Clinical Findings With the First Generation of Thrombopoietic Agents

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Thrombocytopenia is a common problem in hematology/oncology patients. In the past two decades a number of thrombopoietic growth factors and related cytokines have become available for clinical investigations. Unfortunately, most of the pleiotropic cytokines have been limited by their modest activity and toxicity profile. The discovery of thrombopoietin (TPO), a key regulator of platelet production, led to the clinical development of two recombinant versions of the molecule: full-length, recombinant human thrombopoietin (rhTPO), and truncated and pegylated, megakaryocyte growth and development factor (Peg-rHuMGDF). Both agents showed significant biologic activity in various clinical settings, including nonmyeloablative chemotherapy, mobilization of progenitors, platelet apheresis, and treatment of thrombocytopenia related to other conditions. Despite promising thrombopoietic activity, the clinical development of the first generation of recombinant TPOs was discontinued due to the neutralizing antibodies observed with PEG-rHuMGDF. This has led to the development of TPO agonists with no sequence homology to TPO, which can bind to the TPO receptors and activate signaling, leading to an increase in platelet production. The clinical experience with the first generation of thrombopoietic agents has provided insight into the biology and future directions for a second generation of thrombopoietic agents in various disorders of thrombocytopenia.
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Thrombocytopenia is a common hematologic problem that results from an imbalance between the normal production and destruction cycle of platelets. Although several factors can contribute to thrombocytopenia in cancer patients, including defects in production related to bone marrow infiltration from malignancy, myelosuppression, and concomitant liver disease, or increased destruction, due to immune thrombocytopenia or disseminated intravascular coagulation (DIC), or splenic sequestration, the most common etiology in cancer patients is myelosuppressive treatment.[1,2] Thrombocytopenia increases the risk for hemorrhagic complications, chemotherapy dose reduction, and treatment delays, which may compromise the treatment outcome and increase healthcare costs. Although platelet transfusions have been widely used for the management of severe thrombocytopenia, they provide only a temporary solution[3] (see article by McCullough in this issue) and have several potential risks, including transfusion reactions, transmission of infectious agents, and alloimmunization with platelet refractoriness. Clearly there is a need for new strategies to reduce the number of platelet transfusions and the burden on the platelet supply system.[4]

To address these concerns, a number of studies in the past decade have examined and demonstrated the safety of lowering the threshold for platelet transfusions from the old standard of less than 20×10^9/L to less than 10×10^9/L, in patients who are otherwise stable clinically.[3,5] In addition, progress is being made in the pharmacologic management of thrombocytopenia.[6,7] In the last two decades, various multifunctional cytokines with thrombopoietic activity have been investigated, including interleukin (IL)-1, IL-3, IL-6, IL-11, PIXY321, and promegapoietin. Unfortunately, most of these agents have modest thrombopoietic activity and some have unfavorable toxicity profiles. IL-11 is the only cytokine approved by the US Food and Drug Administration to date for chemotherapy-induced thrombocytopenia. However, its use has been limited given its toxicities, which include edema, dyspnea, arrhythmias, and syncope in some patients.[8]

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FIRST GENERATION OF THROMBOPOIETIC GROWTH FACTORS

After the purification and cloning of human thrombopoietin, a key regulator of platelet production, two versions of recombinant thrombopoietins entered clinical development: recombinant human thrombopoietin (rhTPO) and pegylated, recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF). rhTPO (initially developed by Genentech, San Francisco, CA) was a full-length molecule with the amino acid sequence identical to the endogenous TPO.[6,7] It was produced in mammalian cells and glycosylated. PEG-rHuMGDF (Amgen, Thousand Oaks, CA) was a truncated version of TPO, consisting of 163 amino acids, amino terminal of native TPO, and conjugated to a polyethylene glycol moiety to increase the circulating half-life. It was produced in *Escherichia coli*, and nonglycosylated. In addition, promegapoietin, a chimeric construct of IL-3 and the receptor-binding region of the Mpl ligand, was also developed. Unfortunately, due to the development of neutralizing antibodies to both PEG-rHuMGDF and promegapoietin, the clinical development of all three molecules was halted. Both recombinant versions of TPO were extensively investigated in various clinical settings and observations made from these studies have provided directions for the future development with new TPO agonists.

CLINICAL AND BIOLOGIC EFFECTS OF RECOMBINANT TPOs IN PHASE I STUDIES

Initial dose-escalation studies in cancer patients prior to chemotherapy showed that both rhTPO and PEG-rHuMGDF were well tolerated and very effective in raising platelet counts.[9–12] In the pre-chemotherapy phase, rhTPO administered as a single dose intravenously resulted in a dose-dependent increase in platelet counts up to fourfold in sarcoma patients. The rise in platelet count began on day 4 with the peak response around day 12, and a return towards baseline around day 21.[9] The response in platelets was associated with a fourfold increase in the bone marrow megakaryocytes, expansion of bone marrow progenitors, and mobilization of progenitors of multiple lineages (Figure 1).

When rhTPO was administered as a single dose by the subcutaneous route in heavily pretreated patients with gynecologic malignancy, the rise in platelets was more modest and the peak was seen around day 16.[13] Similar kinetics of platelet response was seen when PEG-rHuMGDF was administered before chemotherapy as a daily subcutaneous injection.[9,11,12] The platelets produced with these agents appeared to be normal in morphology and function. Treatment with both these agents resulted in mobilization of myeloid, erythroid, and megakaryocytic progenitors in the peripheral blood.[9–11,14]

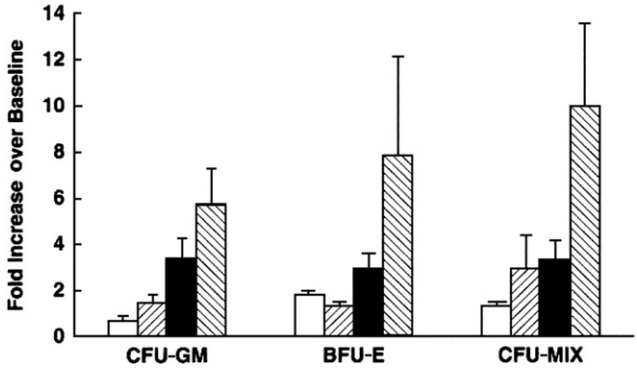

Figure 1. Effect of thrombopoietin treatment on mobilization of myeloid (colony-forming unit-granulocyte-macrophage [CFU-GM], erythroid (burst-forming unit-erythroid [BFU-E], and myelo-erythroid [CFU-MIX] progenitors at 0.3 (open bars), 0.6 (striped bars slanting up), 1.2 (black bars), and 2.4 (striped bars slanting down) μg/kg of body weight. Data shown represent the peak response (mean + SE), which was seen between days 3 and 7. Adapted with permission from Vadhan-Raj et al, Ann Intern Med. 1997; 126:673–81.

CHEMOTHERAPY-INDUCED THROMBOCYTOPENIA

The clinical trials reported in the myelosuppressive, dose-intensive, or myeloablative settings are described in Table 1.

Solid Tumors and Lymphoma

The initial trials were designed in patients with solid tumors, with TPO agents given post-chemotherapy, similar in manner to the myeloid growth factor administration. In these studies, PEG-rHuMGDF administered daily up to 7 days, 16 days, or 20 days post-chemotherapy increased the recovery of platelets and/or nadir.[11,12,15] However, the need for the platelet transfusions was unaffected or inconclusive since the regimens used were only moderately myelosuppressive.

The trials with rhTPO involved dose-intensive regimens that result in cumulative thrombocytopenia.[10,13,16] In the trial with rhTPO in patients with gynecologic malignancies receiving high-dose carboplatin, there was a significant impact on the need for platelet transfusions. In this study, patients received cycle 1 of chemotherapy without rhTPO as internal control.[13] In cycle 2, patients received rhTPO subcutaneously every other day for only four doses. The platelet nadir in cycle 2 with rhTPO was significantly higher with a significantly shorter duration of grades 3 and 4 thrombocytopenia, and platelet recovery was faster as compared to cycle 1 without rhTPO (Figure 2). As a result, at the optimal