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Pregnancies in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitor

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ABSTRACT

We presented our experience in chronic myeloid leukemia (CML) patients who conceived children and/or became pregnant while receiving tyrosine kinase inhibitor (TKI). Among 7 male patients, 7 pregnancies resulted in the birth of 7 healthy babies. Among 18 female patients, 8 ended in elective abortion; 3 had spontaneous abortion, and 7 carried to term, resulting in the birth of 8 healthy babies. All children have normal growth and development. All patients remain in TKI therapy and in good response. It is suggested that female patients are advised to practice adequate contraception. No special precautions apply for male patients receiving TKI.

1. Introduction

The use of tyrosine kinase inhibitor (TKI), including imatinib, nilotinib and dasatinib, has profoundly revolutionized the management of chronic myeloid leukemia (CML), significantly improving the long term prognosis of the disease. The efficacy of the drug combined with its ease of administration and a low level of toxicity has resulted in many patients leading relatively normal lives. For many patients, one of the clearest indications of normal life is the ability to conceive children and raise a family. We used to conduct a retrospective study to review the newly diagnosed CML patients administered in Shanghai from 2001 to 2006. A total of 615 cases entered study. High incidence of the disease was observed in the child-bearing age (20–50 years old), which accounted for 48.2% of all the population [1]. The management of CML during pregnancy remains a great challenge for both physicians and patients.

Imatinib inhibits not only BCR-ABL, the putative cause of CML, but also other tyrosine kinase, such as c-ABL, c-KIT, platelet-derived growth factor receptor (PDGFR) and ARG [2]. Nilotinib, one of the second generation TKI, also inhibits these proteins known to have function that may be important in gonadal development, implantation, and fetal development. So the safety of TKI on conception should be considered. For obvious reasons, the effects of TKI on fertility, pregnancy, and lactation remain quite limited. Most information was derived primarily from animal experiments and case reports. Therefore, clinical observations are very important.

In this report, we presented our experience accumulated to date in CML patients who conceived children and/or became pregnant while receiving TKI.

2. Patients and methods

From January 2003 to March 2013, more than 500 patients with CML in any stage of the disease were treated with TKI in our hospital. All patients were instructed to practice barrier contraception for as long as they were receiving therapy with TKI. Hematologic response, cytogenetic response and molecular response were monitored regularly. Drug toxicity was evaluated at each visit and graded according to the National Cancer Institute Common Toxicity Criteria version 2.0. The drug dosage was adjusted according to the effect and adverse events. The records of all CML patients treated with TKI were reviewed. Data associated with pregnancy, delivery and neonate were collected retrospectively.

3. Results

25 patients (7 men and 18 women) conceived while on therapy with TKI in our hospital until March 31, 2013. Twenty-four patients received imatinib and the rest one received nilotinib.

4. Characteristics of CML patients

4.1. Male patients

There were 7 male patients conceived while on TKI therapy. The male patients' characteristics were listed in Table 1. Six patients were in chronic phase (CP), 5 received imatinib of 400 mg/d and 1 received nilotinib 400 mg q12h. The other one was in accelerated phase (AP) and received imatinib of 600 mg/d. The median age of these patients was 29 years old (range, 26–46 years old) at the

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Table 1
Characteristics of male patients conceiving while on TKI therapy.

Case	Before IM		At time of conception						Outcome of pregnancy	Current disease status
	Phase	Disease duration (months)	Age (years)	Disease duration (months)	Time on TKI (months)	TKI dose (mg/d)	Cumulative dose (g)	Disease status		
1	CP	21	33	53	32	IM 400	384	CMR	Uneventful	CMR
2	CP	2	26	15	13	IM 400	156	CCyR	Uneventful	MMR
3	AP	5	45	40	35	IM 600	630	MMR	Uneventful	MMR
4	CP	1	29	79	78	IM 400	936	CMR	Uneventful	CMR
5	CP	1.5	26	7	5.5	IM 400	66	CCyR	Premature Birth	CCyR
6	CP	2	27	16	14	IM 400	174	CCyR	Uneventful	CCyR
7	CP	1.5	46	33	31.5	Nilo 800	756	CMR	Uneventful	CMR

IM, imatinib; Nilo, nilotinib.

time of conception. Median duration of CML was 33 months (range, 7–79 months). The patients had been on imatinib for a median of 23 months (range, 5.5–78 months). The rest one had on nilotinib for 31.5 months. All patients tolerated TKI therapy and achieved a significant response, 3 CCyR, 1 MMR and 3 CMR. One patient conceived by artificial insemination and the others were naturally. Partners of 6 male patients had uneventful full-term delivery and the other one had premature birth. None of the patients interrupted TKI therapy after the conception. At the time of this report, all the patients remained in TKI therapy and in good response, 2 CCyR, 2 MMR and 3 CMR.

4.2. Female patients

Two distinct scenarios existed regarding pregnancy and CML. The first was CML was diagnosed when the patient underwent the blood tests associated with pregnancy. The second was when pregnancy occurred, planned or unplanned, after CML was diagnosed and treatment was already initiated.

4.2.1. Diagnosis during an established pregnancy

In our hospital, there were 8 female patients diagnosed CML during pregnancy (Table 2). Two patients (8, 9) had a spontaneous abortion at 5 or 4 weeks of gestation. Meantime, CML was discovered. The other 6 patients were discovered CML when they did routine blood tests and found increased WBC in early pregnancy. Five patients decided to have a therapeutic abortion shortly after the pregnancies were discovered. Seven patients received imatinib after the pregnancy was ended.

After discussion of all the treatment option, patient 15 decided to continue the pregnancy without treatment. She and her baby were monitored closely. No therapeutic interventions for leukemia were used during her first six months of pregnancy. From the 7th month, leukapheresis was administered three times because of significantly increased WBC and platelet count. She started imatinib one week after delivery and achieved PCyR within 5 months to this date.

4.2.2. Pregnancy after CML diagnosis and initiation of treatment

We had 10 female patients become pregnant while they were receiving TKI. The characteristics of these patients were listed in Table 3. All patients were in CP and received imatinib of 400 mg/d. When the pregnancy was recognized, median age was 31 years old (range, 28–35 years old). Median duration of CML was 16 months (range, 7–110 months). The patients had been on imatinib for a median of 15 months (range, 6–70 months). Cumulative imatinib dose prior to conception ranged from 72 g to 840 g. All patients achieved a significant response, 2 MCyR, 2 CCyR, 2 MMR and 4 CMR. The median time of exposure to imatinib from conception to treatment discontinuation was 4 weeks (range, 0–8 weeks). Although given informing of contraception during the treatment of TKI, patient 16 and 18 who had pregnant plan discontinued imatinib without consulting with the doctor. They both got pregnant 3 months later. Imatinib was immediately discontinued in patient 17, 19, 20 and 21 when pregnancies were discovered. Patient 22 and 23 took therapeutic abortion without imatinib interruption. Patient 24 and 25 decided to carry on the pregnancy without imatinib interruption. However, the fetus of patient 24 was found intrauterine growth restriction (IGR) at 10 weeks of gestation and she had to undergo therapeutic abortion. Patient 25 experienced a spontaneous abortion at 8 weeks of gestation. There were no other known medical conditions, family history, or other factors of the father or mother that were considered to increase the risk of abortion.

Here specialized patient 19 aged of 35 who experienced an unplanned first pregnancy followed 9.5 months of therapy. The patient responded well to the imatinib, who achieved CCyR and MMR at 3 and 9 months of therapy, respectively. She was in the 4th week of gestation when the pregnancy was detected. She chose to continue the pregnancy, despite being made aware of the possible teratogenic effect of using imatinib. After discontinuing of imatinib, she received regular monitoring of blood tests every 2 weeks and real-time quantitative PCR monthly. The patient remained in CHR, however, the level of BCR-ABL increased significantly in 3 months, from 0.05% to 59%. The patient decided to continue her pregnancy and resume imatinib treatment at the 19 weeks of gestation. She obtained MMR after 7 months of therapy, 3 months after her delivery.

Table 2
CML diagnosed during pregnancy.

Case	Age (years)	Diagnosis phase	Weeks of pregnancy at time of diagnosis (weeks)	Pregnancy outcome
8	30	CML-CP	5	Spontaneous abortion
9	26	CML-CP	4	Spontaneous abortion
10	27	CML-CP	8	Elective abortion
11	32	CML-CP	12	Elective abortion
12	28	CML-CP	8	Elective abortion
13	31	CML-CP	6	Elective abortion
14	32	CML-CP	13	Elective abortion
15	27	CML-CP	16	Continue the pregnancy without therapy

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