Successful ovarian stimulation and pregnancy in an infertile woman with chronic myeloid leukemia

Silvina J. Rios¹ · Lorena Martínez-Montesinos¹ · Cristina Aroca¹ · Raul Teruel-Montoya^{1,2,3} · Francisca Ferrer-Marín^{1,2,3}

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Abstract

Background Tyrosine kinase inhibitors (TKI) treatment has transformed chronic myeloid leukemia (CML) from a fatal neoplasm to a chronic disease with normal life expectancies. Indeed, half of CML patients are able to discontinue TKI without relapse. However, it seems clearly demonstrated that exposure to TKI may result in fetal malformations. Regarding its effects on fertility, preclinical studies and clinical case reports provide inconclusive evidence. Furthermore, due to the risk of CML relapse after TKI discontinuation, the optimal time to stop TKI represents a real dilemma.

Case report We describe a 23-year-old woman who, after more than 6 years with imatinib and 1 year in deep molecular response [(DMR), MR ≥ 4], interrupted treatment to become pregnant. After 2 failed artificial insemination cycles, she underwent one process of controlled ovarian stimulation, achieving 2 blastocyst-embryos. In the meantime, BCR-ABL1^{IS} levels increased despite interferon-alpha therapy, she lost the mayor molecular response (MMR), and the 2 embryos had to be cryopreserved. A stable second MR ≥ 4.0 was again obtained with nilotinib, and after stopping it, the 2 blastocyst-embryo transfers were unsuccessfully performed. Under DMR, a second ovarian stimulation and in vitro fertilization (IVF) was performed and 1 blastocyst embryo was transferred. This time, she became pregnant and a healthy baby was born. After more than 3 years of follow-up, she remains in treatment-free remission (TFR).

Conclusion Compared with imatinib, nilotinib achieves earlier and deeper MR that allows safe and timely pregnancies in infertile CML women through IVF process, while patients remain in TFR after delivery.

Keywords Chronic myeloid leukemia · Pregnancy · In vitro fertilization · Imatinib · Fertility · TKI

Introduction

In the last decade, tyrosine kinase inhibitors (TKI) treatment has transformed chronic myeloid leukemia (CML) from a fatal neoplasm into a chronic disease with normal life expectancies. Importantly, although the median age of CML onset is 65 years, up to 25–37% of patients are in reproductive age at the time of diagnosis [1]. While there is a consensus that TKI are strongly

discouraged at the time of conception and during the pregnancy due to the risk of fetal abnormalities and miscarriage [2, 3], the information on the effects of imatinib and other TKI on fertility is still limited. Preclinical studies in female rats seem to show that imatinib is teratogen, but not gonadotoxin [4]. Furthermore, the fact that hundreds of women have become pregnant during/after the use of imatinib [5, 6] has led to the belief that imatinib does not appear to have a deleterious effect on fertility. Indeed, the European Leukemia Net (ELN) 2020 [3] does not specifically recommend fertility preservation in young women before the TKI onset. However, the effect of prolonged administration or higher doses of imatinib on gonadal function has not been fully evaluated. Even less is known about the influence that TKI have on ovarian stimulation and in vitro fertilization (IVF) procedures. We report a case of a 23-year-old woman patient who, after 6 years under imatinib treatment (the last 2 years with relative higher doses), achieved stable mayor molecular response (MMR) that allowed her to

✉ Francisca Ferrer-Marín
fferrermarin@gmail.com

¹ Hematology and Medical Oncology Unit, Hospital Morales-Meseguer, Centro Regional de Hemodonación, IMIB-Arixaca, UCAM, C/Ronda de Garay, 30003 Murcia, SN, Spain

² CIBERER (U/765), Murcia, Spain

³ Grado de Medicina, UCAM, Murcia, Spain

interrupt the TKI to become pregnant. She needed 2 IVF cycles and to switch from imatinib to nilotinib in order to get a safe pregnancy. This is the first report of an infertile CML woman who, after having intentionally discontinued CML treatment, achieved a successful IVF, and both a healthy pregnancy and newborn, remaining in TKI-free remission (TFR) after more than 3 years of follow up.

Case report

A 23-year-old female without relevant past medical history was diagnosed in September 2007 of CML in chronic phase (CP), after admission in the Hematology Department for the study of leukocytosis, thrombocytosis, and anemia after a routine analysis. Sokal and Hasford risks were intermediate and low, respectively. The patient started imatinib 400 mg per day reaching a quick hematological response. Imatinib toxicity was limited to GI/gastrointestinal toxicity, weight gain, and periorbital edema. Six months after starting imatinib, she reached a complete cytogenetic response and a BCR-ABL^{IS} by qRT-PCR of 1.28%. During the follow-up (+12, +24, +36 months), however, the patient maintained a suboptimal response with BCR-ABL^{IS} between 0.1 and 1.0% (Fig. 1). Following recommendations reported at that moment from ELN for suboptimal responders [7], in June 2011, imatinib was increased to 600 mg/day, achieving MMR and deep molecular response [(DMR), MR ≥ 4.0] 9 and 15 months later, respectively. While she was under 600 mg/day of imatinib, she

suffered 3 hemorrhagic corpus luteum (October and November 2011; and June 2012) and oral contraceptives were started in July 2012. After almost 2 years in MMR and 16 months in DMR, due to her desire for pregnancy, in January 2014, imatinib and contraceptives were interrupted. At that moment, BCR/ABL^{IS} was undetectable (MR 4.5). Four months later, she lost MMR (BCR-ABL^{IS} 0.72%) and interferon-alpha (INF- α) was started (4.5×10^6 UI/48 h) without toxicity. Because she did not get pregnant, while on INF- α , she underwent two unsuccessfully artificial insemination processes with the husband's semen (January and March 2015). At that time, she lost the MMR again, INF- α was gradually increased up to 4.5×10^6 UI/day, and an ovarian stimulation was planned. She underwent controlled ovarian stimulation with recombinant FSH treatment (r-hFSH, Follitropin- α) and GnRH antagonist. Unfortunately, at that moment, G3 neutropenia related to higher INF- α doses was observed and INF- α was stopped (June 29, 2015). Thirty-six hours after GnRH agonist trigger (July 8, 2015), 17 oocytes were extracted, 7 were mature (metaphase II, MII), 6 were fertilized with sperm injection, and 2 developed into blastocyst-stage embryos. Because, in case of pregnancy, she would need high doses of INF- α with a likely neutropenia that could not be treated with G-CSF (since it crosses the placenta), the 2 embryos were cryopreserved, postponing the embryo transfer until a new DMR was recovered. With this aim, nilotinib 300 mg/12 h was started (July 9, 2015) achieving MR ≥ 4.0 from the second month of treatment (Fig. 1). After 14 months in DMR, in November 2016, nilotinib was stopped and two consecutive frozen blastocyst embryo transfer processes

Fig. 1 Clinical course of a young woman with CML and desire for pregnancy. A young CML woman failed to achieve a mayor molecular response (MMR) on standard dose imatinib after 4 years of treatment. The imatinib was increased to 600 mg daily and MMR and MR4 were achieved. To become pregnant, after 12 months in MR4, she stopped imatinib. She failed to become pregnant by 2 artificial inseminations and she underwent one process of controlled ovarian stimulation,

achieving 2 blastocyst-embryos. In the meantime, BCR-ABL^{IS} levels increased, she lost MMR on interferon, and the 2 embryos had to be cryopreserved. She was re-started on nilotinib and achieved a MR4 again, allowing a second attempt at therapy discontinuation. After a failed embryo transfer, she underwent further ovarian hyperstimulation, embryo transfer, and the delivery of a healthy daughter. After more than 3 years of follow-up, she remains in treatment-free remission (TFR)

were performed: the first one 7 days after the cease of nilotinib under a hormone replacement cycle. Unfortunately, both implants were unsuccessful. In these circumstances, the patient underwent a second ovarian stimulation process with r-hFSH (follitropin), hMG (FSH/LH, menotropin), and GnRH antagonist, followed by h-CG triggering. On March 2, 2017, 7 oocytes were extracted, 5 of which were fertilized. Later on, 4 blastocyst embryos were cryopreserved and 1 was transferred being the successful implantation. Pregnancy proceeded without complications, while the patient remained in MR ≥ 4.0 , without CML treatment throughout pregnancy. Serial ultrasonography showed fetal normal growth. At 38 weeks of gestation (November 11, 2017), vaginal labor was induced and a healthy baby girl, weighing 2935 g, was born. On her last visit, the mother remains in MMR (42 months in TFR), and the child grows up without complications.

Discussion

Since the introduction of TKI, most patients with CP-CML now have a normal life expectancy. For young women, “one of the clearest synonyms of normal quality of life is the ability to conceive and raise a family” [8]. However, data about TKI safety before and during gestation are yet limited. Studies in female Wistar rats have shown that imatinib induces histological changes in the ovary (atretic follicles increase, extravasation of blood vessels and hemorrhage); alterations in the plasma concentrations of progesterone, estrogen, and gonadotropins; and a significantly decrease in the number of corpus luteum. [9]. All these findings seem to be related to the off-target effect of imatinib on PDGFR, which has a potential role in the maintenance of ovarian vasculature [9]. Other preclinical studies, by contrast, suggest that at least in adult mice, imatinib does not affect the fertility [4]. In humans, an increasing number of women are reported to have become pregnant during/after the use of imatinib [5, 6], suggesting that imatinib exposure, at standard doses, has no a substantial impact on fertility.

Here, we report a young woman who after more than 6 years with imatinib (the last 2.5 years with relative high dose), needed up to 2 processes of IVF and a switch from imatinib to nilotinib to become pregnant during her second stable DMR. Christopoulos et al. reported the occurrence of primary ovarian failure in a woman within 2 years of starting imatinib and 6 months after the dose was increased to 600 mg/day [10]. Seshadri et al. also described the development of oligospermia in a young man with hypereosinophilic syndrome during the therapy with high dose of imatinib (800 mg daily) [11]. It is unknown, however, if the relative high doses of imatinib that all these patients received, including our case, might contribute to the problem. In our patient, at diagnosis, imatinib 400 mg/day was started achieving a suboptimal response (BCR-ABL1^{IS} 0.1–1.0%). Provided that the patient tolerated it, dose

escalation to 600 daily was an option [7, 12]. In fact, after increasing the doses, patient achieved stable DMR. Imatinib dose escalation, however, is currently not considered in young patients in warning (BCR-ABL1^{IS} > 0.1–1.0%) and a change to second-generation (2G) TKI is preferred. 2G TKI achieve a deeper and more rapid molecular response and should be preferred in first line for young women of childbearing age [2]. Unfortunately, nilotinib was not approved in first line at the time of the patient’s diagnosis.

Corpus luteum is a functional cyst developing in the luteal phase of the ovarian cycle which regresses spontaneously when pregnancy does not occur. Being a thin-walled vascular structure, corpus luteum is prone to hemorrhage. Hemorrhagic corpus luteum is a rare complication noted in the imatinib data sheet ($\geq 1/10,000$ to $< 1/1000$) [4]. This finding is in line with the pathological changes seen in ovary of female Wistar rats exposed to imatinib [9]. Interestingly, in our patient, hemorrhagic corpus luteum occurred only after increasing the dose of imatinib. Given that imatinib inhibits kinases which are expressed in mammalian ovaries and are important in the development of oocytes and follicles (c-kit and PDGFR) [13], it would be speculated that higher doses of imatinib may have effects on female fertility. However, the existence of hemorrhagic corpus luteum is not synonymous to infertility, and gonadal toxicity has not been studied in either standard or high-dose imatinib trials.

Zamah et al. reported a patient who consented to analyze her intra-ovarian follicular response to gonadotropin stimulation while she was on and off imatinib [14] (2 months apart). In this patient, imatinib and its active metabolite were present in the first intra-follicular fluid (FF) (under imatinib) but not in the second one (off imatinib). Furthermore, intra-follicular estradiol concentrations and oocyte recovery were lower while on imatinib than after stopping it. Overall, these findings suggest that, despite a comparable number of developing ovarian follicles, ovarian hormone production and oocyte recovery are compromised during imatinib treatment [14]. Despite these observations, there are numerous reports of successful conception in women receiving imatinib [5, 6]. While in general terms, female CML patients seem to preserve their reproductive potential during imatinib treatment; according to the precautionary principle, it would seem “prudent” to discuss strategies to preserve fertility to CML women at the time of diagnoses [8].

Beyond reasonable doubts about its potential gonadotoxic effect, all TKI can be teratogenic. Therefore, contraception in CML women is mandatory through the whole treatment [2, 3]. When they achieve a stable MMR (BCR-ABL1^{IS} $\leq 0.1\%$) or more (DMR), TKI discontinuation and pregnancy can be planned. Although our patient started IFN- α when she lost the MMR, nowadays, women who lose MMR and are not yet pregnant are recommended to restart treatment with a more potent TKI and try to discontinue again when DMR has been re-established [3].

Information about the influence TKI in ovarian stimulation and IVF process is very limited. There are only two previous case reports of CML women who underwent ovarian stimulation processes and IVF. The first one was performed for fertility preservation before a hematopoietic stem cell transplant but successful zygote transfer and pregnancy were not reported thereafter [15]. In the second one, by contrast, after IVF, a successful vitrified-warmed embryo transfer was performed, but CML patient had to undergo an elective cesarean due to a meningocele diagnoses in the newborn [16]. She had been exposed to INF- α during IVF treatment cycle, and INF- α plus dasatinib up to 3 months before she underwent embryo transfer. To the best of our knowledge, this is the first report of a patient with CML and infertility who, after undergoing 2 IVF processes, became *pregnant*, a healthy term neonate was delivered, and 3 years later, remains in TFR. This case report points out that starting with a stable DMR, an infertile woman with CML can achieve a successful pregnancy and birth after an IVF process. Compared with imatinib, nilotinib achieves earlier and deeper MR that allows safe and timely pregnancies in infertile CML women through IVF process.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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