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Case Report

Successful Planned Pregnancy through Vitrified-Warmed Embryo Transfer in a Woman with Chronic Myeloid Leukemia: Case Report and Literature Review

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Abstract. A 35-year-old female patient with chronic myeloid leukemia (CML) wanted to have a child. She had been treated with imatinib and had achieved major molecular remission, after which imatinib was intentionally discontinued, and interferon-α treatment was initiated. After three failed cycles of artificial insemination with her husband's semen, the patient underwent treatment with assisted reproductive technology. After two cycles of *in vitro* fertilization, two embryos (8-cell stage and blastocyst) were cryopreserved. The patient again had elevated major *BCR-ABL* mRNA levels; thus, infertility treatment was discontinued. After 18 months of dasatinib treatment, major molecular remission was again observed, and the patient underwent vitrified–warmed embryo transfer with a single blastocyst. After that, she became pregnant. Discontinuation of tyrosine kinase inhibitors combined with the timely initiation of infertility treatments, including assisted reproductive technology, might thus be useful for treating women with CML who wish to become pregnant.

Keywords: Assisted reproductive technology; Chronic myeloid leukemia; Major molecular remission; Tyrosine kinase inhibitors.

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Introduction. The number of adolescent and young adult (AYA) cancer survivors is increasing due to advances in cancer treatment. Male and female AYA cancer survivors exhibit sequelae for future fertility and late-onset complications. Many cancers that occur in the AYA population are hematological diseases such as leukemia. Further, patients with acute lymphocytic and myeloid leukemia generally undergo chemotherapy with multiple anticancer drugs and radiotherapy, which can be gonadotoxic.

Tyrosine kinase inhibitors (TKIs) can be used as a standard treatment for chronic myeloid leukemia (CML) instead of chemotherapy with multiple anticancer drugs. For example, imatinib improves the prognosis for women with CML and preserves fertility, unlike conventional anticancer drugs; however, it is contraindicated in women of childbearing age due to its teratogenic effects. Moreover, intentional imatinib withdrawal has been reported to restore the possibility of spontaneous pregnancy in previous infertile women with CML;[1-7] however, there have been no reports of successful pregnancies following assisted reproductive

technology (ART) treatment for infertile women with CML. Here, we report a successful planned pregnancy through vitrified–warmed embryo transfer in a woman with CML showing molecular remission.

Case Report. When the patient was 27 years old, she got married and was diagnosed with CML in the chronic phase. Cytogenetic studies showed a (9;22)(q34;q11) translocation in all 20 metaphase cells and *BCR-ABL* fusion gene signals were observed in 95 % of the cells by fluorescent in-situ hybridization and polymerase chain reaction amplifying major BCR-ABL (p210). She had low-risk Sokal and Hasford scores, and her performance status was zero at diagnosis. She immediately started to receive imatinib (Glivec®, NOVARTIS, Tokyo, Japan) treatment at a daily dose of 400 mg and achieved major molecular remission (MMR). At 35 years of age, the patient was admitted to our hospital as she desired a child. At that time, she had received imatinib for 96 months and had been in MMR for more than 80 months. Imatinib treatment was discontinued and switched to 3,000,000 IU interferon-α (IFN-α, Sumiferon®, Sumitomo Dainippon Pharma, Tokyo, Japan) along with twice-weekly consultations with a hematologist before infertility treatment. Additionally, both the patient and her husband were screened to check for causes of infertility. The patient's menstrual period was regular, and her body mass index was 27.6 kg/m^2 (overweight). Although there were no abnormal findings based on bimanual palpitation, transvaginal ultrasonography revealed a 3-cm subserosal fibroid and polycystic ovary on the left side. On the fourth day of the patient's menstrual cycle, the levels of luteinizing hormone, follicle-stimulating hormone (FSH), prolactin, 17β-estradiol, and free testosterone were 6.95 mIU/mL, 5.01 mIU/mL, 18.98 ng/mL, 33 pg/mL, and 0.6 pg/mL, respectively. On the nineteenth day of her menstrual cycle, 17β-estradiol and progesterone levels were 126.1 pg/mL and 12.6 ng/mL, respectively. Hysterosalpingography revealed bilateral tubal patency. The husband's semen findings were within normal ranges according to World Health Organization criteria as follows: semen volume, 2.0 mL; sperm concentration, 157×10^6/mL; total motility, 68 %. The patient's peripheral blood showed a white blood cell count of 4300/μL (47 % lymphocytes, 39 % neutrophils, 10 % monocytes, and 2 % eosinophils), a red blood cell count of 4.23×10^6 /μL, hemoglobin of 12.1 g/dL, hematocrit of 36.1 %, and a platelet count of 26.7×10^4 /μlL, with a major BCR-ABL mRNA copy number of 8 per assay. After the infertility workup, the patient's doctor recommended and implemented an initial treatment of artificial insemination with the husband's semen (AIH) with ovarian stimulation and clomiphene citrate (CC). After three rounds of AIH treatment, the patient failed to become pregnant. By this time, six months had passed since the start of infertility treatment, and despite IFN-α treatment, her major BCR-ABL mRNA copy number and ratio of BCR-ABL to ABL mRNA (converted to international scale-normalized copy number [IS-NCN]) had increased. Under these circumstances, the patient decided to undergo *in vitro* fertilization (IVF) treatment, receiving controlled ovarian stimulation (COS) with a gonadotropin-releasing hormone (GnRH) agonist-long protocol. Oocyte retrieval was canceled during the first attempted IVF treatment cycle due to the risk of ovarian hyperstimulation syndrome (OHSS). At this time, the IFN-α treatment dose (3,000,000 IU) was increased from twice to three times per week due to the increasing BCR-ABL levels. During the second IVF treatment cycle, the patient underwent COS with CC and recombinant FSH treatment, followed by triggering with a GnRH agonist to prevent OHSS. One mature cumulus-oocyte complex was retrieved and subjected to IVF. The fertilized oocyte developed to an eight cell-stage cleavage embryo, which was vitrified and stored in liquid nitrogen. During the third IVF treatment cycle, COS was performed using the GnRH antagonist protocol, followed by triggering with a GnRH agonist; one mature oocyte was retrieved. The fertilized oocyte developed into a blastocyst-stage embryo, which was vitrified and stored in liquid nitrogen. Therefore, a total of two embryos were vitrified and stored. Since the IS-NCN level was 1.2847 % during IFN-α treatment, the hematologist suggested that it was necessary to administer dasatinib (Suprycel®, Bristol-Myers Squibb, Tokyo, Japan) in addition to IFN-α. Consequently, the patient received a daily dose of 100 mg of dasatinib in addition to IFN-α (3,000,000 IU) three times per week and temporarily suspended infertility treatment. Five months later, BCR-ABL levels became undetectable and were maintained at this level for a further 12 months. The patient then stopped IFN-α and dasatinib treatment and resumed infertility treatment three months after the last dose, undergoing vitrified–warmed embryo transfer using the 8 cell-stage embryo under a hormone replacement cycle. Two weeks after embryo transfer, the patient was found to be pregnant, testing positive for urinary human chorionic gonadotropin. Two weeks later, the patient was confirmed to have one fetus with a heartbeat in her uterus. In total, it took 34 months from the start of infertility treatment until the pregnancy was achieved, at which point the patient was 38 years old. She underwent non-invasive prenatal testing (NIPT) after genetic counseling at 12 weeks of gestation, the NIPT report for trisomy 13, 18, and 21 being negative. The course of the pregnancy was uneventful until 27 weeks of gestation when the patients′ BCR-ABL levels showed a slight increase (0.1059 % IS-NCN); therefore, IFN-α treatment (3,000,000 IU) was resumed three times per week. At 31 weeks of gestation, ultrasonography showed fetal

ventricular brain enlargement and a mass in the sacral area, which was thought to be a meningocele. The patient was admitted to the hospital and received a tocolytic agent to prevent preterm labor as her cervix had shortened to 25 mm, and her amniotic fluid index had increased to 25 cm at 33 weeks of gestation. The patient was scheduled to undergo an elective cesarean section to prevent perforation of the meningocele, delivering a female infant with an Apgar score of 8 and weighing 2634 g at 37 weeks of gestation. After delivery, the infant was diagnosed with a meningocele without other congenital anomalies, and the meningocele was repaired the same day. The patient was discharged from the hospital seven days after delivery without any complications. The clinical course of the patient's infertility treatment is shown in **Figure 1**.

Discussion. We report a successful planned pregnancy in a woman with CML showing MMR via the vitrified–warmed transfer of an embryo derived from IVF. To the best of our knowledge, this is the first report of a planned pregnancy using ART in a female patient with CML and infertility. The ability of TKIs to improve prognosis and preserve fertility has increased the number of CML patients of reproductive age desiring children. Although the median age of disease onset for CML is > 60 years, the proportion of men and women of reproductive age is 30–40 %.[8] Although imatinib has been reported to affect testosterone production in male CML patients, TKIs have little or no effect on male fertility.[9] Conversely, TKIs can exhibit major teratogenicity in female CML patients; therefore, female CML patients who desire children must discontinue TKI therapy.

Recently, a guideline regarding TKI discontinuation in female CML patients who wish to have children was revised and published.[10] The guideline recommends that such individuals should discontinue TKI treatment before conceiving and maintain TKI discontinuation during pregnancy. However, the major problem associated with this strategy is CML relapse during

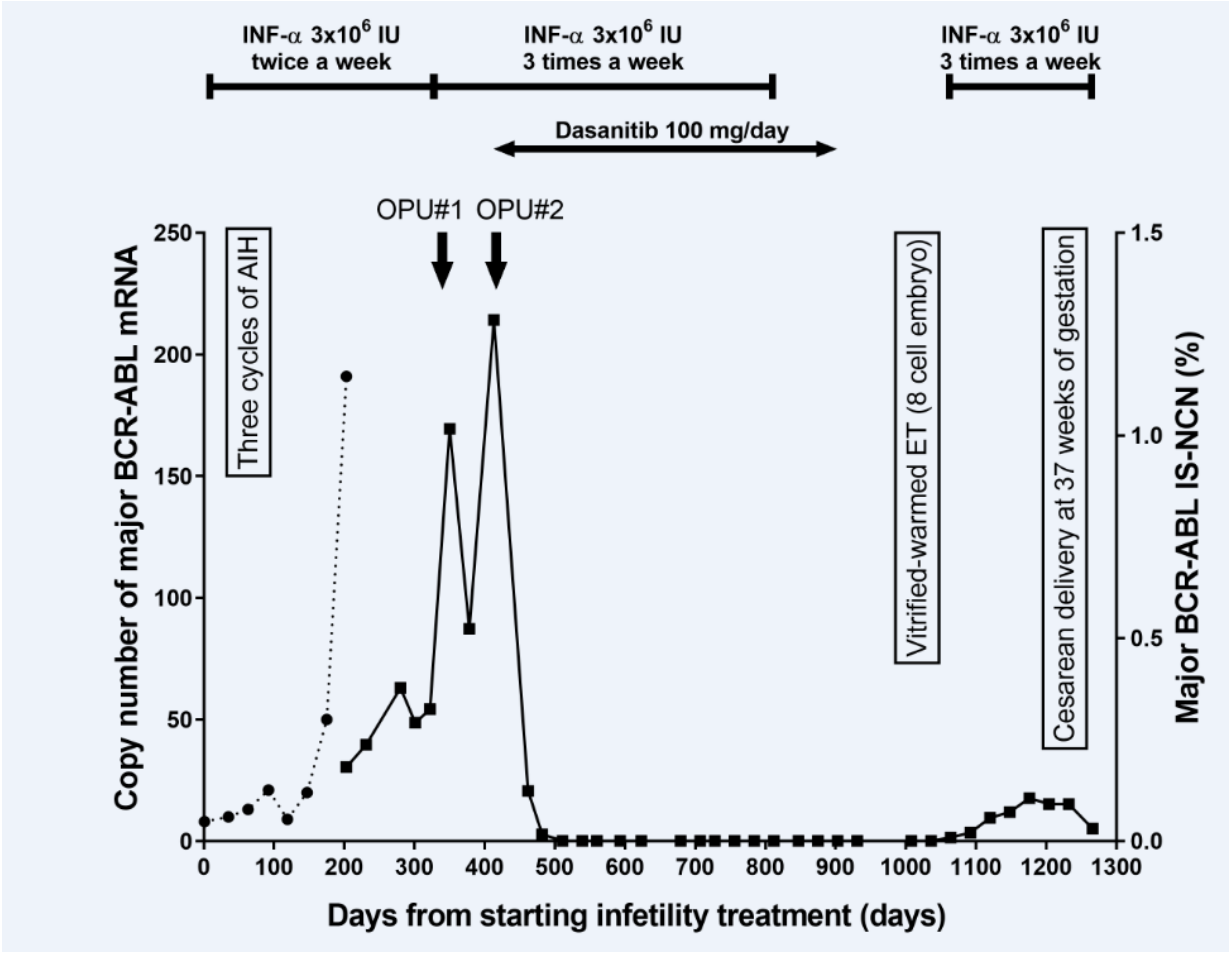

Figure 1. Clinical course of planned pregnancy in a woman with chronic myeloid leukemia (CML). After three cycles of AIH treatments, she underwent an in vitro fertilization program. After two steps of oocyte retrieval, two embryos, an 8 cell-stage and blastocyst-stage embryo, were vitrified and stored. Due to an increase in major *BCR-ABL*, infertility treatment was temporally interrupted. After that, dasatinib plus INF-α was administrated until major molecular remission (MMR). After MMR was achieved for 12 months, vitrified–warmed embryo transfer of the 8-cell embryo was performed. Finally, she got pregnant and delivered via cesarean delivery at 37 weeks of gestation. The dotted line indicates the major *BCR-ABL* mRNA copy number. The solid line indicates the major *BCR-ABL* IS-NCN. AIH: artificial insemination with husband's semen, ET: embryo transfer, IFN: interferon, IS-NCN: international scale-normalized copy number, OPU: ovum pickup.

TKI discontinuation. There have been several reports on TKI discontinuation criteria and relapse rates following TKI interruption in CML patients. According to reports from TKI discontinuation trials, the recurrence rate is approximately 50–60 % in CML patients with complete MMR or a deep molecular response.[9] Moreover, if untreated after TKI discontinuation, recurrence is generally observed within six months.[9] Therefore, female CML patients who wish to become pregnant must switch from imatinib to another CML treatment and have a limited amount of time to achieve pregnancy successfully.

Treatment options during TKI withdrawal or pregnancy include the administration of hydroxyurea and INF-α.[10-13] Hydroxyurea is not a safe option due to observed teratogenic effects in an animal model. However, INF-α is safe for women who wish to have children or for pregnant women.[13] In this case, INF-α was administered after TKI withdrawal and was continued during infertility treatment. Due to prolonged infertility treatment, interferon-α monotherapy was unable to suppress the CML disease state. Therefore, another TKI, dasatinib, was administered for disease control.

There are multiple ways to achieve pregnancy and, subsequently, delivery, such as natural pregnancy and infertility treatment. Although natural pregnancy is ideal, infertility treatment (particularly ART) is effective in achieving pregnancy in a limited time. As shown in **Table 1**, 11 cases of planned pregnancy have been reported in female CML patients with TKI interruption, including this case.[1-7] Besides one, all cases exhibited MMR at the time of TKI interruption. IFN-α therapy was performed in three of the 11 cases, including ours, after TKI discontinuation. Four of the cases conceived naturally, and two underwent infertility treatment without ART. However, there have been no previous reports of ART treatment for planned pregnancy in female CML patients; therefore, our report might be the first case in which pregnancy was achieved via vitrified–warmed embryo transfer.

ART treatment with frozen embryos increases the chance of pregnancy in women with CML as well as other AYA cancer survivors.[14] It might also be appropriate even if infertility treatment is interrupted due to CML relapse. In this case, ART treatment was administered after six months of non-ART infertility treatment. During this time, levels of CML molecular markers started to increase, forcing the infertility treatment to be interrupted when frozen embryos were obtained after two cycles of ART treatment. The patient was then treated with dasatinib, another TKI, in addition to IFN-α treatment. After MMR had been confirmed after more than 12 months, vitrified–warmed embryo transfer was scheduled, and pregnancy was established. Thus, ART, particularly with frozen embryos, could be a useful treatment option for female CML patients who have a limited period to achieve pregnancy.

Given that there is currently no effective strategy to prevent age-related fertility declines in women, cryopreservation of eggs or ovarian tissue to preserve fertility for women who wish to have children is an important issue.[15] In this case, the patient was already 35 years old when she was referred to our hospital, having been diagnosed with CML at 27 years when she was already married to her partner. The patient might have been able to undergo embryo cryopreservation by ART as soon as she was judged to be in MMR. Recently, Gazdaru et al. reported successful embryo cryopreservation for a TKI-resistant female CML patient who changed from TKI to IFN-α treatment prior to conditioning chemotherapy with hematopoietic stem cell transplantation.[16] Accordingly, all female CML patients who wish to have children, even those who are unmarried without a partner, should consider undergoing embryo or oocyte cryopreservation to preserve their fertility.

Another critical issue to consider in such cases is the teratogenicity of treatment drugs during pregnancy in women with CML.[6,17] In this case, we stopped dasatinib, a TKI, and IFN-α before the scheduled vitrified–warmed embryo transfer; nonetheless, the child was born with a meningocele despite the long drug-free period. There have been previous reports of meningoceles occurring in the children of female CML patients who became pregnant during imatinib treatment.[17,18] Moreover, Cortes et al. reported that an infant with encephalocele, a type of neural tube defect, was observed in a woman treated with dasatinib.[19] In this case, since the pregnancy was established more than three months after the discontinuation of dasatinib administration, there might be almost no drug-related effects on the fetus. In contrast, IFN-α has not been reported to exhibit teratogenicity and can be used safely during pregnancy.[13]

Neural tube defects, such as meningoceles are associated with folate deficiency.[20] Generally, hematological malignancies, such as leukemia and pregnancy, require large amounts of folate for cell growth.[21,22] Moreover, polymorphisms in the gene encoding methylenetetrahydrofolate reductase, an enzyme involved in folate metabolism, have been associated with CML in Asian patients.[23] In this case, additional folate supplementation might be required in addition to that generally recommended.

Conclusions. TKI discontinuation and the timely initiation of infertility treatments such as ART might be useful for treating women with CML who wish to become pregnant.

Table 1. Reported cases of planned pregnancy in patients with CML with TKI interruption.

Patient no.	Publication	Age at diagnosis (years)	Phase	TKI used	TKI treatment period (months)	State at TKI interruption	Age at TKI interruption	CML treatment after TKI interruption	Infertility treatment	Age at pregnancy (years)	Delivery (weeks)	Mode of delivery	Fetal congenital anomaly
1	Kobayashi K et al.	24	CP	Imatinib	19	CCyR	25	None	Ovulation induction	26	38	Vaginal	None
2	Pavlovsky C et al.	27	CP	Imatinib	54	MMR	36	None	AIH with ovulation induction	38	39	Vaginal	None
3	Santorsola D et al.	27	CP	Nilotinib	74	MMR	33	None	None	34	42	Vaginal	None
4	Osawa et al.	36	CP	Imatinib	28	MMR	37	INF-α	None	38	N/A	Vaginal	None
5	Law AD et al.	23	CP	Imatinib	N/A	MMR	33	Pegylated INF-α-2b	None	33	38	Vaginal	None
6	P P et al.	23	CP	Imatinib	N/A	N/A	29	None	None	29	38	N/A	None
7	Dou X et al.	26	CP	Imatinib	102	MMR	34	None	N/A	N/A	37	N/A	None
8	Dou X et al.	28	CP	Nilotinib	51	MMR	32	None	N/A	N/A	39	N/A	None
9	Dou X et al.	25	CP	Imatinib	48	MMR	29	None	N/A	N/A	40	N/A	None
10	Dou X et al.	26	AP	Imatinib	48	MMR	31	None	N/A	N/A	39	N/A	None
11	Present case	27	CP	Imatinib	96	MMR	35	INF-α	ART: vitrified-warmed ET	38	37	Cesarean section	Meningocele

AIH, artificial insemination with husband's semen; ART, assisted reproductive technology; CCyR, complete cytogenetic response; CP, chronic phase; ET, embryo transfer; IFN, interferon; MMR, major molecular response; N/A, not applicable; TKI, tyrosine kinase inhibitor

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