Review Article

Management of chronic myeloid leukemia (CML) in pregnant women: a comprehensive literature review

Tala Najdi[1]^, Toufic Zeidan[1], Nizar El Bcherawi[2], Joyce Labaky[2], Hampig Kourie[1]^

[1]Department of Hematology-Oncology, Faculty of Medicine, Saint Joseph University and Hotel Dieu de France University Hospital, Beirut, Lebanon; [2]Saint Joseph University and Hotel Dieu de France University Hospital, Beirut, Lebanon

Contributions: (I) Conception and design: T Najdi, T Zeidan; (II) Administrative support: H Kourie; (III) Provision of study materials or patients: T Najdi; (IV) Collection and assembly of data: T Najdi, N El Bcherawi, J Labaky; (V) Data analysis and interpretation: T Najdi, T Zeidan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Tala Najdi, MD. Department of Hematology-Oncology, Faculty of Medicine, Saint Joseph University and Hotel Dieu de France University Hospital, Beirut, Lebanon. Email: tala.najdi@net.usj.edu.lb.

Background and Objective: The occurrence of chronic myeloid leukemia (CML) during pregnancy poses a complex presentation, encompassing risks to both the maternal host and the developing fetus, resulting from the disease process and its therapeutic interventions. The management of this dual concern entails a contentious approach, compounded by inconclusive outcomes from preceding studies. The aim of this review is to synthesize a robust framework for an optimal approach to addressing CML in the context of pregnancy.

Methods: In this comprehensive literature review, we systematically examined peer-reviewed articles published in reputable academic journals.

Key Contents and Findings: Pregnancy in patients diagnosed with CML can proceed if the CML is in the chronic phase and on the way to achieving major molecular response (MMR). Treatment risks, CML progression, and complication should be discussed, with treatment becoming necessary when risks become significant. Leukapheresis is limited in reducing white blood cell count temporarily. Interferon (IFN) is the safest option during the first trimester. Previous studies advised against tyrosine kinase inhibitor (TKI) use before 15 weeks, but recent research suggests potential use after organogenesis with careful risk-benefit analysis. Dasatinib isn't recommended during pregnancy due to limited safety data. Decision-making varies based on treatment response and risks, with discontinuation leading to potential complications and continuing treatment leading to some fetal malformations. TKI discontinuation remains recommended if MMR achieved. The decision to stop TKI treatment involves continuous monitoring factors like relapse and recurrence.

Conclusions: While potent treatments like TKIs are essential, their adverse effects complicate their use in pregnant individuals. The use of TKIs and other possible treatments of CML during pregnancy has its own accepted indications and limitations. This review of literature aids hematologic oncologists in managing CML during pregnancy.

Keywords: Chronic myeloid leukemia (CML); pregnancy; tyrosine kinase inhibitors (TKIs); management; treatment

Received: 12 September 2023; Accepted: 24 November 2023; Published online: 09 January 2024.
doi: 10.21037/aob-23-34
View this article at: https://dx.doi.org/10.21037/aob-23-34

^ ORCID: Tala Najdi, 0009-0004-3090-127X; Hampig Kourié, 0000-0002-2502-5402.

Introduction

Background

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the overproduction and growth of mature granulocytes. The development of CML is linked to a translocation between chromosomes 9 and 22, known as t(9;22) resulting in the fusion of two genes: *BCR* and *ABL1*.

It tends to affect males slightly more than females with a yearly occurrence estimated to be between 1 to 2 cases per 100,000 people according to the national cancer institute (1) and can occur in approximately 10% of leukemia cases associated with pregnancy (2).

Tyrosine kinase inhibitor (TKI) therapy is the standard treatment for CML. TKIs are successful in managing CML for long periods of time. Other treatment options include immunotherapy [interferon (IFN)], hydroxyurea, chemotherapy, and donor stem cell transplantation.

Previous studies report the teratogenic effects of TKI and others suggested birth complications among mothers with CML. Managing CML during pregnancy poses a challenge in balancing treatment-associated risks to the fetus with potential benefits of the treatment to the mother.

Objectives

It is very important to consider which therapeutic approaches are safe during pregnancy and which are to be avoided. While there have been discussions on this topic in the literature, few review articles specifically address this topic.

It should be a subject of careful consideration because in contrast to other leukemias, treatment of this disease is lifelong and many patients plan to become pregnant while on treatment (3). Currently, there is no consensus or established guideline regarding the optimal management for cases involving pregnancy. Here we present a review article on the best practice approach to consider. We present this article in accordance with the Narrative Review reporting checklist (available at https://aob.amegroups.com/article/view/10.21037/aob-23-34/rc).

Methods

A review of literature of the management of CML was performed in this study to determine the best approach to consider for pregnant women with CML already started on treatment.

The inclusion criteria of the research included peer reviewed journals (*Journal of Hematology and Oncology*, *Leukemia and Lymphoma Journal*), clinical trials, case reports and other expert opinions. Exclusion criteria were studies concentrating solely on the fertility implications TKI treatment in pre-pregnant women and studies restricted to evaluating pregnancy outcomes exclusively in male patients subjected to TKI therapy.

Electronic sources including PubMed, MEDLINE, were mostly looked at. Studies dated from the last decade were prioritized. The search was completed by manually sorting the management approach in each study according to the treatment option used, the timing of the pregnancy, the status of CML and the outcomes results. Data were then reviewed and analyzed to extract an understandable approach to CML management in the context of pregnancy.

The search strategy is summarized in *Tables 1*,*2*.

Results

After the review of 50 articles, we included 28 articles (*Table 3*) that were the most consistent with the aim of the study. The main question we need to answer today is the possibility and timing of discontinuing TKI in predominantly expectant women.

TKI have changed the treatment course in patients with CML. TKIs function by inhibiting the catalytic activity of the mutant *BCR-ABL1* protein, which plays an essential role in the proliferation, differentiation, and apoptosis of CML cells. Treatment discontinuation is considered one of the main aims of therapy.

The European Leukemia Net (ELN) recommendations (2020 version) (30) and the National Comprehensive Cancer Network (NCCN) guidelines (5) consider TKI discontinuation feasible in selected patients. The criteria for discontinuing TKI in CML patients are known and include consistent use if TKI for a minimum of three years, no prior resistance to a second-generation (2G) TKI that necessitated switching to another, maintaining a stable molecular response (MR) with the achievement of MR4 (*BCR-ABL1* ≤0.01%) and a reliable quantitative polymerase chain reaction (PCR) test detecting at least MR4.5 (31).

Balancing the need for maternal health and fetal safety is important. The potential for teratogenicity (ability to cause birth defects) with TKIs has been addressed and contraindications have been recognized according to labeling and health authority precautions.

Table 1 The search strategy summary

Items	Specification
Date of search	July 5 to August 15, 2023
Databases and other sources searched	PubMed, MEDLINE, NCCN Clinical Practice Guidelines in Oncology, LeukemiaNet expert panel, *Journal of Hematology Oncology*
Search terms used (a detailed search strategy of one PubMed is presented in *Table 2* as an example)	MeSH terms:
	"Tyrosine Kinase Inhibitors" [MeSH]
	"Pregnancy" [MeSH]
	"Chronic myeloid leukemia" [MeSH]
	Free text search terms:
	"tyrosine kinase inhibitors"
	"pregnancy"
	"safety of tyrosine kinase inhibitors in pregnancy"
	"maternal and fetal outcomes"
	"teratogenicity of tyrosine kinase inhibitors"
	"treatment of CML"
	"hydroxyurea in pregnancy"
	Filters:
	Publication date: articles published from January 1, 2014, to August 31, 2023
	Language: English, French
	Peer-reviewed journals
	Study types: original research articles, systematic reviews, and meta-analyses.
Timeframe	2011–present
	5 articles prior to 2011 included, which were deemed crucial for our analysis
Inclusion and exclusion criteria	Inclusion criteria:
	Peer reviewed journals (*Journal of Hematology and Oncology, Leukemia and Lymphoma Journal…*), case reports, clinical trials, expert opinions
	Primary languages used for search: English, French
	Exclusion criteria:
	Studies concentrating solely on the fertility implications TKI treatment in pre-pregnant women
	Studies restricted to evaluating pregnancy outcomes exclusively in male patients subjected to TKI therapy
Selection process	The selection process was conducted by the authors of this article. Each reviewer assessed the eligibility of articles based on the inclusion and exclusion criteria
	Disagreements about a selected article were resolved by the consensus of the majority

NCCN, National Comprehensive Cancer Network; CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor.

Studies addressing the teratogenicity of TKIs

Studies by Pye *et al*. have reported that congenital risks occurred mostly when imatinib was used during organogenesis. Even if most pregnancies exposed to imatinib are likely to have a safe outcome, there remain potential fetal malformations risk such as skeletal and cardiovascular abnormalities (6). The effect of TKI use held the highest risk in the first trimester. In total of 70% of patients receiving TKI in the first trimester and 26% from the first to third trimester throughout their pregnancy, 12

Table 2 Detailed search strategy for PubMed database

Search query	Terms/keyword used
Search terms for the main topics	
Tyrosine kinase inhibitors	"Tyrosine kinase inhibitors"
Pregnancy	"Pregnancy"
Chronic myeloid leukemia	"Chronic myeloid leukemia"
Search operators and connectors	
Boolean AND	AND
Parentheses for grouping	()
Final search query	("Tyrosine kinase inhibitors" AND "Pregnancy" AND "Chronic myeloidleukemia")

pregnancies resulted in fetal abnormalities; of these there were 8 live births, 1 stillbirth, and 3 terminations.

In a recent observational study on conception and pregnancy in patients with CML, 204 patients were exposed to imatinib, and 180 were reported in literature. Of those with known outcomes, 50% of deliveries were normal and 28% underwent elective terminations. Of the total of 12 infants in whom abnormalities were describes, 3 were complex malformations of concern (7).

Dasatinib has also been found to be harmful to the fetus during both early (first trimester) and late (second/third trimester) gestation and should not be recommended for use at any time during pregnancy. In a series studied by Cortes *et al.*, 33% delivered a normal infant; 39% and 17% had an elective due to documented abnormalities or spontaneous abortion; 11% had an abnormal pregnancy involving intrauterine growth retardation (IUGR), prematurity or placental abruption (8).

Rare studies address Bosutinib (Bosulif, Pfizer) and Ponatinib (Iclusig, Aria Pharma). Adverse effects of bosutinib exposure at conception or during pregnancy in humans was included in a recent report from Pfizer's bosutinib safety database with three abortions (two by choice and one due to molar degeneration), one miscarriage unrelated to bosutinib in a series of 16 patients with maternal exposure (9).

After evaluating TKI concentrations in maternal blood, umbilical cord blood, and placental samples collected during labor, Bosutinib was found to have the highest calculated rate of passive placental transfer (10).

Ponatinib was studied in two pregnancies in the same patient while using ponatinib. In both cases the drug was stopped at the first positive pregnancy test (FPT). The first pregnancy led to a miscarriage at 9 weeks (blight ovum), while the second pregnancy resulted spontaneous healthy delivery (11).

Studies resulting in successful pregnancies exposed to TKIs

The US Food and Drug Administration (FDA) states using TKIs in Pregnancy Category D "*there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks*".

Some case reports described successful pregnancy without maternal nor child complications if exposed to imatinib during pregnancy (12).

In a study of 22 pregnancies (male and female included) who gave birth while treated with TKIs, all pregnancies except one were uneventful (13). In another single center experience where twenty-six patients conceived while on TKI, only five ended in miscarriage and of 20 born babies, only one had minor abnormality (14).

As for nilotinib conflicting evidence of congenital abnormalities have been described. Limited studies address the transfer of these drugs through the placenta and thus may support careful introduction of imatinib or nilotinib after placental formation (around the 15^{th}–16^{th} week). In a study described by Etienne *et al.*, a patient's exposure to nilotinib in the first pregnancy resulted in an elective abortion after the identification of an omphalocele in the third month (32).

In a study by Conchon *et al.*, a non-eventful pregnancy was reported in a patient with CML who became pregnant two years after a treatment with nilotinib 400 mg orally b.i.d. The unplanned pregnancy was chosen to be continued so nilotinib was stopped until delivery. There were no

Table 3 Articles reviewed

Study	Authors	Type	Publication year
Maternal and perinatal outcomes in pregnant women with leukemia (4)	Nomura RMY *et al.*	Retrospective study	2011
How I treat leukemia during pregnancy (3)	Milojkovic D *et al.*	Review of literature	2014
Chronic Myeloid Leukemia, NCCN Clinical Practice Guidelines in Oncology (5)	Deininger MW *et al.*	Guidelines and recommendations	2020
The effects of imatinib on pregnancy outcome (6)	Pye SM *et al.*	Retrospective study	2008
Observational study of conception/pregnancy in adult patients with chronic myeloid leukemia (CML) treated with tyrosine kinase inhibitors (7)	Malattie E *et al.*	Observational study	2022
The impact of dasatinib on pregnancy outcomes (8)	Cortes JE *et al.*	Pharmacovigilance database review	2015
Pregnancy outcomes in patients treated with bosutinib (9)	Cortes JE *et al.*	Study analysis	2020
Placental transfer of tyrosine kinase inhibitors used for chronic myeloid leukemia treatment (10)	Chelysheva E *et al.*	Observational study	2018
Chronic myeloid leukemia and pregnancy (11)	Abruzzese E *et al.*	Review article	2021
Imatinib use during pregnancy and breast feeding: a case report and review of the literature (12)	Ali R *et al.*	Case report	2009
Outcomes of the pregnancies with chronic myeloid leukemia in the tyrosine kinase inhibitor era and literature review (13)	Castillo DR *et al.*	Literature review	2022
Management of chronic myeloid leukemia during pregnancy among patients treated with a tyrosine kinase inhibitor (14)	Assi R *et al.*	Single center study	2021
Two successful pregnancies in a woman with chronic myeloid leukemia exposed to nilotinib during the first trimester of her second pregnancy (15)	Conchon M *et al.*	Case study	2009
Delivery of two normal twins exposed to imatinib and nilotinib during the first trimester of pregnancy in a woman with chronic myeloid leukemia (16)	Mseddi SH *et al.*	Case report	2012
A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs (17)	Rea *et al.*	Randomized study	2021
Exposure to hydroxyurea during pregnancy: a case series (18)	Thauvin-Robinet C *et al.*	Case series	2001
Management of chronic myeloid leukemia in the setting of pregnancy: when is leukocytapheresis appropriate? (19)	Staley EM *et al.*	Case report and review of the literature	2018
Chronic myelocytic leukemia in pregnancy: report of a case treated with leukapheresis (20)	Broccia G *et al.*	Case report	1984
Chronic myeloid leukemia prognosis and therapy: criticisms and perspectives (21)	Russo D *et al.*	Review manuscript	2020
Risks and challenges of CML management during pregnancy (22)	Chelysheva E *et al.*	Report	2019
The argument for using imatinib in CML (23)	Claudiani S *et al.*	Manuscript report	2018
Kinetics of the leukemic clone in patients with chronic myeloid leukemia during pregnancy (24)	Chelysheva E *et al.*	Retrospective review	2018
Discontinuation of dasatinib in patients with chronic myeloid leukaemia who have maintained deep molecular response for longer than 1 year (DADI trial) (25)	Imagawa J *et al.*	Multicenter phase 2 study	2015
Pregnancy among patients with chronic myeloid leukemia treated with imatinib (26)	Ault P *et al.*	Retrospective study	2006
Treatment-free remission in chronic myeloid leukemia: can we identify prognostic factors? (27)	Saifullah HH and Lucas CM	Review article	2021
A case report using leukapheresis and literature review (28)	Yellu M *et al.*	Case report	2015
A systematic review of the fetal safety of interferon alpha (29)	Yazdani Brojeni P *et al.*	Systematic review	2012

obstetrical nor malformation in the neonate observed (15). Another uneventful pregnancy with a delivery of a healthy newborn was reported by Alizadeh *et al.* when the use of nilotinib was considered from the time of conception and continuously. One more successful outcome included a 9 weeks exposure to nilotinib reporting the delivery of two healthy twins (16,33).

In 2021, FDA approved asciminib in chronic phase of CML in adults previously treated with more than 2 TKIs but there are no available data on this drug regarding its use in pregnant women (17). Until then, its use is not recommended.

After placental formation and crucial fetal organ development are complete (around 15–16 weeks), selective reintroduction of specific TKIs (such as imatinib or nilotinib) may be considered in certain cases, following clear discussions regarding the risks and benefits.

The largest study of pregnancies in female patients with CML was presented in the ELN (European LeukemiaNet). This database points out the consideration and relative safety of using TKI in pregnancy.

Of 182 patients who were exposed to TKIs, 141 (77%) were treated with imatinib, and 41 (23%) received second or third generation TKIs. TKIs use was interrupted in the first trimester when pregnancy declared (around the 4^{th}–5^{th} week of gestation). Resuming treatment during the 2^{nd}–3^{rd} trimester was done in 82 pregnancies, following the formation of the placenta. Treatment strategies involved the use of imatinib in 33 cases (40%) and nilotinib in seven cases (9%). Imatinib was continued during pregnancy in 13 cases (16%). In results, four congenital abnormalities were noted (1.7%): one case of polydactyly, one case of hypospadias (1 case), and non-closed foramen ovale of the interatrial septum in two cases. Thirteen children exposed to imatinib or nilotinib in late pregnancy ended in low birth weight (34). None of the abnormalities were severe or life-threatening.

Alternative treatment options to TKIs

In cases where the use of TKI in pregnant women are prohibited or not advisable, other treatment options may be considered.

For instance, hydroxyurea is another option used for the treatment of CML in the phase of significant leukocytosis and thrombocytosis and systemics symptoms (31). Thauvin-Robinet *et al.* studied the effect of hydroxyurea during pregnancy and described a rare teratogenic effect. Of 50 cases, there were two intra-uterine fetal death (IUFD), nine cases of premature delivery, and three malformations cases. Pre-eclampsia was a notable risk if hydroxyurea was taken in the second and third trimester (18).

Leukapheresis is described in limited previous studies. A review by Staley *et al.* reported a case of CML described by Strobl *et al.* in a pregnant woman who was treated with leukapheresis that led to a drop in the patient's white blood cell count (WBC) dropped from 242,000/μL to 19,300/μL and remained stable to time of delivery (19). Broccia *et al.* (20) and Ali *et al.* (35) described this treatment without any adverse effects on the patient and fetus. Rare recent data is available regarding the consequences associated during pregnancy (15).

During pregnancy, IFN-α remains the safest therapeutic option is considered safe for use in pregnant women as it is not detectable in fetal blood (13). The mechanism of action of IFN includes immune activation and selective targeting of CML stem cells. Treatment with IFN has been shown to result in a reduction of the Philadelphia chromosome-positive (Ph+) in around 30% of patients (21). The use of IFN was restricted to patients without complete hematologic response before the 15^{th} week. All newborn babies were healthy without congenital abnormalities (22).

In a series of 12 pregnancies with *BCR-ABL*-positive leukemia diagnosed during pregnancy or decided to conceive children and become pregnant while on TKI, whose leukemia was managed with IFN-α, all children had normal growth and development and all women remained in an hematological response (36).

In another case report, a successful pregnancy and delivery was described in a patient treated with imatinib who was in complete remission and had to stop TKI and replaced it with IFN-α for the rest of the pregnancy (37). However, its effectiveness may be limited by the slow time it takes to achieve a response. To address this, a polyethylene glycol molecule has been attached to IFN-α to prolong its half-life and reduce the likelihood of an immune response.

The resulting modified form is called pegylated IFN-α (PegIFNα), which is available commercially as PegIFNα-2a (Pegasys) and PegIFNα-2b (PegIntron). However, pegylated IFN has been described in some studies to have a small risk of toxicity due to polyethylene glycol.

Management and monitoring of pregnant patients with CML

The two main factors to consider for the management of pregnant patients with CML are the timing of the treatment

and the MR. According to the international scale deep MR (DMR) is considered as *BCR-ABL* ≤0.01%, major MR (MMR) as *BCR-ABL* >0.01% and ≤0.1% and MR2 as *BCR-ABL* >0.1% and ≤1%.

In the case of a patient who hasn't reach MMR (no MR2 or *BCR-ABL* >1%) while on treatment, continuation of conception is generally not recommended due to the risk of fetal abnormalities. Patients who have been on TKI for more than three years can either be considered ideal candidate for discontinuation of TKI and treatment free remission (TFR) and continue the pregnancy or possible candidate if despite prolonged TKI exposure have not achieved DMR. Patients who have been in DMR (MR4 or better) for >12–24 months can be considered for TFR and thus eligible for discontinuation of TKI without risk (23).

NCCN guidelines recommended monthly monitoring of MR for the first year after discontinuation of TKIs, then every six weeks for the second year, and every 12 weeks for the next year. In pregnant patients the recommendations for monitoring include *BCR-ABL* levels or relapse kinetics every four weeks. Once TKI are restarted after the first trimester, monitoring CBC monthly and *BCR-ABL* every 1–3 months is indicated (37).

The patient who conserve MMR can give birth and a personalized plan follow-up is required (38).

Outcomes after TKI interruption in pregnancies

Now we explore the studies regarding the prediction factors of relapse after TKI interruption and the assessment of treatment efficacy and disease progression.

DMR or a minimum duration of MMR of 3.5 years were found to be significantly associated with the maintenance of MMR during pregnancy (39). TFR monitoring and TKI discontinuation is attempted for a TKI treatment of more than 3–4 years for second generation TKIs or >5 years for imatinib. *BCR-ABL* transcript levels should be monitored around week 15, and if they rise above 1–10%, TKI therapy may be considered, with a preference for imatinib.

The largest databases of CML outcome after TKI interruption in pregnancies are those of GIMEMA and the ELN previously described and were presented at ASH 201820 and EHA 2019.

In the presentation of the 2018 annual meeting of the European Hematology association, in a series of 49 patients all TKI were discontinued after pregnancy until the 15th week of pregnancy. Imatinib and nilotinib were reintroduced in patients with no CHR or MR2 loss.

In the GIMEMA database, of 56 female pregnancies known to have CML, 27 were in DMR, 19 (70%) delivered without the use of TKI, indicating a treatment free pregnancy (TFP) status (40).

Eleven were in MMR, while eight patients with high tumor burden (≤ MR2 at time of pregnancy) all required therapy during pregnancy. Treatment generally was attempted upon the loss of MMR. To note, none of the patients lost CHR. All patients stopped TKI treatment when pregnancy was discovered (3–6 weeks' gestation). TKIs were reintroduced in four patients, two with imatinib, and two nilotinib, after >20 weeks. All deliveries were successful without complications in either the mothers or the developing children.

The kinetics of rise of the kinetics wasn't correlated to the MMR status in this study. But interestingly the *BCR-ABL* doubling time was longer in pregnant than non-pregnant patients. Results were described for 19 patients with MMR loss in 12 (68%) and for 28 in ≥ MR4 less loss of MMR (39%, 11 cases) was marked. Because the highest risk of relapse is within 3–6 months generally, good monitoring is recommended after discontinuation. The median time from MMR loss to delivery was around five months, allowing such cases to deliver without therapy (24).

Stopping TKI is feasible according to many studies (41). For example, in the DADI trial discontinuing dasatinib in 63 pregnant patients, 30 patients maintained DMR. The estimated overall treatment-free remission was 49% (95% confidence interval: 36–61%) at 6 months. Even in patients with relapse, 88% regained DMR within 3 months (25).

In a study involving a total of 17 patients diagnosed with CML who had achieved at least MMR through prior treatment with imatinib (n=13) or nilotinib (n=4), we attempted discontinuation of TKI therapy. Among these patients, TKI therapy was interrupted 6 weeks prior to conception (range, 2–15 weeks) in 4 patients, while in 13 patients, it was ceased at a gestational age of 4 weeks (range, 2–5 weeks) after confirmation of pregnancy. Of these patients, 16 experienced uneventful deliveries, with only 1 patient encountering a spontaneous abortion (39).

In another report on 19 pregnancies who were treated with imatinib, and treatment interrupted at the recognition of pregnancy, all except three spontaneous abortions and one elective one, were uneventful. Among those patients five of nine lost CHR and six presented an increase in Philadelphia chromosome-positive metaphases but after 18 months of resuming imatinib eight presented a cytogenetic response (26).

In the single centered experience mentioned ahead, of seven women who lost response after discontinuing TKI during treatment all but two resumed TKI and regained responses. Seven women involved in nine planned pregnancies discontinued TKI prior to conception; three lost responses during pregnancy. Only five patients resumed therapy after delivery (14).

Relapse percentage is not predicted and MMR loss is evaluated around 40–60% (27). Cumulative incidence (CI) of MMR loss at 6 and 12 months after TKI cessation was 57% and 66%, and it is noted that CI of MMR recovery at 6 and 12 months after TKI restart, was 50% and 75% (24).

Discussion

After reviewing the results of these studies, we attempt to break down the management of CML during pregnancy into three different scenarios.

The management of CML in women on therapy who becomes pregnant

In pregnant patients who have been on TKI therapy for less than 3 years, and thus is less likely to have achieved a sustained MMR or deeper response (no MR2 or *BCR-ABL* >1%), they usually present with high residual leukemia response and there is a significant risk of losing MR, interruption of treatment results in possible hematologic or cytogenetic relapse. Whenever no MMR is achieved pregnancy interruption is suggested. In the case of a patient insisting on continuing pregnancy patients should be informed about the treatment risk but also the progression and complications of CML and when those risks become significant, treatment is deemed necessary. Some solutions were presented in many studies about substituting TKI with IFN during the first trimester. According to the previously mentioned studies, using IFN can be considered to control the disease and to avoid congenital abnormalities.

IFN during the first trimester is attempted and considering TKI after the 15th week. IFN is considered the safest option for the fetus and is generally used during the first trimester without putting the baby at risk of congenital malformations. IFN has previously undergone investigation for alternative therapeutic applications, such as in the context of hepatitis B, C and essential thrombocytopenia (ET). These investigations provide support for women who are undergoing IFN treatment to proceed with their pregnancies. The use of PegIFNα during pregnancy has insufficient data, so caution is advised.

Dasatinib should not be used at any time during pregnancy. We think the restriction of dasatinib is more recommended because of rare use of this treatment in CML patients and lack of multiple studies to be informed of the possible women and fetal risks. Even though safety data in mid-to-late pregnancy from large studies are lacking, and this conclusion is not universally accepted by experts.

The studies mentioned do not suggest a dosage reduction if TKIs are continued specifically for pregnancies. In one study, five out of seven pregnant patients receiving nilotinib treatment had their dosages reduced to 400 mg daily (37). Dose reduction may be a consideration in certain cases, but it should be primarily for the usual reasons like intolerance, side effects, or toxicities, rather than solely due to pregnancy.

Patients who have been on TKI for more than three years and pregnant can either be considered ideal candidate for discontinuation of TKI and TFR and continue the pregnancy or possible candidate if despite prolonged TKI exposure have not achieved DMR.

The decision to discontinue treatment for CML during pregnancy is a complex matter that has not been extensively studied. Some patients may not meet the criteria for discontinuing treatment during pregnancy but should be offered discontinuation given the risk faced with TKI in pregnancy. A personalized approach is necessary, considering many factors such as timing of diagnosis, treatment, and MR levels.

Planning the management of CML in the woman on therapy who wants to become pregnant

In the case of a patient who hasn't reach MMR (no MR2 or *BCR-ABL* >1%) while on treatment, the patient should be managed as refractory and offered another TKI, so the patient should be deferring immediate pregnancy planning until a later date.

The goal is to achieve a stable and DMR before pregnancy. The decision-making process is straightforward. However, for patients who have reached MMR, the decision becomes more complex. Because of the described side effects from TKI exposure, risk/benefit of continuing and discontinuing TKIs must be carried out personally with careful counseling.

Previous studies recommended a strict avoidance of TKI during pregnancy due to described teratogenic effect especially before the 15 weeks. But recent studies consider

possible use of TKI especially after organogenesis. This decision should be attempted after careful discussion about the risk and benefits for both the mother and the fetus.

For some pregnant women, discontinuing the treatment may mead to loss of molecular, cytogenetic, or hematologic response and progression of the disease added to the increasing risk of abnormality of coagulation already in the pregnancy and the course of the pregnancy including placental insufficiency, intrauterine growth retardation, and an increased risk of intrauterine death. However, attempting to discontinue TKI is possibly considered in previously mentioned studies with the rapid response after restarting TKI treatment.

Even though optimal cut off duration for attempting to stop TKI is indicated, the probability of successful discontinuation varies and knowledge of factors that could influence late relapse or recurrence is still necessary. An additional rationale for considering discontinuation of TKI treatment, which has not yet been addressed, pertains to the potential cost savings associated with such discontinuation.

The management of newly diagnosed CML in pregnancy

The disease diagnosis is in general found in an incidental finding during the routine blood investigations done during pregnancy. There is no specific consensus about what treatment options are considered. Treatment options considered safe during pregnancy include leukapheresis and IFN. Treatment with IFN-α controls the high cell mass in the majority of newly diagnosed patients with CML. However, the degree of response ranges from no 'hematologic' response to complete suppression of the leukemic clone.

Leukapheresis is also another short-term alternative that is used to control the WBC. Leukapheresis can be attempted during any trimester to keep the white blood cell. It was previously used but is considered a temporary procedure that only temporarily reduces the WBC. In this context, hydroxyurea as a treatment may be considered. As mentioned in our results, the treatment is not curative. Using hydroxyurea may result in a clinical and hematological remission until delivery in order to consider the standard treatment of TKI for CML.

If a patient remains in MMR, she can stay off TKI for the whole course of the pregnancy. In the patient present MMR loss during pregnancy, management depends on the level of tumor burden. Many women succeed in reaching conception without losing complete cytogenetic response (CCyR) or complete hematological remission (CHR) and do not require treatment. But if MMR is lost, the choices are identical to those for women presenting in pregnancy.

Limitations

In this review management of CML in pregnant patients, certain limitations highlighting the need for their acknowledgment: limited clinical data mainly due to ethical concerns and conducting clinical trials involving pregnant women, the small number of pregnant women with CML and the absence of standardized guidelines making difficult to reach a definite consensus. CML is an heterogenous disease with different stages, patient characteristics, and treatment approaches. Limited follow-up periods, lack of prospective studies, and the description of TKI teratogenic effects mainly in the animal population, are considered another limitation. Moreover, effective management of CML necessitates collaboration of a multidisciplinary team and impact the objective quality of results.

Nevertheless, recognizing these limitations is crucial for analyzing and applying the result of this study to practical use. Despite these challenges, more research and individualized approach to every patient remain crucial for enhancing results.

Conclusions

Drawing from an analysis of existing literature, a divergence of perspectives persists regarding the optimal management strategy for CML during pregnancy. Managing CML in pregnant women remain and is a multidisciplinary approach. Collaboration between hematologists, oncologists, and obstetricians is mandatory.

In the options of CML therapeutics, the significance of potent agents like TKIs has been underscored. However, these agents bring forth a constellation of adverse effects, which poses a particular challenge when administered to the delicate demographic of pregnant women. Dasatinib is contraindicated for usage at any point during pregnancy due to potential risks (10). In contrast, alternative TKIs as for nilotinib or imatinib may be contemplated for administration following the 15th week of gestation. Among the older therapeutic choices, IFN and hydroxyurea are considered safe during pregnancy, but their efficacy is comparatively less pronounced.

In instances where CML is well-controlled, a sustained treatment response is deemed safe grounds for discontinuing TKI therapy, irrespective of the patient's

pregnancy status. For pregnant individuals yet to achieve a therapeutic response, attaining a MMR is advocated over embarking on pregnancy and deferring conception to a later juncture.

Patients who have attained an MMR are advised to temporarily suspend TKI treatment. Previous investigations suggest the potential for MMR loss yet underscore the feasibility of treatment response restoration upon reinitiating therapy. The most ambiguous side of management emerges among pregnant women who have realized an MMR below the threshold of 2; here, the decision whether to interrupt TKI therapy or transition to IFN, particularly during the initial trimester, represents a clinical challenge.

Vigilant monitoring remains paramount, both prior to and after the cessation of TKI therapy during pregnancy. Equally significant is engaging in comprehensive discussions with the patient concerning the potential complications of continuing or discontinuing treatment throughout all phases of gestation to aid her in making the best-informed decision.

This comprehensive review serves as a pivotal resource for hematologic oncologists, equipping them with informed strategies for addressing CML in pregnant patients. A recent milestone describes the use of a novel agent, classified as a Specifically Targeting the ABL Myristoyl Pocket (STAMP) inhibitor, by the US FDA in 2021 for individuals with CML. Subsequent investigations are necessary to emphasize the safety profile of this novel agent during pregnancy.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Fadi Haddad) for the series "Chronic Myeloid Leukemia" published in *Annals of Blood*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://aob.amegroups.com/article/view/10.21037/aob-23-34/rc

Peer Review File: Available at https://aob.amegroups.com/article/view/10.21037/aob-23-34/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://aob.amegroups.com/article/view/10.21037/aob-23-34/coif). The series "Chronic Myeloid Leukemia" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Surveillance, Epidemiology, and End Results Program [Internet]. SEER. [cited 2023 Aug 20]. Available online: https://seer.cancer.gov/index.html
2. Clinical manifestations and diagnosis of chronic myeloid leukemia - UpToDate [Internet]. [cited 2023 Jul 15]. Available online: https://ezproxy.usj.edu.lb:2071/contents/clinical-manifestations-and-diagnosis-of-chronic-myeloid-leukemia?search=CML%20prevalence%20&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
3. Milojkovic D, Apperley JF. How I treat leukemia during pregnancy. Blood 2014;123:974-84.
4. Nomura RMY, Igai AMK, Faciroli NC, et al. Maternal and perinatal outcomes in pregnant women with leukemia. Rev Bras Ginecol Obstet 2011;33:174-81.
5. Deininger MW, Shah NP, Altman JK, et al. Chronic Myeloid Leukemia, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2020;18:1385-415.
6. Pye SM, Cortes J, Ault P, et al. The effects of imatinib on pregnancy outcome. Blood 2008;111:5505-8.
7. Gruppo Italiano Malattie EMatologiche dell'Adulto. Observational Study of Conception/Pregnancy in Adult Patients With Chronic Myeloid Leukemia (CML) Treated With Tyrosine Kinase Inhibitors [Internet].

clinicaltrials.gov; 2022 Jan [cited 2023 Aug 7]. Report No.: NCT01752062. Available online: https://clinicaltrials.gov/study/NCT01752062
8. Cortes JE, Abruzzese E, Chelysheva E, et al. The impact of dasatinib on pregnancy outcomes. Am J Hematol 2015;90:1111-5.
9. Cortes JE, Gambacorti-Passerini C, Deininger M, et al. Pregnancy outcomes in patients treated with bosutinib. Int J Hematol Oncol 2020;9:IJH26.
10. Chelysheva E, Turkina A, Polushkina E, et al. Placental transfer of tyrosine kinase inhibitors used for chronic myeloid leukemia treatment. Leuk Lymphoma 2018;59:733-8.
11. Abruzzese E, Trawinska MM, de Fabritiis P. Chronic Myeloid Leukemia and Pregnancy: "Per Aspera Ad Astra." Clinical Lymphoma Myeloma and Leukemia. 2021;21:S153-5.
12. Ali R, Ozkalemkas F, Kimya Y, et al. Imatinib use during pregnancy and breast feeding: a case report and review of the literature. Arch Gynecol Obstet 2009;280:169-75.
13. Castillo DR, Park D, Mehta A, et al. Outcomes of the Pregnancies with Chronic Myeloid Leukemia in the Tyrosine Kinase Inhibitor Era and Literature Review. Hematol Rep 2022;14:45-53.
14. Assi R, Kantarjian H, Keating M, et al. Management of chronic myeloid leukemia during pregnancy among patients treated with a tyrosine kinase inhibitor: a single-Center experience. Leuk Lymphoma 2021;62:909-17.
15. Conchon M, Sanabani SS, Bendit I, et al. Two successful pregnancies in a woman with chronic myeloid leukemia exposed to nilotinib during the first trimester of her second pregnancy: case study. J Hematol Oncol 2009;2:42.
16. Mseddi SH, Kallel F, Amouri H, et al. Delivery of two normal twins exposed to imatinib and nilotinib during the first trimester of pregnancy in a woman with chronic myeloid leukemia. Journal of Hematological Malignancies 2012;2:74.
17. Réa D, Mauro MJ, Boquimpani C, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood 2021;138:2031-41.
18. Thauvin-Robinet C, Maingueneau C, Robert E, et al. Exposure to hydroxyurea during pregnancy: a case series. Leukemia 2001;15:1309-11.
19. Staley EM, Simmons SC, Feldman AZ, et al. Management of chronic myeloid leukemia in the setting of pregnancy: when is leukocytapheresis appropriate? A case report and review of the literature. Transfusion 2018;58:456-60.
20. Broccia G, Casula P, Andria M. Chronic myelocytic leukemia in pregnancy: report of a case treated with leukapheresis. Tumori 1984;70:371-4.
21. Russo D, Garcia-Gutierrez JV, Soverini S, et al. Chronic Myeloid Leukemia Prognosis and Therapy: Criticisms and Perspectives. J Clin Med 2020;9:1709.
22. Chelysheva E, Turkina A. Risks and challenges of CML management during pregnancy: Looking for a balanced decision. Eur J Haematol 2019;102:378-9.
23. Claudiani S, Apperley JF. The argument for using imatinib in CML. Hematology Am Soc Hematol Educ Program 2018;2018:161-7.
24. Chelysheva E, Apperley J, Abruzzese E, et al. Kinetics of the Leukemic Clone in Patients with Chronic Myeloid Leukemia during Pregnancy. Blood 2018;132:4254.
25. Imagawa J, Tanaka H, Okada M, et al. Discontinuation of dasatinib in patients with chronic myeloid leukaemia who have maintained deep molecular response for longer than 1 year (DADI trial): a multicentre phase 2 trial. Lancet Haematol 2015;2:e528-35.
26. Ault P, Kantarjian H, O'Brien S, et al. Pregnancy among patients with chronic myeloid leukemia treated with imatinib. J Clin Oncol 2006;24:1204-8.
27. Saifullah HH, Lucas CM. Treatment-Free Remission in Chronic Myeloid Leukemia: Can We Identify Prognostic Factors? Cancers (Basel) 2021;13:4175.
28. Yellu M, Pinkard S, Ghose A, et al. CML in pregnancy: A case report using leukapheresis and literature review. Transfus Apher Sci 2015;53:289-92.
29. Yazdani Brojeni P, Matok I, Garcia Bournissen F, et al. A systematic review of the fetal safety of interferon alpha. Reprod Toxicol 2012;33:265-8.
30. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia 2020;34:966-84.
31. Overview of the treatment of chronic myeloid leukemia - UpToDate [Internet]. [cited 2023 Jul 16]. Available online: https://ezproxy.usj.edu.lb:2071/contents/overview-of-the-treatment-of-chronic-myeloid-leukemia?search=why%20discontinue%20TKI%20in%20pregnancy%20CML&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#
32. Etienne G, Milpied B, Réa D, et al. Guidelines for the management of nilotinib (Tasigna)-induced side effects in chronic myelogenous leukemia: recommendations of French Intergroup of CML (Fi-LMC group). Bull Cancer 2010;97:997-1009.
33. Alizadeh H, Jaafar H, Rajnics P, et al. Outcome of

pregnancy in chronic myeloid leukaemia patients treated with tyrosine kinase inhibitors: short report from a single centre. Leuk Res 2015;39:47-51.
34. Chelysheva E, Turkina A, Rea D, et al. S881 Pregnancy outcome in female patients with chronic myeloid leukemia worldwide: analysis of 305 cases of the European Leukemia Net Registry. HemaSphere 2019;3:395.
35. Ali R, Ozkalemkaş F, Ozkocaman V, et al. Successful pregnancy and delivery in a patient with chronic myelogenous leukemia (CML), and management of CML with leukapheresis during pregnancy: a case report and review of the literature. Jpn J Clin Oncol 2004;34:215-7.
36. Balsat M, Etienne M, Elhamri M, et al. Successful pregnancies in patients with BCR-ABL-positive leukemias treated with interferon-alpha therapy during the tyrosine kinase inhibitors era. Eur J Haematol 2018;101:774-80.
37. Abruzzese E, Mauro M, Apperley J, et al. Tyrosine kinase inhibitors and pregnancy in chronic myeloid leukemia: opinion, evidence, and recommendations. Ther Adv Hematol 2020;11:2040620720966120.
38. Abruzzese E, de Fabritiis P, Trawinska MM, et al. Back to the future: Treatment-free remission and pregnancy in chronic myeloid leukemia. Eur J Haematol 2019;102:197-9.
39. Dou X, Qin Y, Huang X, et al. Planned Pregnancy in Female Patients with Chronic Myeloid Leukemia Receiving Tyrosine Kinase Inhibitor Therapy. Oncologist 2019;24:e1141-7.
40. Abruzzese E, Scortechini AR, Gugliotta G, et al. Gimema Registry of Conception/Pregnancy in Adult Patients Diagnosed with Chronic Myeloid Leukemia (CML) Treated with Tyrosine Kinase Inhibitors (TKIs). Blood 2014;124:1806.
41. Mahon FX. Discontinuation of TKI therapy and 'functional' cure for CML. Best Pract Res Clin Haematol 2016;29:308-13.

doi: 10.21037/aob-23-34
Cite this article as: Najdi T, Zeidan T, El Bcherawi N, Labaky J, Kourie H. Management of chronic myeloid leukemia (CML) in pregnant women: a comprehensive literature review. Ann Blood 2024;9:5.