Pregnancy in Patients With Chronic Myeloid Leukemia

Presented by Ellin Berman, MD

Abstract

Estimates suggest that nearly 30% of patients diagnosed with chronic myeloid leukemia (CML) are aged <49 years, with approximately half being women. For many of these women, childbearing concerns are a major factor as they initiate treatment with tyrosine kinase inhibitors, which are known to be teratogenic. During her presentation at the NCCN 23rd Annual Conference, Dr. Berman identified the challenges in helping women undergoing treatment for CML who want to have children, and emphasized the importance of an individualized and multidisciplinary approach to management. In addition, she encouraged NCCN to create a pregnancy registry of this patient population to enable clinicians to collect firm data to guide clinical decision-making.

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Among the challenges of treating women with chronic myeloid leukemia (CML) who may want to become pregnant is the lack of clear information regarding the dose of tyrosine kinase inhibitors (TKIs) and the exposure time. “The concept of stopping therapy is a relatively new one,” revealed Ellin Berman, MD, Professor of Medicine, Memorial Sloan Kettering Cancer Center, and panel member of the NCCN Guidelines for CML. “There are not, as yet, clear guidelines for who can safely stop therapy,” she told the audience at the NCCN 23rd Annual Conference.

Impact of Response to TKIs

With 4 TKIs currently used in first-line treatment—imatinib, dasatinib, nilotinib, and bosutinib—the question for clinicians managing women with CML who may want to become pregnant is which one to choose. “Many of us would choose a second-generation TKI, such as dasatinib or nilotinib, and more recently bosutinib, because the response is deeper and quicker, and faster response seems to be important,”¹ she stated. “However, all of these TKIs affect a spectrum of targets, which are important for reproduction.”²

Dr. Berman reviewed the types of molecular response to TKI therapy in patients with CML. The optimal response would be a molecular response of a 4.5-log reduction (MR4.5)—defined as BCR-ABL <0.0032 on the International Scale (IS)—which translates to no detectable disease that can be measured. However, Dr. Berman noted that only between 30% to 40% of patients achieve an MR4.5, and that may take up to 4 years of therapy.

As shown in Figure 2, imatinib is the slowest to provide an MR4.5. After 24 months of therapy, the incidence of MR4.5 with imatinib, dasatinib, and nilotinib is 8%, 9%, and 26%, respectively.^{3,4}

Fetal Abnormalities Associated With TKIs

Few data are available regarding the effect of TKIs on the ovaries; however, Dr. Berman shared findings from 2 different studies on fetal abnormalities associated with these agents. The first study by Pye et al⁵ focused on the use of imatinib. Of 180 pregnant women with CML treated with imatinib, the timing of treatment was available for approximately 80% (n=146). During the first trimester, 103 women (71%) received imatinib therapy; during the first and second trimesters, 4 (26%) received imatinib. Approximately one-quarter (n=38) received imatinib throughout pregnancy. The investigators reported 8 cases (5%) of congenital abnormalities, including craniosynostosis, hypoplastic lung, duplex kidneys, hemivertebrae, cerebellar hypoplasia, premature closing of the skull, scoliosis, and cleft palate with polydactyly.

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Dr. Berman has disclosed that she has received consulting fees/honoraria from Bristol-Myers Squibb Company, Novartis Pharmaceuticals Corporation, Pfizer Inc., and Takeda Pharmaceuticals North America, Inc.

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Pregnancy in Patients With CML

Drug	12 mo	24 mo	36 mo	48 mo	60 mo
Imatinib³					
MMR	28%	46%	55%	60%	64%
MR 4.5	3%	8%	13%	23%	33%
Dasatinib³					
MMR	46%	64%	67%	73%	76%
MR4.5	5%	19%	24%	34%	42%
Nilotinib⁴					
MMR	55%	73%	70%	73%	76%
MR4.5	11%	26%	28%	37%	39%

Figure 1. Incidence of major molecular response (MMR) and molecular response of a 4.5-log reduction (MR4.5).

In the second study, 78 pregnant women with CML treated with dasatinib were reported to the drug manufacturer's database.⁶ Of the 46 women (59%) for whom outcomes were available, 8 (17%) had spontaneous abortions (2 with abnormalities) and 18 (39%) had elective abortions (3 with abnormalities).

Limited Long-Term Data on TKI Discontinuation Trials

For women undergoing treatment for CML who want to become pregnant, Dr. Berman explained that there are no clear data on when it is safe to stop therapy. Currently, she is guided by the "stop therapy" trials: to stop therapy, women should have at least MR4, and most trials have used MR4.5 for at least 2 years. "The bulk of data [on discontinuation] are with imatinib, because that's the drug that was

licensed first, and the number of patients is substantial," she reported.

However, she highlighted one preliminary trial (EURO-SKI) that suggested MR4.5 may not be necessary: Mahon et al⁷ demonstrated that patients with a deep molecular response (*BCR-ABL* <0.01% on the IS) had the same recurrence rate as those with MR4.5 (46%).

The 2018 NCCN Guidelines for CML provide a table of limited longer-term follow-up data from TKI discontinuation trials. Based on these studies, Dr. Berman noted, there is a recurrence rate of approximately 55% to 65%. "The time to relapse is consistent within the first 3 to 9 months of stopping therapy." Women who opt to stop TKI therapy after at least 2 years of MR4.5 response should be monitored monthly with quantitative reverse transcriptase–polymerase chain reaction (qRT-PCR), she suggested (Figure 2).

Regarding restarting therapy, the NCCN Guidelines recommend a *BCR-ABL* threshold of >1.0% on the IS. As for other cutoff guides, such as WBC or platelet count, Dr. Berman said "we don't know what cutoff to use. Most patients seem to recover their response quickly when restarted on a TKI, she added.

Natural Option: In Vitro Fertilization

As for the natural option of in vitro fertilization (IVF), Dr. Berman called it a personal decision. "For

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Table 2. Summary of Limited Longer-term Follow-up Data from the TKI Discontinuation Trials						
Study	Treatment prior to discontinuation	No. of patients	Depth and duration of molecular response (MR) required for discontinuation	Trigger to resume TKI therapy	Median duration of follow-up	Treatment-free remission (TFR) rate
STIM ^{116,117}	Imatinib ± interferon	100	MR5.0 for at least 2 years	Loss of MR5.0	77 months	43% at 6 months; 38% at 60 months
TWISTER ¹¹⁸	Imatinib ± interferon	40	MR4.5 for at least 2 years	Loss of MR5.0	42 months	47% at 24 months
HOVON ¹¹⁹	Imatinib + cytarabine	15	MR4.5 for at least 2 years	Loss of MR4.5	36 months	33% at 24 months
A-STIM ¹²⁰	Imatinib ± interferon	80	MR5.0 for at least 2 years	Loss of MMR	31 months	64% at 24 months; 61% at 36 months
KIDS ¹²¹	Imatinib ± interferon	90	MR4.5 for at least 2 years	Loss of MMR	27 months	62% at 12 months; 59% at 24 months
Stop 2G-TKI ¹²²	Dasatinib/Nilotinib (first-line or second-line)	60	MR4.5 for at least 24 months	Loss of MMR	47 months	63% at 12 months; 54% at 48 months
DADI ^{172,173}	Dasatinib (second-line)	63	MR4.0 for at least 12 months	Loss of MR4.0	36 months	44% at 36 months
ENESTFreedom ^{174,177}	Nilotinib (first-line)	190	MR4.5 for 12 months	Loss of MMR	96 weeks	52% at 48 weeks; 49% at 96 weeks

MR5.0: 5-log reduction in *BCR-ABL* levels and undetectable minimal residual disease on qPCR with a sensitivity of ≥4.5-log reduction;
MR4.5: ≤0.0032% *BCR-ABL* IS or ≥4.5-log reduction of *BCR-ABL* and undetectable minimal residual disease on qPCR with a sensitivity of ≥4.5-log reduction;
MR4.0: <0.01% *BCR-ABL* IS; Major molecular response (MMR): ≤0.1% *BCR-ABL* IS.

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Figure 2. Summary of limited longer-term follow-up data from the TKI discontinuation trials from the NCCN Guidelines.

Berman

a woman who wants to get pregnant naturally, she probably has to be off the drug for a minimum of 10 months,” she stated. In her experience, when guiding women who want to stop treatment to become pregnant (perhaps for IVF), she monitors their qRT-PCR monthly. If the patient becomes pregnant, therapy can be resumed when the qRT-PCR is 1.0%.

However, according to Dr. Berman, although IVF “seems a safer option,” it is not always a real alternative for some women. Time off from work, insurance issues, cost, and religious, legal, and cultural restrictions may complicate the matter for many women. “In having worked with numerous women [who want to become pregnant] through IVF, the best [strategy] is good communication among the patient, oncologist, gynecologist, and obstetrician,” she suggested.

Treatment Options During Pregnancy

Well established data regarding fetal and neonatal exposure to TKIs in pregnant women with CML are lacking, and thus caution is warranted. Dr. Berman briefly explored possible treatment options for women with CML during pregnancy. Although hydroxyurea is not indicated during any trimester of pregnancy, leukapheresis is a possibility during the first, second, and third trimesters.⁸ In addition, interferon-alfa is not indicated during the first trimester

but may be considered during the second and third trimesters. As for TKIs, the use of these therapies during the first and second trimesters is not recommended, although they might be a possible option during the third trimester.

How About Men?

Dr. Berman mentioned that men being treated for CML with TKIs might ask about their fertility if their partner is interested in becoming pregnant. They tend to ask (1) what is the effect of TKI therapy on sperm, and (2) whether they have to stop therapy if their female partner wants to become pregnant.

Dr. Berman’s answer to the first question is that TKI therapy seems to have no effect on sperm. However, TKIs do seem to inhibit platelet-derived growth factor and c-kit, she reported, which are important for Leydig cell development, as well as the proliferation, migration, and survival of sperm. According to Dr. Berman, findings on the impact of TKIs in men appear to be consistent: although there is a decrease in testosterone and sperm count, there is no effect on male fertility.^{6,9,10}

As for the second question, Dr. Berman said that men do not need to stop therapy if their female partner wants to become pregnant. “The accumulated data from the drug companies suggest ‘no’; that it’s safe for men to get their partner pregnant,” she added.

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