appeared before blinatumomab treatment [30]. In previous reports, serum anti-Mullerian hormone (AMH) levels in patients with hematological malignancies have been shown to be lower than those in healthy controls even before treatment [31]. Chemotherapy has been shown to decrease AMH levels and to tend to increase the cancellation rate due to a poor response to ovarian stimulation [31,32]. Low AMH has been significantly associated with a low number of oocytes retrieved [7,33,34,35,36]. Considering these factors, cytotoxic chemotherapy before blinatumomab treatment may have reduced the number of oocytes retrieved and have caused impaired fertilization. There are factors other than blinatumomab that could have a negative impact on fertility; therefore, more cases are needed to determine the degree of ovarian toxicity exerted by blinatumomab.

If cytotoxic chemotherapy before blinatumomab treatment has a negative impact on fertility preservation, treatments with less-cytotoxic chemotherapy before blinatumomab treatment may make the best use of blinatumomab for fertility preservation. Although the effect of tyrosine kinase inhibitors (TKI) on fertility remains unclear, many cases of uneventful pregnancies after imatinib treatment have been reported [37,38]. It has been reported that enough oocytes could be retrieved in a Philadelphia chromosome-positive (Ph^+) ALL patient immediately after dasatinib treatment and PSL administration [39]. If treatment with PSL, TKI, and blinatumomab for Ph^+ALL patients can be realized in the future, it may be possible to achieve a high therapeutic efficacy with less ovarian toxicity.

In this study, we explained the risks of various possible complications caused by chemotherapy such as DNA damage and decreased number of retrieved oocytes to the patients before performing oocyte retrieval [10,25,40]. We have discussed with obstetricians the possibility and safety of ovarian stimulation during and after blinatumomab treatment. Although it has not been supported by clinical evidence, we considered that the effect of

blinatumomab on ovarian toxicity seemed small, since blinatumomab targets only CD19+ lymphocytes [11]. Both patients in our cases were informed that the risk of ovarian toxicity caused by blinatumomab treatment was unclear. Since the effects of blinatumomab on ovarian function and the course of pregnancy and the postnatal period are unknown at present, we believe that oocyte retrieval after blinatumomab administration should be performed only with a thorough explanation and the consent of the patient.

In the future, the patient in Case 2 may try to become pregnant. A published clinical guide has reported that a general recommendation is to delay pregnancy for at least 2 years after hematopoietic cell transplantation, primarily because of the risk for relapse [41]. In our case, considering that the patients are with ALL, duration of the high risk for relapse is relatively long among hematologic malignancies. Therefore, we consider that it is appropriate to delay pregnancy for 5 years after allo-HSCT in our case.

In conclusion, we have reported two cases of oocyte retrieval after ovarian stimulation performed during and after blinatumomab treatment. We used the two-week rest period in blinatumomab treatment for collecting oocytes, and therefore high therapeutic efficacy was retained while preserving fertility. Although the number of oocytes retrieved was small, this method may expand the therapeutic strategy for fertility preservation in AYA patients with ALL; therefore, the accumulation of additional cases is needed to determine the degree of ovarian toxicity exerted by blinatumomab.

Figures

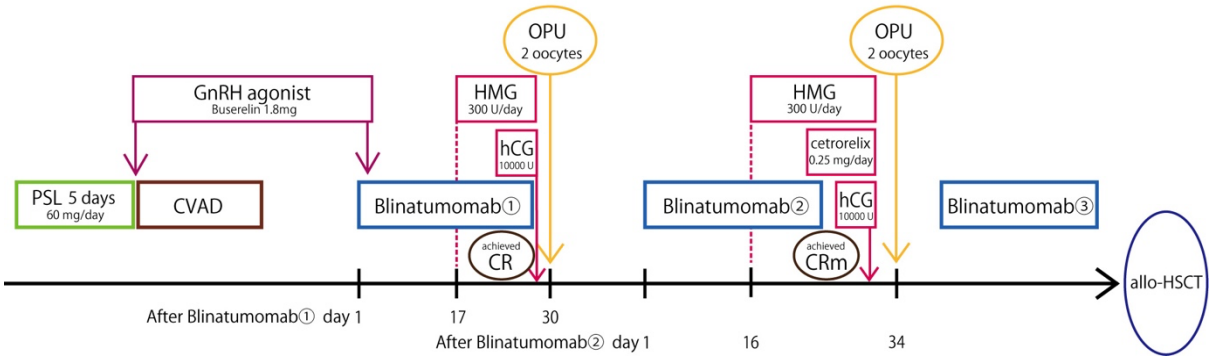

Figure 1

Treatment of ALL and the course of ovarian stimulation in Case 1. Ovarian stimulation was performed during and after blinatumomab treatment. Ovum pick-up (OPU) was performed 36 hours after hCG administration; PSL, prednisolone; CVAD, (hyperfractionated) cyclophosphamide, vincristine, doxorubicin, and dexamethasone; GnRH, gonadotropin-releasing hormone; CR, complete remission; CRm, molecular complete remission; HMG, human menopausal gonadotropin; hCG, human chorionic gonadotropin; allo-HSCT, allogeneic hematopoietic stem cell transplantation.

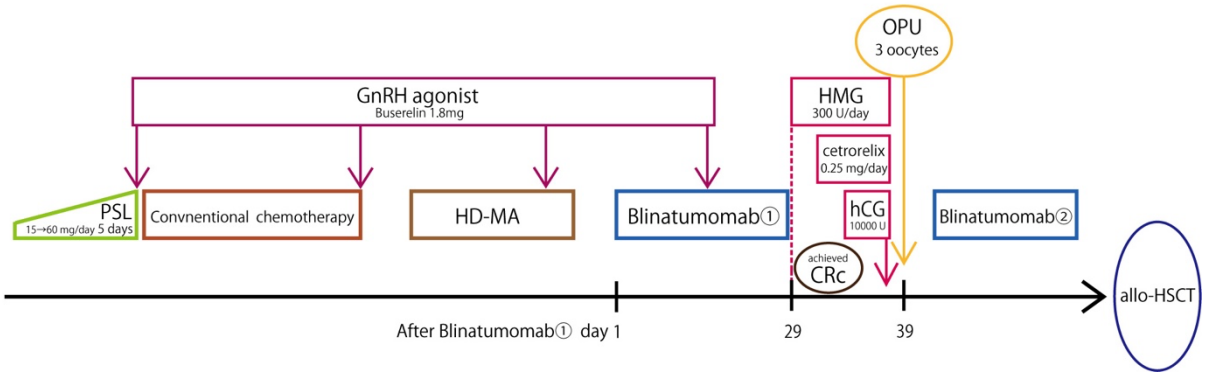

Figure 2

Treatment of ALL and the course of ovarian stimulation in Case 2. Ovarian stimulation was performed during and after blinatumomab treatment. Ovum pick-up (OPU) was performed 36 hours after hCG administration. Conventional chemotherapy consisted of treatment with cyclophosphamide, daunorubicin, vincristine, L-asparaginase, and prednisolone; PSL, prednisolone; HD-MA, high-dose methotrexate and cytarabine; GnRH, gonadotropin-releasing hormone; CRc, cytogenetic complete remission; HMG, human menopausal gonadotropin; hCG, human chorionic gonadotropin; allo-HSCT, allogeneic hematopoietic stem cell transplantation.

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