Key words

PML-RARα, acute promyelocytic leukemia, BMT

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Cırculatıng thrombopoietin and interleukin-6 in newly diagnosed autoimmune versus aplastic thrombocytopenia

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Circulating thrombopoietin and interleukin-6 concentrations were investigated in two different settings of thrombocytopenia. Twenty patients with autoimmune thrombocytopenic purpura (ATP), 12 patients with aplastic anemia (AA) and 15 healthy subjects were studied. Thrombopoietin was significantly increased in AA and deficient in ATP. Interleukin-6 was significantly increased in ATP, compared to both other groups.

Assaying thrombopoietin (TPO) and interleukin-6 (IL-6) levels in autoimmune thrombocytopenic purpura (ATP) and aplastic anemia (AA) may provide important clues for understanding the regulation of plasma TPO levels and pathobiology of thrombocytopenia in these disorders. In this study, plasma concentrations of these molecules were measured in newly diagnosed patients with ATP and AA before any therapies, including immunosuppressive drugs and transfusions, were initiated.

The study groups consisted of 20 patients with ATP (12 females, 8 males; mean age, 30±3 years), 12 patients with AA (5 females, 7 males; 36±3 years); the control group was formed of 15 healthy adult subjects (10 females, 5 males; 28±2 years). Plasma TPO and IL-6 concentrations were assayed by sandwich type ELISAs (TPO Quantikine™, R&D Systems, Minneapolis, USA and Human IL-6 ELISA Kit, Serotec Ltd, Oxford, UK).

TPO was significantly increased in AA, and deficient in ATP. IL-6 levels were significantly increased in ATP, compared to both other groups. IL-6 concentrations in AA patients were not statistically different from those in the control subjects (Table 1).

The proliferation and maturation steps of megakaryocytopoiesis are regulated by many lineage nonspecific megakaryocytopoietic cytokines, including IL-6, and the lineage-specific cytokine, TPO.[1] Lineage

Table 1. Median (range) thrombopoietin and interleukin-6 concentrations in the control group and in the patients with autoimmune thrombocytopenic purpura and aplastic anemia.[a]

	ATP (n= 20)	*AA (n= 12)*	*Control group (n= 15)*
Thrombopoietin (pg/mL)	0[b,c] (0-28)[e]	20.91[d] (6-125)	15.73 (4-45)
Interleukin-6 (pg/mL)	22.4[f] (6-76)	10.6 (4-32)	7.6 (1-24)
Platelet count (mm^3)	17400 (2,000-45,000)	18000 (10,000-35,000)	229000 (145,000-420,000)

Abbreviations: ATP = autoimmune thrombocytopenic purpura; AA = aplastic anemia.

[a]The Mann-Whitney U test was used for statistical comparisons (p values < 0.05 are significant); [b]Not detectable; [c]p< 0.0001 vs. aplastic anemia and control group; [d]p< 0.001 vs. control group; [e]below the detection limit (15 pg/mL) in 13 patients; [f]p< 0.01 vs. aplastic anemia and control group.

non-specific cytokines cannot yield morphologically normal megakaryocytes without TPO. In contrast, TPO promotes the full spectrum of megakaryocyte growth and development, even when the effect of other cytokines is neutralized.[2]

TPO is produced at a constant rate and catabolized by platelets and megakaryocytes.[3] Platelet and megakaryocyte masses have been proposed to be the only known factors determining the rate of TPO catabolism.[4,5]

Consistent with several previous reports,[4,6,7] TPO levels in this study were decreased in ATP, while IL-6 concentrations were significantly elevated. On the other hand, plasma TPO and IL-6 concentrations in the patients with AA were significantly increased and normal, respectively. It could be suggested that increased mass and/or c-mpl expression of the megakaryocytes leading to enhanced TPO absorption, and release of sufficient numbers of platelets to absorb TPO prior to their rapid destruction by immune mechanisms may be responsible for the decreased circulating TPO concentrations in ATP. Significantly increased TPO concentrations in AA support the current theory regarding TPO catabolism. Decreased megakaryocyte and platelet masses could lead to diminished TPO absorption and catabolism, and consequently increased circulating levels of this molecule.

TPO-knockout mice provide a model in which TPO deficiency leads to thrombocytopenia.[8] The megakaryocytes produced in TPO-knockout mice are relatively immature, unable to yield sufficient amounts of platelets. Ineffective/impaired platelet production ahs been identified in most patients with ATP, suggesting that the mechanism of thrombocytopenia in ATP may be both impaired production and increased platelet clearance.[9] Decreased TPO concentration in ATP may not be only a result of the disease process, but it could also be involved in the immature megakaryocytopoiesis and impaired thrombopoiesis. We have proposed a hypothesis indicating a causal relationship between TPO deficiency, immature megakaryocytopoiesis/thrombopoiesis, and autoimmunity in ATP.[10] High IL-6 concentrations in ATP may be for a compensatory mechanism, i.e augmentation of the megakaryocytopoiesis. IL-6 has the most potent thrombopoietic activity of any agent except thrombopoietin. However megakaryocytopoiesis stimulated by IL-6 is morphologically abnormal.[11] These observations suggest that increased plasma IL-6 concentration may also be involved in the ineffective megakaryocytopoiesis in ATP.

Key words

Thrombopoietin, ITP, interleukin-6, megakaryocytopoiesis

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