Zu et al. Journal of Hematology & Oncology (2024) 17:82
https://doi.org/10.1186/s13045-024-01603-z

Journal of Hematology & Oncology

CORRESPONDENCE Open Access

Outcome after short exposure to tyrosine kinase inhibitors in pregnant female patients with chronic myeloid leukemia

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Abstract

Unintended pregnancy for female patients with chronic myeloid leukemia (CML) raises the discussion of treatment choices due to the teratogenicity of tyrosine kinase inhibitor (TKI). We report 51 accidental pregnant CML chronic phase (CP) patients with TKI withdrawal immediately after pregnancy from December 2010 to February 2024 to observe the effect of short exposure to TKI on the fetus and the infant outcomes. 59 pregnancies resulted in 100% normal childbirth without birth abnormalities. The median TKI exposure duration was 4 (4–20) weeks in 58 pregnancies, and one pregnancy avoided TKI exposure due to treatment discontinuation of the patient with treatment-free remission (TFR). All newborns had normal birth weight except one premature infant with low birth weight less than the 10th percentile. Up to now, all the children are in good health. 13 (25.5%) and 30 (58.8%) patients had achieved major molecular response (MMR) and deep molecular response (DMR) at pregnancy, respectively. After TKI discontinuation, loss of MMR and complete hematologic response occurred in 6 (46.2%) and 2 (25.0%) patients at delivery, respectively. 38 patients resumed TKI treatment after delivery, and 13 patients without DMR loss sustained TFR after delivery. The median time to regain MMR and DMR were 3 (2–6) months and 6 (1–28) months, respectively. These results demonstrate that TKI discontinuation during pregnancy is feasible for CML-CP patients, and short TKI exposure of pregnant patients has little influence on children's growth and development.

Keywords Tyrosine kinase inhibitor, Pregnancy, Short exposure, Chronic myeloid leukemia

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To the Editor.

In the era of tyrosine kinase inhibitor (TKI), improving the quality of life has become main therapeutic goal for patients with chronic myeloid leukemia (CML). Fertility is an extremely important issue. Due to the recognized teratogenicity of TKIs, female pregnant patients with CML are recommended to discontinue TKI [1]. Nevertheless, patients with unintended pregnancy have the risk of short TKI exposure. The adverse effects of short exposure to TKI on the fetus and the infant are still unclear. We retrospectively observed the data of accidental pregnancy in 51 patients stopping TKI immediately after pregnancy from December 2010 to February 2024.

The median ages of patients at CML diagnosis and pregnancy were 22 (12–38) years and 28 (18–40) years. All patients had CML chronic phase at pregnancy and the majority (68.6%) was low Sokal score. TKI therapy at the first pregnancy included imatinib (45.1%), nilotinib (43.1%), dasatinib (5.9%) and flumatinib (5.9%). The median duration from diagnosis to the first pregnancy was 60 (8-185) months, and the duration of TKI treatment was 48 (8-132) months. The characteristics of patients is depicted in Table 1.

Table 1 The characteristics of pregnant female patients with CML

Parameter	Median [range] or N (%) Total *N* = 51
Age at CML diagnosis (years)	22 (12–38)
Sokal score	
Low risk < 0.8	35 (68.6)
Intermediate risk 0.8–1.2	16 (31.4)
Duration from diagnosis to the first pregnancy (months)	60 (8–185)
TKI treatment at the first pregnancy	
Imatinib	23 (45.1)
Nilotinib	22 (43.1)
Dasatinib	3 (5.9)
Flumatinib	3 (5.9)
Duration of TKI treatment (months)	48 (8–132)
TKI exposure before the first pregnancy (weeks)	4 (4–20)
Disease status at pregnancy	
without MMR	8 (15.7)
MMR	13 (25.5)
DMR	30 (58.8)
Disease status at delivery	
without MMR	14 (27.5)
MMR	13 (25.5)
DMR	24 (47.1)
Time of pregnancy	
One	44 (86.3)
Two	6 (11.8)
Three	1 (1.9)
Restart TKI treatment	
yes	38 (74.5)
no	13 (25.5)
Time of restart TKI treatment after delivery (days)	7 (1–120)
Disease status at follow-up	
without MMR	8 (15.7)
MMR	18 (35.3)
DMR	25 (49.0)

CML chronic myeloid leukemia, *TKI* tyrosine kinase inhibitor, *MMR* major molecular response, *DMR* deep molecular response

Data of 59 pregnancies in 51 patients was available. TKI exposure before pregnancy was 4 (4–20) weeks, the majority within 8 weeks but one in 20 weeks. Retrospective studies showed embryotoxicity and teratogenicity were induced by imatinib and dasatinib [2, 3]. There is few reports about the effects of nilotinib and flumatinib on the fetus. However, whether short TKI exposure could be safe is a controversial subject. It is worth mentioning that a 18-years old patient had a healthy baby after exposure to dasatinib for 20 weeks.

Fifty-nine pregnancies resulted in live births. The median height of newborns was 50 (46–54) cm, and the median weight was 3200 (2050–4280) g. Only one newborn who premature at week 36 had a low birth weight less than the 10th percentile, exposed to nilotinib in first 4 weeks of pregnancy. Nevertheless, the infant recovered normal weight by the second month without medical intervention. 20 (33.9%) newborns were breastfed for median 5(2–10) months, and mothers continued treatment-free observation during breastfeeding. Baby colostrum, the first 2–5 days postpartum, could be conducive to immune system of newborn. Thus, short-term breastfeeding was recommended even the patient with need to restart TKI [4, 5]. None of congenital malformations, abnormal liver function and hematological indices were observed. Different doses of imatinib and dasatinib resulted in various embryo-fetal toxicity [6, 7]. Whether none congenital malformations is associated with unreached teratogenic dose due to short exposure to TKIs is the next to be studied. The median follow-up was 47 (3-124) months and all are generally in good health to date (Table 2).

In terms to the outcomes, all patients are still alive now. 13 (25.5%) and 30 (58.8%) patients had achieved major molecular response (MMR) and deep molecular response (DMR, BCR-ABL < 0.01%) at pregnancy, respectively. 20% (6/30) and 46.2% (6/13) of patients lost DMR and MMR at delivery. But none with initial DMR lost MMR. The median time of DMR and MMR loss was 3 (2–4) months and 6 (5–7) months. Two experienced loss of complete hematologic response. No difference in resistance rate to front-line treatment was found between patients with or without therapy during pregnancy [8]. Interestingly enough, three patients with MMR at pregnancy achieved DMR after 7 months without TKI therapy. The regenerative dynamics of residual CML in pregnant women maybe distinct from that in non-pregnant patients [9].

Table 2 Newborns characteristics and outcomes

Parameter	Median [range] or N (%) Total *N* = 59
Gender	
Male	33 (55.9)
Female	26 (44.1)
Delivery mode	
Natural delivery	12 (20.3)
Caesarean section	47 (79.7)
Gestational age	
Full term	58 (98.3)
premature delivery	1 (1.7)
Breast feeding	
Yes	20 (33.9)
No	39 (66.1)
Birth weight	
Normal weight	58 (98.3)
Low weight	1 (1.7)
Median height (cm)	50 (46–54)
Percentile[a] at birth	
< 10	1 (1.7)
25–75	58 (98.3)
Median follow-up, months	47 (3–124)

[a]Calculated according to INTERGROWTH-21st Project tables

Despite low tumor burden, immune surveillance systems maybe committed to control disease with untreated based on deep level of response [10]. Further studies evaluating the correlation of pregnancy and immune surveillance should be consider. TKI reinitiated in 38 patients, and the median time was 30 (1-366) days after delivery. Treatment-free remission (TFR) was chosen in 13 patients without DMR loss after delivery. 42.9% (6/14) and 53.8% (7/13) patients regained MMR and DMR, which might mean that the conceiving in DMR for female patients was safer than that in MMR. The median times to regain MMR and DMR were 3 (2–6) months and 6 (1–28) months, respectively.

Although a limited number of patients, our results suggest that short exposure to TKI is promising to normal pregnancy and growth of children, facilitating the balance between TKI treatment and pregnancy.

Abbreviations

TKI	Tyrosine kinase inhibitor
CML	Chronic myeloid leukemia
TFR	Treatment-free remission
DMR	Deep molecular response
MMR	Major molecular response

Acknowledgements
We thank all the patients, their families, and the institutions involved in this study.

Author contributions
YLZ contributed in the data collection, statistical analysis, and writing of the manuscript. HFZ did the data collection and edited the manuscript. JLC, HBD, YRS, LXL and SHM took part in the data collection. YPS and YLZ participated in the study design and manuscript editing. All authors read and approved the final manuscript.

Funding
This work was supported by Henan provincial Medical Science and Technology Research Project (232102311143, YL. Zu), Provincial and Ministry Joint Co-construction Project of Henan Medical Science and Technology Research Plan (SBGJ202103034, YL. Zu).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of the Affiliated Cancer Hospital of Zhengzhou University. Written informed consent was secured from all participating patients.

Consent for publication
All patients signed written informed consent for treatment, data collection and usage of data for clinical research in accordance with modified Declaration of Helsinki.

Competing interests
The authors declare no competing interests.

Received: 8 July 2024 / Accepted: 30 August 2024
Published online: 11 September 2024

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