Case Study: 47-Year-Old Woman With New-Onset AML and Leukostasis

A 47-year-old woman presents to the emergency department complaining of fatigue and shortness of breath. She reports a two-week history of worsening exercise tolerance and a rather abrupt onset of shortness of breath over the past several hours. The patient has no major past medical history and works as an architect. Prior to this illness, she exercised three to four times weekly. Her breathing appears somewhat labored. Physical examination is notable for tachycardia, tachypnea, an erythematous rash on her chest and back, and scattered ecchymosis on the extremities. Her laboratory results reveal the following:

Count	Value	Reference Range
White blood cells	174.1 × 10^9/L	4 x 10^9/L – 10 × 10^9/L
Hemoglobin	7.3 g/dL	14 – 18 g/dL
Platelet count	24 × 10^9/L	150 × 10^9/L – 450 × 10^9/L

White blood cell (WBC) differential is notable for 89 percent blasts. Peripheral blood smear shows a vast majority of cells are large blasts with occasional cytoplasmic granules and pseudopodia. Bone marrow aspiration and biopsy is performed, revealing a hypercellular marrow involved with monocytic-appearing blasts comprising 80 percent of bone marrow cellularity. Cytogenetics reveal t(6;11)(q27;q23) present in 19 out of 20 metaphase cells. Molecular studies show wild-type CEPBA and NPM1 genes and a FLT3-ITD mutation (FMS-like tyrosine kinase 3, internal tandem duplication) is present. She is admitted to the hospital to initiate induction chemotherapy for acute myeloid leukemia (AML).

Following acute cytoreductive strategies to treat pulmonary complications of leukostasis, which of the following FDA-approved induction regimens is most likely to result in long-term overall survival?

A. 7+3 chemotherapy with infusional cytarabine and an anthracycline (daunorubicin or idarubicin) plus gemtuzumab ozogamicin

B. 7+3 chemotherapy with infusional cytarabine and an anthracycline (daunorubicin or idarubicin), plus etoposide

C. 7+3 chemotherapy with infusional cytarabine and an anthracycline (daunorubicin or idarubicin), plus midostaurin

D. 7+3 chemotherapy with infusional cytarabine and an anthracycline (daunorubicin or idarubicin), plus sorafenib

Answer

C. 7+3 chemotherapy with infusional cytarabine and an anthracycline (daunorubicin or idarubicin), plus midostaurin

The correct answer is (C), 7+3 chemotherapy with infusional cytarabine and an anthracycline (daunorubicin or idarubicin), plus midostaurin. The patient is a younger adult woman with no prior medical history who presents with *de novo* AML with t(6;11) as well as a *FLT3*-ITD mutation. Her clinical presentation is explained by her anemia (fatigue), thrombocytopenia (ecchymoses), and extreme leukocytosis (pulmonary leukostasis). Her cytogenetics reveal an 11q23 translocation, associated with therapy-related AML secondary to topoisomerase II inhibitors (such as etoposide and anthracyclines), which she does not have given her lack of prior history of such exposures, and monocytic differentiation of the leukemia, which she does have on the basis of her morphology. Monocytic differentiation may increase the chance of leukemic blasts infiltrating into tissues, which may result in leukemia cutis (likely based on her exam), gingival hyperplasia, and a higher likelihood of central nervous system involvement. Her very high WBC count is likely a result of her *FLT3*-ITD mutation, which is associated with extreme elevations in the WBC count at presentation, a shorter WBC doubling time, and an increased likelihood of relapse following consolidation therapy. Midostaurin is a newly developed inhibitor of FLT3 that is FDA-approved, along with standard 7+3 combination chemotherapy, for the induction therapy of *FLT3* mutation-positive AML. This is based on a multicenter phase III trial of 717 adult patients with newly-diagnosed *FLT3* mutation-positive AML who were randomized to either standard 7+3 induction chemotherapy plus placebo or 7+3 induction chemotherapy plus midostaurin (on days 8 through 21, following chemotherapy). After a median of 59 months of follow-up, median overall survival was superior in the midostaurin group (75 months vs. 26 months), with a hazard ratio for death of 0.78.

While induction therapy with midostaurin has not been directly compared to such therapy with gemtuzumab ozogamicin (answer choice A), etoposide (answer choice B), or sorafenib (answer choice D), studies have examined the impact of adding etoposide to 7+3 and no benefit over 7+3 alone has been found. Sorafenib is a multi-tyrosine kinase inhibitor with activity against FLT3, and small studies have suggested a possible role for this drug in the management of patients with *FLT3* mutation-positive AML, but more investigation is necessary, and the agent is not currently FDA-approved for this purpose. Gemtuzumab ozogamicin is a recombinant anti-CD33 monoclonal antibody linked to a cytotoxic agent. It had initially been approved by the FDA for use in older adults (age >60) with AML in first relapse, but it has since been pulled from the U.S. market following a more recent randomized trial showing no benefit from adding gemtuzumab ozogamicin to standard induction in younger adults with newly diagnosed AML. Trials are ongoing investigating other possible uses of this agent.

Case study submitted by Hanny Al-Samkari, MD, of Massachusetts General Hospital, Dana-Farber Cancer Institute, Harvard University, Boston, MA

References

1. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. N Engl J Med. 2017; doi:10.1056/NEJMoa1614359. [Epub ahead of print].
2. Bishop JF, Lowenthal RM, Joshua D, et al. Etoposide in acute nonlymphocytic leukemia. Australian Leukemia Study Group. Blood. 1990; 75:27-32.
3. Röllig C, Serve H, Hüttmann A, et al. Addition of sorafenib versus placebo to standard therapy in patients aged 60 years or younger with newly diagnosed acute myeloid leukaemia (SORAML): a multicentre, phase 2, randomised controlled trial. Lancet Oncol. 2015; 16:1691-1699.
4. Petersdorf SH, Kopecky KJ, Slovak M, et al. A phase 3 study of gemtuzumab ozogamicin during induction and postconsolidation therapy in younger patients with acute myeloid leukemia. Blood. 2013; 121:4854-4860.