NCCN Guidelines® Insights
Chronic Myeloid Leukemia, Version 1.2017
Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Chronic Myeloid Leukemia (CML) provide recommendations for the management of chronic-phase and advanced-phase CML in adult patients. The median age of disease onset is 67 years. However, because CML occurs in all age groups, clinical care teams should be prepared to address issues relating to fertility and pregnancy with patients who are of reproductive age at the time of diagnosis. CML is relatively rare in children and there are no evidence-based recommendations for the management of CML in pediatric population. These NCCN Guidelines Insights discuss special considerations for the management of CML during pregnancy and for the management of CML in the pediatric population.

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to NCCN Guidelines for Chronic Myeloid Leukemia
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Chronic Myeloid Leukemia

Disclosure of Relevant Financial Relationships

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NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Management of Chronic Myeloid Leukemia During Pregnancy

Tyrosine kinase inhibitor (TKI) therapy with small molecule inhibitors of BCR-ABL tyrosine kinase (imatinib, dasatinib, and nilotinib) is the standard first-line therapy for patients with newly diagnosed chronic-phase chronic myeloid leukemia (CML). The median age of disease onset is 67 years, but CML occurs in all age groups. The European Treatment and Outcome Study (EUTOS) population-based registry reported that approximately 36.5% of patients are of reproductive age at the time of diagnosis.[1] TKI therapy has significantly reduced the annual mortality rate among patients with CML. With most patients achieving complete cytogenetic response (CCyR) to TKI therapy, CML is now managed as a chronic disease, requiring long-term treatment and supportive care. Recent clinical studies suggest that TKI therapy can be discontinued (with close monitoring) in carefully selected patients who have achieved and maintained a deep molecular response (≥MR4) for 2 or more years.[2–8] In light of these widely publicized trials, more women on TKIs are inquiring about the safety of becoming pregnant. Clinical care teams should be prepared to address issues relating to fertility and pregnancy, as well as counsel these patients about the potential risks and benefits of treatment discontinuation and possible resumption of TKI therapy should CML recur during pregnancy. Referral to a CML specialty center is recommended.

TKI Therapy and Conception

Imatinib, dasatinib, and nilotinib have been shown to be teratogenic and are known to cause embryonic or fetal toxicities in animal studies. There are several case reports in the literature regarding the outcome of pregnancy in patients receiving TKI therapy at the time of conception.[9–22] TKI therapy appears to affect some male hormones at least transiently, but these drugs do not appear to have an effect on fertility in men, nor is the miscarriage or fetal abnormality rate higher in female partners of men on TKI therapy.[14,15,22] The situation is more complex for women, because TKI therapy during pregnancy has been associated with both a higher rate of miscarriage and fetal abnormalities.[16,22] In a study of 180 women exposed to imatinib during pregnancy, Pye et al[16] reported that 50% of pregnancies with known outcome were normal and 10% of pregnancies with known outcome had fetal abnormalities; 18 pregnancies ended in spontaneous abortion. In a study of the outcomes of pregnancy and conception during dasatinib treatment, Cortes et al[22] reported that among 46 women treated with dasatinib, 15 (33%) delivered a normal infant. Elective or spontaneous abortions were reported in 18 (39%) and 8 women (17%), respectively, and 5 women (11%) had an abnormal pregnancy. Fetal abnormalities were reported in 7 cases. Among 33 women fathered by dasatinib-treated men, 30 women (91%) delivered infants who were normal at birth. Although there are no data regarding the outcome of pregnancy in patients receiving bosutinib and ponatinib at time of conception, these agents must be considered unsafe to use in pregnant women.

Discontinuation of TKI Therapy

TKI discontinuation trials have reported recurrence rates of approximately 50% to 60% among patients who stop TKI therapy after having achieved either a complete molecular response (CMR) or deep molecular response (≥MR4), usually within 6 months of treatment cessation, with some relapses noted as early as 1 month off therapy.[2–8] Several factors may help predict relapse (eg, Sokal score, natural killer [NK] cell count, CD4+ regulatory cell count).[3,5,6]

In the STIM trial (the largest discontinuation study reported to date), patients were in CMR for at least 2 years before discontinuation of imatinib.[5,23] At the median follow-up of 65 months, the probabilities of relapse-free and treatment-free survival were 38% and 41%, respectively, at 24 months after discontinuation of imatinib.[5] Resumption of imatinib immediately following relapse resulted in the achievement of undetectable minimal residual disease in almost all patients. In the original report, potential risk factors for relapse included a higher Sokal risk score, shorter duration of imatinib therapy before stopping, and female sex.[23] However, in the updated report, a multivariate analysis (including age, sex, previous treatment with interferon, and duration of treatment) showed that Sokal risk score was the only variable associated with a significant probability of maintaining CMR.[5] The Australasian CML8 (TWISTER) study also required patients to have been in a CMR for at least 2 years before stopping imatinib. At the median follow-up of 42 months, the estimated rate of treatment-free remission at 2 years was 47.1%.[3] Most relapses occurred within 4 months after discontinuation of imatinib, with no relapses beyond 27 months. High Sokal risk score and shorter duration of interferon treatment were associated with increased risk of relapse. In the DADI trial, patients who were taking dasatinib as second-line treatment had maintained a deep molecular remission defined as *BCR-ABL1* 0.0069% IS for more than 1 year before discontinuation of dasatinib.[6] At a median follow-up of 20 months, the estimated overall treatment-free remission rate at 6 months was 49%. In the univariate analysis, prior resistance to imatinib, NK cell counts, γδ+ T-cell count, and CD4+ regulatory T-cell count were identified as predictors of molecular relapse at 12 months. High NK cell counts and low γδ+ T-cell and CD4+ regulatory T-cell counts were significantly associated with treatment-free remission. Of the 63 patients who had stopped dasatinib, 33 (52%) experienced molecular relapses, all within the first 7 months of discontinuation. Resumption of dasatinib resulted in rapid molecular responses in all patients who experienced relapse. Further validation studies are needed to confirm these findings.

Discontinuation of TKI therapy because of pregnancy in women who were not in a CMR has only been reported in 2 small series.[12,24] Ault et al[12] reported 10 women who stopped imatinib because of pregnancy after a median of 8 months of therapy. Of the 9 women who had achieved a complete hematologic response (CHR), 5 lost the response after stopping therapy, and 6 had an increase in Ph-positive metaphases. At 18 months after resuming therapy, all 9 patients had achieved a CHR, but only 3 women achieved a CCyR and none had achieved a major molecular response (MMR). Kuwabara et al[24] reported on the outcomes of 7 women who were not in a CMR at the time imatinib was stopped because of pregnancy, 3 of whom were in an MMR. All 7 women had disease progression. The 3 women who had an MMR at the time imatinib was stopped were able to regain the same response once the drug was restarted, whereas the remaining 4 patients were not. Depending on other factors, such as age, a natural pregnancy may occur months after stopping TKI therapy. Assuming the earliest time a woman could conceive and give birth naturally, without any washout period, is 10 months after stopping her TKI, the likelihood is in the range of 60% that her PCR will become positive if she was in a CMR when she became pregnant and it is even higher if she was not in a CMR when she became pregnant.[12,24]

Planning a Pregnancy

Before attempting pregnancy, women and their partners should be counseled that no guidelines exist regarding how best to monitor CML during pregnancy, nor how best to manage progressive disease should it occur during pregnancy. Conception while on active TKI therapy is strongly discouraged because of the risk of fetal abnormalities.

TKI therapy does not appear to have a deleterious effect on male sperm and the general recommendation is that men who take TKIs do not need to stop therapy if a pregnancy is planned, although experience is limited. Sperm banking can also be performed before starting TKI therapy, although there are no data regarding quality of sperm in untreated men with CML.

In women, because of the risk of miscarriage and fetal abnormalities during pregnancy, TKI therapy should be stopped before natural conception and the patient should remain off therapy during pregnancy. Consultation with a high-risk obstetrician is recommended. Referral to an in vitro fertilization (IVF) center is recommended and, in coordination with the patient's obstetrician, TKI therapy should

be stopped before oocyte retrieval. It is not known how long TKI should be stopped before attempting a natural pregnancy or oocyte retrieval. Compounding the high incidence of disease recurrence off TKI therapy are the significant obstacles that exist for women who choose one of the aforementioned forms of IVF, chief among which is the lack of access to centers that perform the procedure, high costs associated with the drugs and surgical procedures that may not be covered by insurance, costs of embryo/oocyte storage, and access to surrogate programs. Some women may require more than one IVF cycle to obtain enough potentially viable embryos for implantation. In addition, women may need a family medical leave from work to attend IVF appointments. It is also important to note that not all states allow surrogacy.

TKI therapy can be restarted after the baby is born. Women on TKI therapy should also be advised not to breastfeed, because TKIs pass into human breast milk.[25,26] If TKI therapy should be provided during pregnancy, the potential benefit for the mother and the potential risk to the fetus of continuing TKI therapy versus the risk of treatment interruption leading to the loss of optimal disease response must be carefully evaluated on an individual basis before initiation of TKI therapy. Fertility preservation should be discussed with all patients of childbearing age before initiation of TKI therapy.

Monitoring and Treatment During Pregnancy

It is recommended to check monthly peripheral blood via quantitative real-time polymerase chain reaction, and initiate treatment if the *BCR-ABL1* increases to greater than 1.0 % IS. Most of the literature regarding treatment during pregnancy consists of case reports. Koh and Kanagalingam[27] provide the largest review of case reports published to date. Leukapheresis can be initiated for an increasing WBC count, although there are no data that recommend at what threshold this should be started.[27–29] Low-dose aspirin or low-molecular-weight heparin can also be considered for patients with thrombocytosis.[30,31] Interferon-alfa (in wide range of doses: 3–6 million units every other day to 5–8 million units daily) has been shown to be safe during pregnancy, although it has a low rate of molecular response.[27,32–35] Hydroxyurea (in a wide range of doses) is also considered safe during pregnancy.[27,36–38] The potential risk/benefit balance should be carefully evaluated in terms of maternal health and fetal risk before initiation of treatment during pregnancy, especially during the first trimester.

Specific Considerations for Children With CML

CML accounts for less than 3% of all pediatric leukemias. In general, children are diagnosed at a median age of 11 to 12 years, with approximately 10% presenting in advanced phase. Because of its rarity, there are no evidence-based recommendations for the management of CML in the pediatric population. Many pediatric oncologists follow treatment guidelines designed for adult patients. However, clinical presentations and host factors are different between children and adults, and some factors should be considered when treating pediatric patients with CML.[39–41]

Selection of TKI

Imatinib has been evaluated in pediatric patients with newly diagnosed chronic-phase CML in clinical studies.[42–44] It is the only TKI currently approved by the FDA as first-line treatment for children with CML. In the French national phase IV study, 44 patients from age 10 months to 17 years with newly diagnosed chronic-phase CML were treated with imatinib (260 mg/m^2).[43] At a median follow-up of 31 months, a CHR was achieved in 98% of the patients and the estimated progression-free survival (PFS) rate at 36 months was 98%. At 12 months, the rates of CCyR and MMR were 61% and 31%, respectively. The updated results of this trial showed that early molecular response at 3 months (*BCR-ABL1* ≤10% IS) correlated with better PFS and higher rates of CCyR and MMR at 12 months.[44]

Higher-dose imatinib (340 mg/m^2) has also been shown to be effective and well tolerated in children, inducing a high rate of hematologic, cytogenetic, and molecular responses.[45,46] Long-term results of an Italian multicenter study (47 patients with chronic-phase CML) showed that higher dose imatinib (340 mg/m^2) induced CCyR in 91.5% of the evaluable patients at a median time of 6 months.[46] At 12 months, *BCR-ABL1* of 0.1% or less (MMR) and *BCR-ABL1* of 0.01% or less (molecular response) were observed in 66.6% and 33% of patients, respectively. Imatinib has also been effective in children with late chronic-

phase and advanced-phase CML as well as for disease relapse after allogeneic hematopoietic cell transplant (HCT).[47]

Dasatinib has been evaluated in phase I/II studies in the pediatric population with relapsed or refractory CML.[48,49] In a dose-escalation study that evaluated dasatinib (60–120 mg/m^2) in 58 children with relapsed or refractory leukemia, CCyR and MMR were achieved in 82% and 47%, respectively, of patients with imatinib-pretreated chronic-phase CML.[49] After 24 months of follow-up, median CHR and major cytogenetic response durations were not reached. Nilotinib has also been evaluated in a small series of pediatric patients with CML refractory to prior TKI therapy.[50] The efficacy and safety of nilotinib in pediatric patients with newly diagnosed CML are being evaluated in an ongoing phase II trial. Bosutinib and ponatinib[51] have not been tested in children in clinical trials; therefore, there is little information on the safety of these drugs in this population.

Using Prognostic Scores for Risk Stratification

The validity of prognostic scores (eg, Sokal, Hasford, and EUTOS scores) has not been established in the pediatric population.[52–54] For instance, a 10-year-old with CML would have a lower risk of mortality than a 70-year-old patient using the Sokal score if they had the same spleen size and blood cell counts. In an analysis that attempted to validate the 3 prognostic scoring systems in a cohort of 90 children (median age, 12 years), there was a high discordance among the scoring methods.[55] Therefore, it is not recommended to use these scoring systems for risk assessment or to make treatment decisions for children with CML.

Monitoring for Long-Term Side Effects

Children have a much longer life expectancy than adults, and TKI therapy may be needed for many decades; therefore, there is potential long-term morbidity that may not be seen in adults. There are no data available on the cessation of TKI therapy in the pediatric population, and discontinuation of TKI therapy in children is not recommended outside the context of a clinical trial.[56]

A number of studies have reported impaired longitudinal growth in children with CML treated with TKIs.[57–65] It appears that prepubertal children are affected more significantly.[62,65,66] Growth should be monitored closely and a bone age study should be obtained if longitudinal growth is delayed. A dual-energy x-ray absorptiometry scan should be obtained if bone mineral density is decreased on plain radiograph or if there is unprovoked fracture. Further evaluation and referral to an endocrinologist is also warranted.

Immunizations

There are few data on immune function with patients on TKI therapy, and it potentially hinders routine vaccination for children with CML.[67] In general, administration of inactivated killed vaccines to children on TKI therapy is safe, although response may be insufficient as in any immunocompromised patient. A study showed a higher seroconversion rate to H1N1 influenza vaccine in adult patients with CML compared with patients with B-cell malignancies or HCT recipients.[68] Administration of live vaccines during TKI therapy is not recommended in general, although one study showed that varicella vaccine could be safely given to some children with immune deficiency.[69] Live vaccines could be considered after stopping TKI therapy for several weeks in patients with a deep molecular response. In the United States, all required live vaccines are completed by the age of 4 to 6 years (http://www.cdc.gov/vaccines/). Because CML is rarely seen in children younger than this, few patients face this issue. For the annual influenza vaccine, the live attenuated vaccine (nasal spray) should be avoided, and the inactivated killed vaccine (flu shot) should be used for children receiving TKI therapy.

Summary

TKI therapy is the standard of care for all patients with newly diagnosed CML. In most patients with chronic-phase CML responding to TKI therapy, CML is managed like a chronic disease, requiring long-term treatment and supportive care. TKI therapy does not appear to have an effect on male fertility or fetal malformation rate of their partner's pregnancy. However, significant challenges exist for women, because TKI therapy has been associated with fetal abnormalities and spontaneous abortions. Each woman needs to make the decision that fits her best after an in-depth discussion regarding relapse rates off TKI therapy and treatment if needed dur-

ing pregnancy, and clinical care teams should be supportive of her choice, whatever that choice may be. Children have a much longer life expectancy than adults, and TKI therapy may be needed for many decades. Therefore, monitoring for growth and other long-term side effects should be an integral part of management of CML in the pediatric population.

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Posttest Questions

1. Which of the following are identified as predictors of molecular relapse after discontinuation of TKI therapy?
   a. High Sokal risk score
   b. NK killer cell counts
   c. T-cell count (γδ+ or CD4+ regulatory)
   d. All of the above
2. Which of the following is TRUE regarding the management of CML in patients who are of reproductive age?
   a. TKI therapy during pregnancy is associated with both a higher rate of miscarriage and fetal abnormalities
   b. Men who take TKIs do not need to stop therapy if a pregnancy is planned
   c. In women, TKI therapy should be stopped before natural conception
   d. All of the above
3. Which of the following TKIs is currently approved as first-line treatment for children with CML by the FDA?
   a. Imatinib
   b. Dasatinib
   c. Nilotinib
   d. None of the above