Response:

**Lenalidomide therapy and deep-vein thrombosis in multiple myeloma**

The importance of thromboprophylaxis with the use of lenalidomide and high-dose dexamethasone is well illustrated in this report by Zonder and colleagues. The incidence of deep-vein thrombosis (DVT) in their study decreased significantly when mandatory prophylaxis with aspirin was instituted but remains higher than the 3% risk of DVT observed with the same regimen in our trial, in which routine aspirin prophylaxis was used from the outset.

We believe that there are 2 factors that may affect the incidence of DVT in this setting, namely, the dose of dexamethasone and the use of concomitant erythropoietin. As we noted in our paper, a higher risk of DVT has also been observed in an Eastern Cooperative Oncology Group (ECOG) randomized trial testing lenalidomide plus either high- or low-dose dexamethasone as initial treatment for myeloma. In this trial, the increased DVT risk was seen in the high-dose dexamethasone arm, which uses doses of dexamethasone similar to those used in the Southwest Oncology Group and Mayo Clinic trials. In contrast, the risk of DVT did not appear to be much increased in patients treated on the lenalidomide plus low-dose dexamethasone arm. These findings, coupled with earlier observations that show no increased risk of DVT with single-agent lenalidomide, suggest that it may be possible to reduce DVT risk by optimizing the dose of dexamethasone that is used in combination with lenalidomide.

A higher risk of DVT has been observed with the concurrent use of erythropoietic agents in patients receiving either thalidomide or lenalidomide. Clinical trials sponsored by the National Cancer Institute Cancer Therapy Evaluation Program now recommend routine thromboprophylaxis when lenalidomide and erythropoietin are used concurrently.

We recommend that all patients receiving lenalidomide plus dexamethasone receive routine thromboprophylaxis. More data are needed on the best form of DVT prophylaxis. In the ECOG trial, we are requiring aspirin as the minimum mandatory prophylaxis, with a recommendation to consider either low-molecular-weight heparin or warfarin in the high-dose dexamethasone arm.

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**References**


To the editor:

**DMT1 mutation: response of anemia to darbepoetin administration and implications for iron homeostasis**

Recently we reported the first human mutation of *DMT1* in a patient homozygous for G>C transversion in the ultimate nucleotide of exon 12. The patient exhibits iron-deficient erythropoiesis, elevated serum iron level, mild serum ferritin level elevation, and liver iron overload out of proportion to the number of transfusions received. Figure 1 illustrates the patient’s response to darbepoetin. Hemoglobin level did not improve following administration of 100 μg of darbepoetin weekly for 3 months (hemoglobin level, 75 ± 1.0 g/L [7.5 ± 0.1 g/dL]). Three months after the last 100-μg dose, darbepoetin at 200 μg weekly was begun; the patient’s hemoglobin level increased to 90 ± 1.0 g/L (9.0 ± 0.1 g/dL) and remained stable on darbepoetin (*P* < .001 for the difference in mean hemoglobin level on 100 μg vs 200 μg). The patient reported an increased sense of well-being. There was no change in other parameters including hepcidin level, which remained significantly below the lower limit of normal.

Since the description of this patient, 2 more patients who are compound heterozygotes for different *DMT1* mutations and have hypochromic microcytic anemia have been reported. One patient received erythropoietin from infancy, with improvement in hemoglobin level and decline in serum ferritin level, but persistence of liver iron overload. We presume that, like our patient, she has low hepcidin levels allowing increased dietary iron absorption and increased iron release from macrophages, resulting in elevated serum iron level. Hepcidin production is increased by inflammation and iron loading and decreased by anemia and hypoxia. While cellular mechanisms by which iron and anemia regulate hepcidin production are unknown, data from *DMT1* mutant patients and β-thalassemia intermedia (TI) patients suggest that anemia is dominant over the iron stores signal. It is unclear whether the anemia signal is mediated by hepatic hepcidin, by the effects of anemia on erythropoietic activity, or by both. Our patient has ineffective erythropoiesis based on mild erythroid hyperplasia in the bone marrow (39.2% of nucleated cells were erythroid precursors) and high soluble transferrin receptor level (0.038 g/L; normal range, 0.0019-0.0044 g/L), but the ineffective erythropoiesis of *DMT1* mutant patients is much milder than in TI.

The discrepancy between the slightly elevated ferritin levels in these patients and the striking liver iron overload is remarkable. We speculate that the relatively low serum ferritin level reflects a bottleneck in iron transport from macrophage vacuoles that digest senescent erythrocytes into macrophage cytoplasm. Low hepcidin levels and resulting high macrophage expression of ferroportin in patients with *DMT1* mutations could further lower macrophage cytoplasmic iron and suppress soluble ferritin secretion.
Patients with anemia due to DMT1 mutations are critically dependent on iron delivery to developing erythrocytes; increased transferrin saturation may be essential to deliver iron when DMT1 activity is diminished. Thus, even if medications that increase hepcidin levels become available for treatment of iron overload, they may not benefit DMT1 patients because increased plasma hepcidin level would limit release of iron into the bloodstream, decreasing serum iron level and transferrin saturation, further limiting available iron for hemoglobin synthesis. Removing excess iron is probably the only viable treatment for iron overload in these patients.

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References


More on prognostic significance of FLT3/ITD size in acute myeloid leukemia (AML)

We read with great interest the paper by Stirewalt et al1 analyzing the prognostic significance of different Fms-like tyrosine kinase (FLT3) gene internal tandem duplication (ITD) size in acute myeloid leukemia (AML). There is a considerable variability in ITD size, and Stirewalt et al1 suggest that with increasing size of ITD there is a more significant loss of autoinhibitory function of FLT3, translating into inferior prognosis. We would like to comment on this issue based on our results, which may suggest different conclusions.

We have analyzed 86 consecutive patients with AML, 37 men and 49 women, with a median age of 57 years (range, 18-85 years), by reverse transcriptase–polymerase chain reaction (RT-PCR) for FLT3/ITD mutation.2 We have found 18 (20.9%) patients with FLT3/ITD mutations, with the highest frequency (3/8; 37.5%) in acute promyelocytic leukemia (APL). ITD was associated with higher white blood cell (WBC) count (67 vs 26 × 109/L, P = 0.013) and somewhat inferior survival (hazard ratio [HR] = 1.98; confidence interval [CI] 1.11-6.11; P = 0.02, when we exclude patients with APL). There was no significant difference in age, sex, cytogenetic risk, and other hematologic parameters between FLT3/ITD-mutated and unmutilated patients.

Median ITD size was 70 bp (range, 30-100 bp). ITD size was negatively correlated with age (R = −0.51; P < 0.05) and cytogenetic risk (R = −0.58; P < 0.05) and was not correlated with WBC count, sex, or other hematologic parameters. We have divided our patients’ FLT3/ITD mutations into long (≥70 bp; 11/18, 61.1%) and short ITD (<70 bp; 7/18, 38.9%) subgroups. We found better survival in the long-ITD subgroup (HR 4.07, CI 2.28-56.32; P = 0.002) (Figure 1), even without patients with APL (HR 3.18, CI 1.31-27.28; P = 0.02). In the multivariate Cox proportional hazard model, with ITD size as continuous variable, in overall series higher age, WBC count, and poor cytogenetic risk were

![Graph](image-url)
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