the importance of the BCL3 gene for the pathogenesis of cHL and PTCL.

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To the editor:

Thrombotic complications in patients with newly diagnosed multiple myeloma treated with lenalidomide and dexamethasone: benefit of aspirin prophylaxis

Lenalidomide (LEN) is an immunomodulatory compound with significant activity versus relapsed/refractory multiple myeloma (RRMM).1 In Blood, Rajkumar et al2 reported striking efficacy of LEN plus dexamethasone (DEX) versus newly diagnosed multiple myeloma (NDMM). While structurally similar to thalidomide (THAL), also used to treat MM,3 LEN has a unique activity profile. Both agents appear to increase the risk of thromboembolic events (TEE), although the actual baseline incidence is unclear. The TEE incidence in NDMM patients receiving THAL+DEX without thrombosis prophylaxis is approximately 15%.4,5 An 8.5% incidence of TEE in RRMM patients getting DEX+LEN without routine prophylaxis has been reported.1 Rajkumar et al6 described a 3% incidence in NDMM with DEX+LEN and daily aspirin (ASA; 80 mg or 325 mg).

The Southwest Oncology Group is conducting a double-blind randomized trial comparing DEX (40 mg/day on days 1-4, 9-11, and 17-20 every 35 days for 3 induction cycles, then 40 mg/day on days 1-4 and 15-18 every 28 days as maintenance thereafter) plus placebo versus DEX (same schedule) plus LEN (25 mg/day on days 1-28 every 35 days during induction, then 25 mg/day on days 1-21 every 28 days during maintenance). Crossover from DEX to DEX+LEN is permitted for progressive MM. Initially, no thrombosis prophylaxis was mandated. After 21 patients were enrolled, an increased incidence of TEEs in 1 arm became apparent: 9 (75%) of 12 patients receiving DEX+LEN developed TEEs (8 lower-extremity deep-vein thromboses with 2 pulmonary embolic events, 1 ischemic stroke) after a median of 50 days, versus 0 (0%) of 9 patients on DEX alone (P < .001). The study was modified to require 325 mg ASA daily, based on the low TEE incidence observed by Rajkumar et al,2 as well as a report showing low-dose ASA reduced TEE risk in MM patients receiving chemotherapy-thalidomide combinations.5

As of October 31, 2005, 76 patients have been enrolled. Since mandating ASA prophylaxis, 6 TEEs have occurred among 55 additional patients: 4 (15%) of 26 randomized to DEX+LEN (P < .001 for comparison of TEE incidence on DEX+LEN before and after aspirin) and 2 (7%) of 29 on DEX alone (P = .41 for DEX vs DEX+LEN after ASA). Of interest, both of the patients randomized to DEX who developed clots had already crossed over from DEX to DEX+LEN due to progressive disease. One of these patients was noncompliant with ASA prophylaxis. Overall, 6 (19%) of 32 patients receiving DEX+LEN have developed TEEs since modification of the protocol to include ASA prophylaxis (P < .001 before vs after ASA).

In summary, although adding ASA markedly reduced the risk of TEEs in NDMM patients receiving DEX+LEN, we observed a much higher incidence of TEE than reported by Rajkumar et al.4 Potential reasons include higher DEX dose, longer LEN exposure during induction in our trial, or other factors such as possible differences in the use of recombinant erythropoietin. The 19% TEE incidence we observed is similar to that reported for NDMM patients treated with anthracycline-THAL combinations plus either 81 mg ASA6 or low-dose enoxaparin.7 At present, using one of these prophylaxis strategies during DEX+LEN treatment for NDMM is highly recommended. Further research is needed to determine the optimal prophylaxis strategy.

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Supported in part by Celgene Corporation.

References

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**


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**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 hypoxia, by the effects of anemia on erythropoietic activity, or by both. Our patient has ineffective erythropoiesis based on mild erythropoietin receptor loss (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.

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