

CLINICAL VIGNETTE

Acute Myeloid Leukemia (AML) Developing in a Patient with Chronic Myeloid Leukemia (CML) in Remission

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Case

A 63-year-old nurse was in good health until the spring of 2008 when she developed neutrophilia and underwent a work up including bone marrow aspiration and biopsy (BM BX). The BM BX revealed chronic phase chronic myeloid leukemia (CML). She was placed on imatinib 400 mg orally daily, which was the only tyrosine kinase inhibitor (TKI) of bcr-abl available in 2008. She developed a low-grade chronic rash and cytopenia, both of which improved with reduction to 300 mg daily. She attained a molecular complete remission (CR) by one year into her imatinib therapy. She was monitored with every 3-month routine blood tests, including complete blood count (CBC), and every 6-month blood tests for the molecular marker for CML, the bcr-abl translocation transcript produced by the primary genetic lesion of CML, the chromosome 9 and chromosome 22 translocation ((t (9, 22) (q34; q11), the Philadelphia chromosome). Peripheral blood analysis of bcr-abl RNA by quantitative RNA polymerase chain reaction (PCR) provides a sensitive and non-invasive measure of minimal residual disease. Molecular CR in CML is associated with long term disease free survival.¹

She had serially stable CBCs and a sustained molecular CR for over 7 years until new onset pancytopenia developed in the fall of 2015. CBCs at that time showed absolute neutrophil counts (ANC) less than 0.5 (x 10³/uL) with circulating blasts and platelets less than 10 (x 10³/uL). She was admitted with the presumptive diagnosis of CML blast crisis and underwent a BM BX, which 22% myeloblasts with associated multi-lineage dysplasia, suggesting antecedent myelodysplastic syndrome (MDS). Cytogenetics and fluorescence in situ hybridization (FISH) demonstrated loss of chromosome 7 (-7) and inv (3) (q21q26.2) but no Philadelphia chromosome. She stopped imatinib and was started on decitabine, a demethylating agent used in high-risk MDS and AML in the elderly as an inpatient and then continued on decitabine as an outpatient initially daily for 5 days every 4 weeks and then daily for 10 days every 4 weeks. She remained platelet and RBC transfusion dependent and serial bone marrow biopsies showed a modest decline in her BM myeloblast percentage. If she attains a remission BM with < 5% myeloblasts and still has an adequate performance status (PS), she might undergo a Human Leukocyte Antigen (HLA) matched, unrelated donor (MUD) and reduced intensity conditioning (RIT) allogeneic bone marrow transplant (allo-BMT). There is currently no evidence for a relapse of CML after over 10 months off imatinib.

Discussion

Chronic myeloid leukemia (CML) represents 15-20% of leukemias in adults with a case rate of 1-2 per 10-5.¹ The key molecular lesion, the chromosome 9 and chromosome 22 translocation, or Philadelphia chromosome, creates a fusion tyrosine kinase bcr-abl which is the primary biological driver throughout the course of CML. With the advent of effective tyrosine kinase inhibitors (TKI) highly specific for bcr-abl, the median survival with CML has increased from several years to many decades, approaching normal survival.¹ Imatinib was the first effective bcr-abl inhibitor and remains the paradigm for effective targeted therapy. Our patient attained a molecular complete remission, which is the optimal subgroup for long-term relapse free CML survival.¹ Interestingly, she has been off imatinib while receiving decitabine for AML and has no evidence of relapse. Studies are currently underway testing the ability to stop bcr-abl TKIs in CML patients after multi-year molecular remissions on therapy.

Acute myeloid leukemia (AML) is relatively uncommon as with CML but has a significant increase in the elderly with an incidence of 1.3 per 100,000 under age 65 and 12.2 per 100,000 over age 65.² The myeloid blast crisis that can occur in CML is still Philadelphia chromosome positive, so AML in a patient with CML should be extremely rare. However, with the substantially longer survival of patients with CML on TKI therapy more cases of AML in settings of controlled CML have been described. An MD Anderson retrospective series of 1701 CML patients on imatinib found 3 cases of MDS and AML.³ In addition, patients with controlled CML have been described with either transient clonal cytogenetic abnormalities or persistent abnormalities that can progress to a second myeloid malignancy. The -7 lesion, particularly if isolated, predicts for a high risk of eventual AML.⁴ At time of diagnosis of AML, our patient had -7 as one of her cytogenetic changes. More recently, clonal cytogenetic abnormalities have been described in patients with CML and Philadelphia chromosome negative status on dasatinib, one of the second generation bcr-abl inhibiting TKIs.⁵

While the number of cases of AML in patients with CML on TKI therapy have been reported, the optimal treatment is unclear. With our patient's AML prognosis is poor for several reasons, including her age over 60, the evidence of prior MDS, and the -7 cytogenetic change. In addition, allo-BMT is the only possibly curative therapy and becomes increasingly risky with age.² If she fails to attain better control of her AML with

decitabine, she will eventually need to switch to supportive care.

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