CLINICAL VIGNETTE

Anemia Due to 5 q Minus Myelodysplastic Syndrome (MDS)

Alexander C. Black, MD

An 88-year-old woman with multiple chronic medical problems was referred for hematology evaluation of a progressive mildly macrocytic anemia. She had a 24-year earlier history of vulvar cancer treated by partial vulvectomy and an unknown three times a week chemotherapy regimen for about 3 months. Since her surgery, she has had no clinical recurrence.

Over the years, she has been diagnosed with several chronic medical problems including coronary artery disease requiring one vessel angioplasty years earlier, essential hypertension, type 2 diabetes mellitus, obesity and Stage 3 chronic kidney disease (CKD). Her chronic medications included baby aspirin, sitagliptin, olmesartan/hydro-chlorothiazie, nebivolol and atorvastatin. Approximately 6 years prior to her referral, she was first noted to have a mild anemia with a hemoglobin (Hb) in the mid 11 gm/ dl range. Her Hb remained in that range for 5 years, but then dropped into the mid 9 range without evidence of bleeding, acute medical illness or changes in medications. In addition, her mean corpuscular volume (MCV) had increased from 97 to 104 fl. Her last colonoscopy had been negative 20 years earlier and she was not interested in repeating the procedure. The reticulocyte count was 2.3 %, which was not elevated after corrected for her Hb, suggesting a hypoproliferative anemia and her iron, B12, folate and thyroid and haptoglobin were all normal. Her white blood cells and platelets were also in the normal range.

She underwent a bone marrow aspiration and biopsy (BM BX) to confirm the clinical impression of myelodysplastic syndrome (MDS). The BM BX showed hypercellularity with trilineage dyspoiesis without increased blasts. Cytogenetics showed an abnormal karyotype with deletion 5q in 20 of 20 metaphases and fluorescence in situ hybridization (FISH) confirming the specific loss of 5q33-34 in 114 of 200 cells scored. Thus, she had refractory anemia with multi-lineage dysplasia. By the Revised International Prognosis Scoring System (IPSS-R), which is based on percentage of bone marrow blasts, karyotype and degree of cytopenias[1], the patient was in the lowest risk group with a median survival of over 8 years. Her erythropoietin (epo) level was only 45.2 mIU/mL, far below the 500 or higher epo level that predicts lack of response to erythropoiesis stimulating agents (ESA) so she was started on therapy with darbepoietin at 500 mcg subcutaneously every 3 weeks[2,3]. In addition, due to the often dramatic response of 5 q minus MDS to lenalidomide[4], she was started on 10 mg daily. She developed significant nausea and fatigue on that dose, perhaps due to the concomitant moderate worsening of her CKD from stage 3 to stage 4 to 5 over the first several months on therapy. She is currently tolerating 5 mg every other day and is beginning to taper off the darbepoietin injections with her Hb back in the mid 11 range.

MDS is a spectrum of clonal hematopoietic disorders associated with impaired blood cell development, as reflected by low blood counts involving one or more lineages, dysplastic precursor maturation on bone marrow morphology, and a variably increased risk of evolving into acute myeloid leukemia (AML). Since the diagnosis in milder, lower risk cases can be difficult, the epidemiology of MDS is difficult to define precisely. There appears to be about 10,000 new cases each year with the majority of patients over age 65, with the exception of the subset of therapy-related MDS[5,6]. The pathogenesis of MDS is unclear, although a subset appears to involve mutations in RNA splicing machinery or ribosomal proteins[7]. In addition, epigenetic abnormalities, specifically excessive DNA methylation of genes involved in hematopoiesis, contiribute to MDS and provide a target for demethylating agent therapy[5,6].

The prognosis of MDS is highly variable. As mentioned above, the IPSS-R separates MDS patients into 5 groups from very low to very high risk, with median survivals of 8.8 years vs. 0.8 years and a 25% risk of having transformed to AML of over 14 years to 0.7 years[1]. Death from MDS can occur from transformation into AML or from infectious or bleeding complications of cytopenia. In longer-term survivors, higher ferritin levels confer a poorer prognosis, reflecting end organ injury from secondary hemochromatosis as a result of chronic RBC transfusions (rev in 8)[6]. Supportive care interventions include using erythropoiesis stimulating agents

(ESAs) to ameliorate anemia, perhaps with priming using filgrastim, and possibly iron chelating agents to reduce iron overload from chronic RBC transfusions. Therapies that can change the natural history of MDS include demethylating agents, either azacitidine or decitabine, immunosuppressive therapies, and allogeneic bone marrow transplant[5,6]. Isolated loss of 5q 33-34 confers a particularly good prognosis in MDS because it can also treat effectively with lenalidomide, an immunomodulatory agent used in multiple myeloma[4]. Dramatic responses were seen at 10 mg daily for 21 days every 28 days. Transfusion independence was achieved in 67 percent, with a median rise in hemoglobin of 5.4 g/dL[4]. The median response duration had not been reached after 104 weeks of follow-up. Complete and partial cytogenetic responses were achieved in 45 and 28 percent of evaluable subjects, respectively[4]. After 24 weeks of treatment there was complete resolution of cytologic dysplasia in all hematopoietic lineages in 36 percent[4]. The mechanism underlying this robust response of both improving blood counts and diminishing the presence of the damaged hematopoietic cell clone in 5 q minus MDS is unknown. In this case, there is no need to check for a cytogenetic response with a repeat BM BX if she maintains her current stable to improving blood counts and transfusion independence.

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