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Review Article

Discontinuation of Tyrosine Kinase Inhibitors and Pregnancy for Female Patients with Chronic Myeloid Leukemia

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Abstract

More than 10 years has passed since the first BCR-ABL Tyrosine Kinase Inhibitor (TKI), imatinib, introduced into clinical practice in treatment for Chronic Myeloid Leukemia (CML). Addition to the development and clinical usage of more potent second generation TKIs, majority of patients with CP-CML can excellently control their disease and enjoy good quality of life. Recent prospective and retrospective discontinuation trials for imatinib suggested that roughly 40% of patients achieved Complete Molecular Response (CMR) for more than 2 years (or 24 months) would continue their CMR without relapse. Three female patients achieved long-term deep molecular response received planned pregnant management involving careful molecular monitoring with or without interefone-α (IFN-α) during her pregnancy after stopping imatinib in our institute. Fortunately all patients delivered healthy babies, however, a patient with Sokal high risk at initially diagnosed lost her molecular, cytogenetic and hematologic response in spite of receiving IFN-α.

It would seem reasonable to recommend female patients who wish to become pregnant to wait until they have achieved CMR and sustained this for at least 2 years. Currently the proportion of patients obtaining prolonged and deep MR by treatment with imatinib is less than 10%, however, the use of second generation TKIs as first-line therapy will increase this percentage in near future. And continuing effort should be made to find optimal management for pregnant female patients with CP-CML.

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Future Aspects of Chronic Myeloid Leukemia Treatment

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INTRODUCTION

Chronic Myeloid Leukemia (CML) is a myeloproliferative neoplasm characterized by disorder of pluripotent Bone Marrow (BM) stem cell and by being associated with *BCR-ABL1* fusion gene located in the Philadelphia Chromosome (Ph) [ie, t(9;22)(q34;q11)] [1].

This abnormal fusion gene produces a unique protein named BCR-ABL, which is a constitutively active tyrosine kinase. It is this deregulated tyrosine kinase that is major cause of development of CML. Since the inhibitors of this tyrosine kinase have been developed, treatment of CML has dramatically changed.

Imatinib was the first Tyrosine Kinase Inhibitor (TKI) available for treatment of patients with CML as the second- or further -line treatment since the end of the 20th century based on the remarkable results from international clinical trials [2-6]. In addition, imatinib obtained approval as the first-line treatment for chronic phase CML (CP-CML) by beginning of the 21st century and provided excellent efficacy from several prospective clinical trials [4,5,7,8].

Then, more potent second generation TKIs (dasatinib and nilotinib) have been developed for CML resistant or intolerant to imatinib. As these second generation TKIs have demonstrated that they produce faster and deeper responses than imatinib as the first-line treatment for CP-CML by randomized trials [9,10], they are now available as the first-line treatment like imatinib for newly diagnosed CP-CML [11].

In the management of Ph+(or *BCR-ABL1+*)CP-CML using these TKIs, it is required for patients to achieve optimal response and to continue therapy indefinitely with careful surveillance [11]. Majority of patients with CP-CML can excellently control their disease and enjoy good quality of life. Recent data gained from new studies as well as from updated of the most relevant previous studies give us a question “Can we discontinue TKIs

if patients have longer and deeper molecular response?" Issue of discontinuation of TKIs is especially important for female patients who strongly wish to have their babies.

DISCUSSION

Discontinuation of TKIs in management of CP-CML

The aim of the first-line treatment for CP-CML with TKIs is to achieve optimal responses in the milestones defined by the guideline such as European Leukemia Net [8,11]. During treatment, it is very important to monitor the patient's leukemic status at regular intervals. Response is assessed with standardized real-time quantitative reverse-transcription polymerase chain reaction (qRT-PCR) and/or cytogenetics at 3,6,12 months. The optimal response is defined as *BCR-ABL1* transcript levels <10% (Ph+ <35%) at 3 months, <1% at 6 months,(Ph+=0) and <0.1% from 12 months. The majority of patients with CP-CML will obtain durable cytogenetic and molecular responses. Based upon long-term follow-up of International Randomised Study of Interferon versus STI571 (IRIS) study [12], annual probability of progression of disease in patients initially treated with imatinib was less than 5%, therefore, treatment with TKIs is recommended to continue indefinitely at the same dose as far as it is tolerable. This is because leukemic cells remain in a quiescent state in spite of therapy and quite a few patients relapse after discontinuation of a TKI [13-17].

Despite of this recommendation, patients frequently ask about possibility of stopping TKIs. Based upon recent case reports and series related to discontinuation of TKIs, the commonest reason for cessation was adverse event including intolerance (50%) followed by patient choice (26%), pregnancy (12%) and cost of drugs (12%) among 42 patients [18-25].

There are several prospective and retrospective clinical trials analyzing discontinuation of imatinib in CML [15,16,26-31].

In the prospective discontinuation trials, the eligibility criteria for enrollment of patients were persistent Complete Molecular Response (CMR) for more than 2 years. Although definitions of CMR, molecular relapse, and restart imatinib treatment varied, 45-61% of patients had molecularly relapsed but provability of sustained CMR were 50-39% within 12 to 36 months (Table 1). Majority of molecularly relapsed patients regained CMR by restart imatinib. It should be noted that definition of CMR have been changed and more precise definitions of International Scale (IS) for deep MRs are being used instead of the term CMR in recent prospective trials. They are MR4 (*BCR-ABL1*<0.01%), MR4.5 (*BCR-ABL1*<0.032%), MR5 (*BCR-ABL1*<0.001%) [32,33].

The retrospective analysis also indicated that about 30-40% of patients with CMR for more than 2 years could discontinue without relapse and to restart imatinib regained CMR even though molecularly relapse [30,31].

Based upon multivariate analysis of these trials, there are important factors for sustained CMR after discontinuation TKIs. High-risk Sokal score [34] is a significant risk factor for relapse after discontinuation of TKIs. Prior IFN therapy, longer duration of CMR and longer duration of imatinib administration (>60 months) before discontinuation are associated with longer continuing CMR that is TKI-free remission (TFR) [15,16,30,35,36]. Recent analysis indicated that attaining early deep MR at 3 months is related to durable deep MR [36-38].

An information of discontinuation of second generation TKI, dasatinib ornilotinib, is limited, but, one trial second line treatment of a few case studies demonstrated similar outcomes after cessation of dasatinib and/or nilotinib [24,25]. In addition, 4-year updated results of first line use of nilotinib indicated that about 40% of patients on nilotinib achieved MR4.5, and these responses appear to be durable [39]. Although discontinuation of TKIs is not recommend in the clinical practice but should conduct in the clinical trials, among these patients attained long-term deep molecular response, stopping TKI therapy will be reasonably safe. These encouraging data related to discontinuation TKIs is cause to increase number of young female patients who wish to have their children after cessation of TKIs.

	STIM trial[15]	TWISTER trial[16]	Keio STIM Study[26]	Rousselot et al[27]	Rea et al*[28]
No. of Patient	100	40	40	12	34
% Female	52	52		50	56
Definition CMR	MR 5.0 IS	MR 4.5 IS	negative Q-PCR	Undetectable BCR-ABL	Undetectable BCR-ABL
Definition Molecular Relapse	>MR5.0 on 2 times, increase by one log	>MR4.5 on 2 times or loss of MMR	Q-PCR value >100 copies	Positive Q-PCR on 2 times	Loss of MMR on 1 time
No. of Molecular Relapse (%)	61 (61%)	22 (55%)	18 (45%)	6 (50%)	15 (44%)
Rate of Sustained CMR (months)	39 % (36M)	47% (24M)	55.4% (12M)	50% (18M)	44% (15M)

CMR: complete molecular response, MR: molecular response, IS: International Score, Q-PCR quantitatve PCR, MMR: major molecular response, []:reference number

*Trial of Stop second-generation TKIs, dasatinib and nilotinib after imatinib

Figure 1 Results from prospective trials of discontinuation of TKIs in CML.

Management of pregnancy in female patients with CP-CML

It is well known that exposure of imatinib in early pregnancy has great risk of congenital abnormalities including skeletal malformations (premature closure of skull sutures, craniosynostosis, absent hemivertebrae, shoulder anomaly, and scoliosis), renal (duplex kidney, renal agenesis), respiratory (hypoplastic lungs), and gastrointestinal (exomphalos, omphalocele) abnormalities [40-42]. These phenomena are considered that TKIs inhibit not only BCR-ABL1 but also other proteins such as c-KIT, platelet derived growth factor receptors alpha and beta (PDGFRA/B), ARG, c-FMS, SRC and related proteins [41]. Some of these proteins are known have functions that might be important in pregnancy and fetal development [41].

Although there are number of favorable pregnant outcome of case reports of female patients who received imatinib [40,43-48], an informative full outcome data reported by Pye et al. [40] indicated that there is considerable concern regarding drug safety (Table 2). Among 125 assessable female patients out of 180 patients exposed to imatinib during pregnancy, 63 patients (50.4%) resulted in the birth of normal live infants. Eighteen of them received imatinib for the duration of their pregnancy. Thirty-five patients (28%) underwent elective terminations, 3 following the identification of abnormalities. Eighteen pregnancies (14.4%) ended in spontaneous abortion that is within the limits expected in the normal population (10-15%). Of the remaining 9 infants, there were 8 live-birth and stillbirth with congenital abnormalities. In total 12 pregnancies resulted in infants with fetal abnormalities above mentioned and 3 of which had strikingly similar complex malformations that were observed in the rodent studies.

Zhou et al. [47] reported outcome of 18 female patients with CP-CML. While 7 patients (38.9%) resulted in the birth of normal live, 8 patients (44.4%) selected termination of their pregnancies and 3 pregnancies (16.7%) ended in spontaneous abortion (Table 3).

Klamova et al. [48] reported 5 successful having normal birth infants, but one of mothers lost complete hematologic response during her pregnancy (Table 3).

In the management of pregnancy of female patients, to avoid risks of disease progression and unsatisfactory results of infants is very important. There are two distinct patterns involving pregnancy and CML, one is the management of patient diagnosed as CML during established pregnancy, and another is the management of pregnancy after diagnosis and initiation of treatment [41,42]. In the latter pattern, there are two types of patients, one is the case of an unplanned pregnancy while taking imatinib and another is the case of a planned pregnancy after achieving optimal response.

Milojkovic and Apperley [42] recently proposed algorithm for management of pregnancy in CML. In their algorithm, female patients diagnosed as CML in pregnancy, leukapheresis in first to third trimesters and interferon-α (IFN-α) in second and third trimesters would be selected. Patients planning an elective pregnancy who have CHR or better response by TKIs are recommended to collect oocyte for future assisted conception, stop TKI at onset of menstrual cycle, and start in vitro fertilization and restart TKIs after oocyte collection. Patients planning pregnancy with stable MMR or better MR for 24 months can stop TKI at onset of menstrual cycle, and qRT-PCR monitoring in addition to examination of peripheral blood during pregnancy.

Authors (Reported Year)	No. of assessable patients	Results	No. of pts (%)
Pye (2008)	125	Normal birth	63 (50.4%)
		Elect Abt	35 (28%)
		Fetal defects	3
		Normal or unknown	32
		Spont Abt	18 (14.4%)
		Live birth with congenital anomaly	8 (6.4%)
		Stillbirth with fetal defects	1 (0.8%)
Klamova (2009)	5	Normal birth	5 (100%)
		Keep CHR dur preg	4
		Loss of CHR	1
Zhou (2013)	18	Normal birth	7 (38.9%)
		Elect Abt	8 (44.4%)
		Spont Abt	3 (16.7%)

Elect Abt: elective abortion, Spont Abt: spontaneous abortion, CHR: complete hematologic response, dur preg: during pregnancy

Figure 2 Outcome from resent reports of pregnancies in female patients with CML.

	Age at Diagnosis	Risk (Sokal/Hasford)	STIM (months from initial IMA)	Treatment post STIM	Outcome	Delivery (at months from initial IMA)	Current Status
Patient 1	25Y	Low/Low	63M	None	Mol Rel at 4M, restart IMA	None	
			76M	HLBI	Successful 2 times-pregnancies	2 Healthy-girl (101M and 127M)	CMR by HLBI
Patient 2	30Y	High/Intermediate	63M	HLBI	Pregnant/ Mol Rel at 1M/ restart IMA	Spont Abt	
			83M	None	Pregnant/ Loss of CCyR and CHR/ restart IMA after 13 wk gestation	Healthy-girl (93M)	MMR by NIL
Patient 3	25Y	Low/Low	129M	HLBI	Successful 1 time-pregnancy	Healthy-boy (142M)	CMR by HLBI

STIM: stop imatinib, IMA: imatinib, Y: year, M:months, Mol Rel: molecular relapse, HLBI: human lymphoblastpod interferon, CMR: complete molecular response,Spont Abt: spontaneous abortion, CCyR; complete cytogenetic response, CHR: complete hematologic response, MMR: major molecular response, NIL: nilotinib

Figure 3 Discontinuation of imatinib and outcome of female patients with CML-CP.

Our experience for 3 pregnant female patients with CP-CML

Recently, our institute has experienced management of female patients who treated with TKIs. Our planned pregnancy management asks patients been treated with natural IFN-α (human lymphoblastoid interferon: HLBI) after stopping imatinib. The reason why we select treatment of natural IFN-α during pregnancies is based upon our experience of successful pregnancies by one of our female patients who had been treated only HLBI and had 3 healthy children in addition to same data reported by others [50,51]. Patients are also required to have monthly molecular monitoring by peripheral blood qRT-PCR all through their pregnancies.

Between June 2007 and Apr. 2014, 3 female CML-CP discontinued imatinib after more than 5 years sustained MMR to plan pregnancies (Table 3).

Patient-1: She was diagnosed as CP-CML at age of 25-years-old (Sokal:Low/Hasford [49]: Low risk) and stopped imatinib at 76 months after initial administration of imatinib (at her 32-years-old) and switched to HLBI. This was her 2nd time stop-imatinib since her MMR had been lost in 4 months after 1st stop-imatinib at 63 months from initial administration of imatinib. She was retreated with imatinib and quickly regained MMR before the 2nd stop-imatinib. Her MMR has been continued during her 1st and 2nd pregnancies with treatment of HLBI and she had 2 healthy girls at 14 months and 26 months of stop-imatinib. Currently she continued to receive HLBI and attained durable Undetectable Minimal Residual Disease (UMRD).

Patient-2: She was diagnosed as CP-CML at age of 30-years-old (Sokal: High/Hasford : Low risk) and stopped imatinib at 83 months after initial administration of imatinib (at her 38-years-old). This was her 2nd stop-imatinib since her 1st stop-imatinib to change HLBI consequently failed to control MMR and had spontaneous abortion. Although she obtained durable MMR after re-started imatinib, she lost quickly her MMR, cytogenetic and hematologic responses by 3.5 months of her pregnancy, again. IMA (300mg) was re-started from her 13 weeks gestation. She continued her pregnancy and delivered a healthy girl at 10 months of stop-imatinib. Currently she received nilotinib because she did not attain complete cytogenetic response (CCyR) with imatinib anymore.

Patient-3: She was diagnosed as CP-CML at 25-years-old (Sokal:Low/Hasford: Low risk) and stopped imatinib at 129 months after initial administration of imatinib (at her 36-years-old) and switched to HLBI. She successfully became pregnant and had a healthy boy at 12 months of stop-imatinib. Currently she continued to receive HLBI and keep durable Undetectable Minimal Residual Disease (UMRD).

In summary of our experience, stable MMR more than 5 years by imatinib is not always safe for discontinuation. Though they regained MMR by shortly after re-start imatinib. Treatment of IFN-α post-cessation of imatinib is effective to keep CMR during pregnancy for patients with Sokal low risk. They continue to receive IFN-α instead of imatinib attaining UMRD in order to prepare for another successful pregnancy. Patient with Sokal high risk failed to treatment of IFN-α, relapsed quickly and lost CHR eventually.

For those who have high risk and hematologic relapse during pregnancy, treatment imatinib from second trimester seemed effective and safe for infants as several reports indicated [40,42].

Although there is no established management of female pregnancy, carefully planned pregnancy after more than 2 years stable MMR or CMR using IFN-α might be one of the feasible approaches.

CONCLUSION

Provability of successful cessation of imatinib in patients continue to maintain a deep response with undetectable BCR-ABL1 transcripts (CMR or MR4.5-5.0) is roughly 40% when imatinib has been discontinued after achievement of CMR for period of 2 years. In this situation, it would seem reasonable to recommend female patients who wish to become pregnant to

wait until they have achieved CMR and sustained this for at least 2 years. Currently the proportion of patients obtaining prolonged and deep MR by treatment with imatinib is less than 10%, however, the use of second generation TKIs as first-line therapy will increase this percentage in near future. And continuing effort should be made to find optimal management for pregnant female patients with CP-CML.

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