Brainteaser

Chronic myeloid leukemia: When the going gets tough

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A 57-year-old man previously fit and well, presented to the Hematology Department with a 3-month history of night sweats and a 2-week history of bruising. Examination revealed no palpable lymphadenopathy; his spleen was palpable 2 cm below the costal margin. Full blood count showed hemoglobin of 89 g/L, platelet count of 116×10^{9} /L and white cell count of 187×10^{9} /L differential; neutrophils 168×10^{9} /L, lymphocytes 3.7×10^{9} /L, basophils 3.7×10^{9} /L, monocytes 7.4×10^{9} /L and eosinophils 3.7×10^{9} /L. The bone marrow aspirate and trephine was markedly hyper cellular with marked myeloid hyperplasia and a blast count of 3%. Cytogenetics showed the patient had the BCR-ABL mutation with a p210 break point.



Figure 1: Bone marrow aspirate showing plentiful lymphoid blasts (black arrow) on a background of myeloid hyperplasia with eosinophilia (green arrow)

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The patient was diagnosed with chronic phase chronic myeloid leukemia (CML). The Sokal score was 0.73 (low risk) and the patient was commenced on hydroxycarbamide initially and then on imatinib 400 mg once daily after the BCR-ABL results. Hematological remission was achieved after 4 weeks.

The patient was given 4 weekly follow-up appointments, but failed to attend his next appointment due to relocation to a different county. The patient presented 6 weeks later with extreme lethargy and abdominal pain. Clinical examination revealed cervical lymphadenopathy and marked splenomegaly (palpable 8 cm below costal margin). Blood film and repeat bone marrow aspirate confirmed blast crisis with transformation to B-acute lymphocytic leukemia [Figure 1]. Cytogenetic analysis confirmed the presence of the T315I mutation. The patient was commenced on hydroxycarbamide and transferred to a specialist center for further treatment.

Question

Which of the following is the most appropriate management strategy for the patient at this stage?

- (a): Increase dose of imatinib
- (b): Start chemotherapy (fludarabine, cytarabine, granulocyte colony-stimulating factor idarubicin [FLAG IDA]) and consider for stem cell transplant
- (c): Start chemotherapy (FLAG IDA) only
- (d): Start ponatinib only
- (e): Start dasatinib and chemotherapy (FLAG IDA)

To verify your answer, turn to page no 96

References

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Answer

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B: Start chemotherapy (FLAG IDA) and consider for stem cell transplant.

The T315I mutation occurs in approximately 15% of imatinib-resistant patients and may be more frequently detected in patients with advanced CML and Philadelphia chromosome positive acute lymphoblastic leukemia.^[1] The T315I mutation results in a threonine to isoleucine change at amino acid position 315 in the deoxyribonucleic acid coding sequence for an adenosine triphosphate (ATP) binding pocket of the BCR-ABL gene.^[2] This changes the structure of the ATP pocket, eliminating a crucial hydrogen bond required for high affinity binding with first and second line tyrosine kinase inhibitors (imatinib, nilotinib and dasatanib). Ponatinib is a potent BCR-ABL inhibitor with activity against the T315I mutation.^[3]

Though we used ponatinib for this patient, please note that on October 31, 2013, the Food and Drug Administration (FDA) asked the manufacturer of the leukemia chemotherapy drug ponatinib hydrochloride to suspend marketing and sales of this drug because of the risk of life-threatening blood clots and severe narrowing of blood vessels. Our patient was treated with the drug 7 weeks before this FDA alert. We discontinued the drug after this alert. Our patient did not have any adverse toxicity secondary to ponatinib.

Currently, one would use FLAG IDA and gear toward an allogenic stem cell transplant (Option B).

Treatment for this patient should involve reduction of the clone of leukemia with chemotherapy. The patient is young and should be considered for allogenic bone marrow transplantation. It is the only established curative modality and remains the ultimate salvage therapy for patients with imatinib-resistant CML.