

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 $3.12 \times 10^5/\mu\text{L}$ compared with $3.62 \times 10^5/\mu\text{L}$ in the 51 patients with detectable serum IL-6 less than 10 U/mL

(Mann-Whitney, $P = .04$) and $4.72 \times 10^5/\mu\text{L}$ 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-

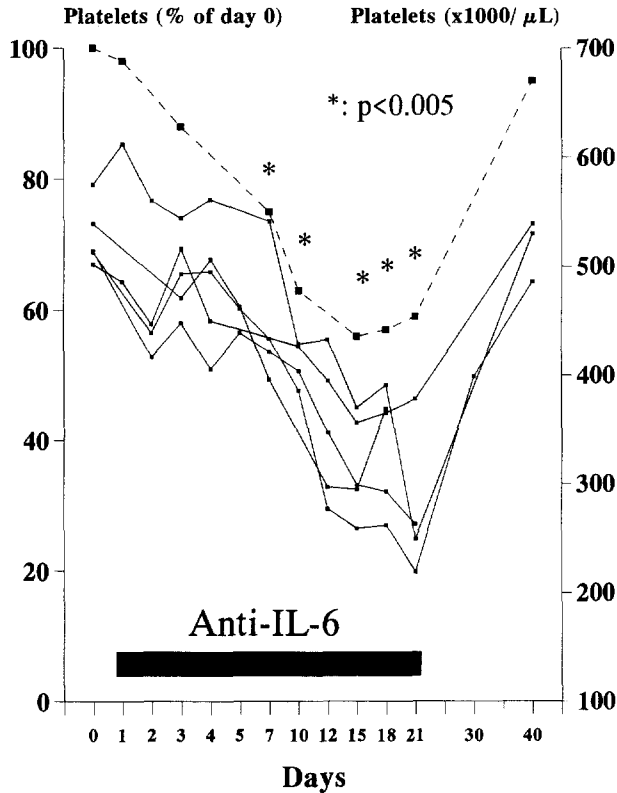


Fig 1. The dashed line (---) shows the median decrease of platelet counts (expressed in percentage of the value at day 0) in the 12 patients treated with anti-IL-6. *Days at which platelet counts of the 12 patients were significantly lower as compared with day 0 (Wilcoxon rank test, $P < .005$). The 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 ($>4.5 \times 10^5/\mu\text{L}$) 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.

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REFERENCES

1. Ishibashi T, Kimura H, Shikama Y, Uchida T, Kariyone S, Hirano T, Kishimoto T, Takatsuki F, Akiyama Y: Interleukin 6 is a potent thrombopoietic factor in vivo in mice. *Blood* 74:1241, 1989
2. Asano S, Okano A, Ozawa K, Nakahata T, Ishibashi T, Koike K, Kimura H, Tanioka Y, Shibuya A, Hirano T, Kishimoto T, Takaku F, Akiyama Y: In vivo effects of recombinant IL-6 in primates: Stimulated production of platelets. *Blood* 75:1602, 1990
3. Weber J, Yang JC, Topalian SL, Parkinson DR, Schwartzentruber DS, Ettinghausen SE, Gunn H, Mixon A, Kim H, Cole D, Levin R, Rosenberg SA: Phase I trial of subcutaneous interleukin-6 in patients with advanced malignancies. *J Clin Oncol* 11:499, 1993
4. Hill RJ, Warren MK, Levin J, Gaudie J: Evidence that interleukin-6 does not play a role in the stimulation of platelet production after induction of acute thrombocytopenia. *Blood* 80:346, 1992
5. Hollen CW, Henthorn J, Koziol JA, Burstein SA: Elevated serum interleukin-6 levels in patients with reactive thrombocytosis. *Br J Haematol* 79:286, 1991
6. Blay J-Y, Negrier S, Combaret V, Attali S, Goillot E, Merrouche Y, Mercatello A, Ravault A, Tourani JM, Moskovtchenko JF, Philip T, Favrot M: Serum level of interleukin 6 as a prognosis factor in metastatic renal cell carcinoma. *Cancer Res* 52:3317, 1992