Macrocytosis and Cobalamin Deficiency in Patients Treated with Sunitinib

TO THE EDITOR: Sunitinib malate is a multitargeted tyrosine kinase inhibitor approved for the treatment of advanced renal-cell carcinoma. We report on an asymptomatic increase in the mean corpuscular volume of erythrocytes and cobalamin deficiency in six patients with metastatic renal-cell carcinoma who were treated for more than 5 months with sunitinib as part of a clinical trial evaluating the efficacy and safety of continuous daily administration of the drug. The starting dose of sunitinib was 37.5 mg daily; three patients required a dose reduction to 25 mg, and one patient had a dose escalation to 50 mg daily. An increase in the mean corpuscular volume was ob-

served after a treatment period of 3 to 4 months (Fig. 1).

We analyzed serum cobalamin, holotranscobalamin, folate, and homocysteine levels 5 to 10 months after the initiation of sunitinib treatment; however, we did not perform such an analysis at baseline. All six patients had cobalamin deficiency (accompanied by an increase in homocysteine), and five of the six patients had holotranscobalamin deficiency with normal serum folate levels. Thyrotropin levels were normal in five of the six patients and elevated in one patient, but in this patient free thyroxine and triiodothyronine levels were normal, findings that ruled out thyroid dysfunction as the cause of the macrocytosis. None of the patients had worsening anemia or symptoms of cobalamin deficiency at the time of measurement, and none of the patients required an interruption or reduction in sunitinib treatment. Cobalamin was administered intramuscularly.

To our knowledge, macrocytosis and cobalamin deficiency have not been reported as adverse events related to treatment with sunitinib. Since macrocytosis preceded declining cobalamin levels in two patients and persisted after cobalamin replacement therapy, multiple mechanisms may be involved in the development of macrocytosis.

Although a causal relationship between sunitinib treatment and cobalamin deficiency could not be established, it is remarkable that cobalamin deficiency was detected in all six patients and that holotranscobalamin deficiency was detected in five of six patients who were treated for more than 5 months with sunitinib with continuous daily administration. The mechanism is unknown, but we hypothesize that oral sunitinib interferes with cobalamin absorption in the gastrointestinal tract.

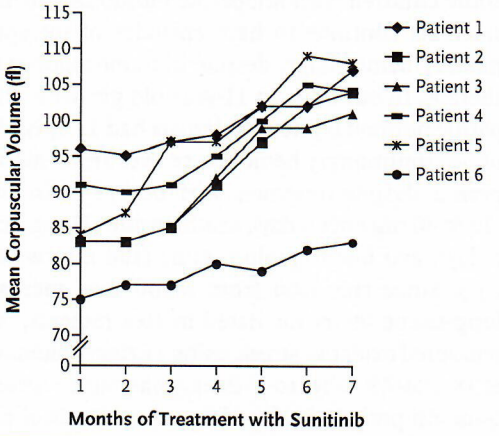

Figure 1. Increases in Mean Corpuscular Volume in Six Patients during Treatment with Sunitinib.

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Dr. Gillessen reports serving on the advisory boards of Pfizer and Bayer, and Dr. Cerny reports serving on the advisory board of Pfizer. No other potential conflict of interest relevant to this letter was reported.