ROLE OF INTERLEUKIN-6 IN PARANEOPlastic THROMBOCYtOSIS

To the Editor:

Interleukin-6 (IL-6) is able to stimulate thrombopoiesis in vitro and in vivo in murine and primate models.1 2 A phase I trial of recombinant IL-6 in humans has demonstrated the capacity of this cytokine for increasing platelet counts in vivo.3 However, the physiologic role of IL-6 in the regulation of thrombopoiesis remains unclear.4 Increased serum IL-6 levels have been reported in patients with reactive thrombocytosis but the causative role of IL-6 for thrombocytosis has not been established.5 We report here on the role of IL-6 in paraneoplastic thrombocytosis associated with metastatic renal carcinoma. We previously showed that serum IL-6 is increased in a subgroup of patients with renal cell carcinoma.6 The possible correlation between serum IL-6 measured with the B9 bioassay and thrombocyte counts was investigated in a series of 100 patients with metastatic renal cell carcinoma. The 26 patients with undetectable serum IL-6 had a mean platelet number of $3.12 \times 10^{11}/\mu L$ compared with $3.62 \times 10^{11}/\mu L$ in the 51 patients with detectable serum IL-6 less than 10 U/mL (Mann-Whitney, $P = .04$) and $4.72 \times 10^{11}/\mu L$ for the 23 patients with serum IL-6 greater than 10 U/mL ($P = .001$).

Twelve patients with metastatic renal cell carcinoma were included in a phase 2 trial of anti-IL-6 (BE-8, IgG1) after written informed consent. Anti-IL-6 was administered at a daily dose of 20 mg in 100 mL of normal saline serum with 0.5% human serum albumin, in 1-hour infusion daily during 21 days. None of these patients received glucocorticoids during the 21 days of anti-IL-6 treatment.

All 12 patients experienced a reduction of platelet counts by at least 20% during anti-IL-6 administration. The figure depicts the median reduction of platelet counts during anti-IL-6 administration observed in the 12 patients. A significant decrease of platelet counts (Wilcoxon rank test, $P < .005$) was observed from day 7 to day 21. In the 12 patients, platelet decrease reached a plateau at 57% of baseline on day 12. Platelet decrease lasted until the end of anti-IL-6 infusion. At day 40, 19 days after the completion of anti-IL-6 treatment, thrombocyte counts were not significantly different from baseline. As shown in the Fig 1, all five patients with thrombo-
Fig 1. The dashed line (---) shows the median decrease of platelet counts (expressed in percentage of the value at day 0) in the 12 patients treated with anti-IL-6. *Days at which platelet counts of the 12 patients were significantly lower as compared with day 0 (Wilcoxon rank test, $P < .005$). The continuous lines (-----) show the platelet counts measured before (day 0), during (days 1 through 21), and after (days 30 and 40) anti-IL-6 administration in the five patients with thrombocytosis at day 0.

cytosis ($>4.5 \times 10^5/\mu L$) achieved a normalization of thrombocyte counts during anti-IL-6 administration.

These results show that platelet counts are highly correlated to serum IL-6 concentrations and that administration of anti-IL-6 is able to normalize thrombocytosis in patients with metastatic renal carcinoma. This demonstrates that an overproduction of IL-6 in vivo is responsible for the paraneoplastic thrombocytosis associated with renal cell carcinoma.

Jean-Yves Blay
Marie Favrot
Centre Léon Bérard
Lyon, France
Jean-François Rossi
Institut Val D’Aurelle
Montpellier, France
John Wijdenes
Centre de Transfusion Sanguine
Besançon, France

REFERENCES
Role of interleukin-6 in paraneoplastic thrombocytosis [letter]

JY Blay, M Favrot, JF Rossi and J Wijdenes