

Current Approach to Treating Chronic Myeloid Leukemia

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QUESTIONS

- 1. Which of the following is not an indication for allogeneic hematopoietic stem cell transplantation (HSCT) in patients with chronic myeloid leukemia (CML) in the chronic phase?**
 - (A) Cytogenetic relapse at 18 months after achieving initial hematologic remission
 - (B) First-line treatment in a chronic-phase CML (CP-CML) patient
 - (C) No cytogenetic response at 6 months
 - (D) Partial cytogenetic response at 18 months
 - (E) Presence of T571 mutation in patients who failed to respond to tyrosine kinase inhibitors (TKIs)
- 2. A 42-year-old man previously diagnosed with Philadelphia (Ph) chromosome-positive CP-CML presents for treatment monitoring. Six months ago, the patient was started on imatinib (400 mg/day). At 3-month follow-up, the patient achieved complete hematologic remission. At the current presentation, repeat cytogenetic analysis of the bone marrow is performed, which reveals a decrease in the Ph-positive metaphases from 100% to 20%. However, a novel clonal trisomy 8 abnormality is documented in 5 of 16 Ph-negative metaphases. The bone marrow morphology is normal, and the patient remains in complete hematologic remission. How should this patient be treated?**
 - (A) Change imatinib to dasatinib
 - (B) Continue with imatinib at the same dose
 - (C) Increase imatinib to 800 mg/day
 - (D) Perform allogeneic HSCT as soon as possible
- 3. Which of the following statements best characterizes the side effects associated with nilotinib treatments?**
 - (A) Monitoring of hepatic transaminases is not required because their elevation is extremely rare
 - (B) Neutropenia and thrombocytopenia (grade 3/4) are rare side effects and are present in only 5% of cases
 - (C) Nilotinib has no significant interactions with other drugs
 - (D) Nilotinib therapy is frequently associated with severe fluid retention and pleural effusions
 - (E) QT prolongation can occur with nilotinib therapy, and a baseline electrocardiogram should be obtained prior to starting treatment
- 4. Which of the following statements about monitoring patients receiving imatinib treatment for CP-CML is correct?**
 - (A) After a patient achieves a major cytogenetic response, quantitative fluorescence in situ hybridization analysis should be performed in peripheral blood every 3 months
 - (B) Conventional bone marrow cytogenetic analysis should be performed every 3 months
 - (C) 1-Log increase of *BCR-ABL* transcript levels as determined by quantitative reverse-transcript polymerase chain reaction (qRT-PCR) without achieving major molecular response should prompt the physician to obtain cytogenetic analysis of the bone marrow
 - (D) qRT-PCR for *BCR-ABL* transcript levels is extremely helpful in monitoring patients who have persistent Ph-positive chromosome in bone marrow karyotype analysis

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5. A 32-year-old man with a history of CP-CML that was previously treated with HSCT (matched sibling donor) 3 years ago and who achieved complete cytogenetic and molecular remission presents for his semi-annual follow-up visit. Repeat qRT-PCR analysis of the peripheral blood for *BCR-ABL* transcripts reveals a 2-log increase with respect to his baseline levels. Cytogenetic analysis of the bone marrow aspirate reveals that 5 of the 20 metaphases assessed are Ph-positive. All of the following are potential treatment options for this patient EXCEPT

- (A) Consider a clinical trial
- (B) Order a donor lymphocyte infusion (DLI)
- (C) Repeat qRT-PCR in 3 months to assess if *BCR-ABL* transcript levels increase
- (D) Start treatment with imatinib or dasatinib

ANSWERS

1. The correct answer is (B), first-line treatment in a CP-CML patient. Allogeneic HSCT is no longer indicated as first-line treatment of CP-CML and is reserved for patients who do not achieve treatment response milestones, relapse, develop imatinib intolerance, experience progression, or have emergence of the T315I mutation, which is insensitive to treatment with current TKIs.¹ A *BCR-ABL* inhibitor should be tried instead.¹

Reference

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2. The correct answer is (B), continue with imatinib at the same dose. Clonal cytogenetic abnormalities such as trisomy 8 have been reported in Ph-negative cells from patients diagnosed with CP-CML who were undergoing treatment with imatinib.¹ Although the significance of these findings is uncertain, it appears that these abnormalities are transient in many cases and disappear with continued therapy. Rarely, myelodysplasia was also found.² A clear distinction should be made if the clonal abnormalities occur in Ph-positive cells, which represents clonal evolution. Clonal evolution is associated with clinical progression and worse outcome, particularly when other features of accelerated-phase CML are present.³ In the case discussed here, the trisomy 8

clonal abnormality was not associated with the Ph chromosome. Recent reports also indicate that the prognosis of clonal evolution in the absence of Ph-positive chromosome is good.⁴ Therefore, changing the treatment strategy (including switching to another TKI, considering HSCT, or increasing the dose of imatinib) is not warranted since the patient achieved the expected therapeutic milestones.⁵

References

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3. The correct answer is (E), QT prolongation can occur with nilotinib therapy, and a baseline electrocardiogram should be obtained prior to starting treatment. Nilotinib is a second-generation *BCR-ABL* inhibitor that is 20 to 50 times more potent than imatinib.¹ In general, nilotinib has a safe toxicity profile. In contrast to imatinib and dasatinib, fluid retention, edema, and pleural effusions are rarely associated with nilotinib treatment.^{2,3} However, nilotinib can prolong the QT interval and baseline and follow-up electrocardiograms are required. Grade 3/4 neutropenia and thrombocytopenia were reported in 29% of 280 patients treated with nilotinib in an open-label, phase II study.⁴ Elevation of hepatic transaminases is also common, and liver function tests should be performed frequently at the beginning of therapy.^{2,5} Nilotinib is a competitor inhibitor of CYP3A4.² Therefore, many CYP3A4 inhibitors such as voriconazole, HIV antiretroviral drugs, and claritromycin may increase

nilotinib plasma levels. In contrast, drugs that reduce CYP3A4 (eg, dexamethasone, carbamazepine) could reduce nilotinib plasma levels.²

References

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4. **The correct answer is (C), 1-log increase of *BCR-ABL* transcript levels as determined by qRT-PCR without achieving major molecular response should prompt the physician to obtain cytogenetic analysis of the bone marrow.** According to the National Comprehensive Cancer Network guidelines for managing CML, cytogenetic analysis of the bone marrow is required at diagnosis as well as at 6 and 12 months during treatment with a TKI.¹ The 12-month marrow cytogenetic analysis, however, is not necessary if the patient achieves complete cytogenetic response at 6 months; repeat cytogenetic analysis at 18 months is recommended if complete cytogenetic response has not been achieved at 12 months.¹ Fluorescence in situ hybridization is a complimentary technique to conventional bone marrow analysis and therefore should be performed using the same schedule. qRT-PCR becomes important when the patient achieves complete cytogenetic response (ie, no detectable Ph chromosome). qRT-PCR is highly sensitive and is the best method to monitor minimal residual disease after achieving complete cytogenetic response.² After achieving a major molecular response, a 1-log increase in the

BCR-ABL transcript levels should prompt a repeat qRT-PCR within 1 to 3 months.¹ Patient compliance and tyrosine kinase mutations should be evaluated.¹ The goal is to achieve nondetectable (complete molecular response) or a 3-log reduction (major molecular response) of the *BCR-ABL* transcripts.¹

References

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5. **The correct answer is (C), repeat qRT-PCR in 3 months to assess if *BCR-ABL* transcript levels increase.** As demonstrated by the presence of Ph-positive metaphases, the patient has experienced a clear cytogenetic relapse 3 years after receiving matched sibling HSCT, which should prompt a change in the treatment strategy. Starting imatinib, ordering a DLI, or considering a clinical trial are all valid strategies.¹ Imatinib has been shown to be effective in inducing responses in patients who relapse after allogeneic HSCT.² Although DLIs are historically associated with higher rates of molecular remissions, in particular for patients with early relapse in CP-CML, no direct comparisons have been made with TKIs in this setting.³ DLIs are also associated with graft-versus-host disease and an increased risk for infectious complications due to immunosuppression.³

References

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