Targeted Approaches for the Treatment of Thrombocytopenia

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ABSTRACT
Molecular targeting of novel therapies has the promise of inducing very specific biologic effects. In clinical hematology and oncology, molecular targeting of specific cell surface receptors with erythropoietin, G-CSF, or GM-CSF has been used to stimulate erythropoiesis and granulopoiesis, respectively. Although anemia and neutropenia can be corrected with targeted therapy, safe and effective treatment of thrombocytopenia remains an unmet medical need. While platelet transfusions still represent the standard of care for severe thrombocytopenia, there are several negative aspects associated with their use, including issues of availability, transient effectiveness, costs, adverse effects, negative perception by patients, and infection considerations. Despite extensive investigations of cytokines which act primarily on primitive levels of hematopoiesis, pharmacologic interventions to date have failed to elevate platelet counts in a reliable, highly effective, and well-tolerated fashion. Recombinant human interleukin-11 has been approved by the U.S. Food and Drug Administration for the treatment of chemotherapy-induced thrombocytopenia but has only modest efficacy and significant side effects. The identification of c-Mpl as the thrombopoietin receptor has opened new avenues for the therapeutic manipulation of thrombopoiesis. The development of specific c-Mpl ligands, including recombinant human thrombopoietin (rHuTPO), has allowed investigators to target this receptor for the treatment of chemotherapy-induced thrombocytopenia and other medical disorders characterized by extremely low platelet counts. As a potent stimulator of platelet production, rHuTPO has the potential to reduce the need for platelet transfusions and their attendant complications. The Oncologist 2001;6(suppl 5):15-23

INTRODUCTION
Cancer and its treatment are frequently accompanied by anemia, neutropenia, thrombocytopenia, or some combination of these conditions. These complications can potentially increase the morbidity or even mortality of the cancer itself or its treatment. Hematologic complications of cancer have been well documented to impair quality of life, increase the rate and severity of medically significant complications, and even lead to death. While cancer-related anemia and neutropenia are often adequately managed by judicious use of currently available hematopoietic growth factors, thrombocytopenia remains a significant contributor to morbidity and mortality in patients with this disease. In addition, the presence of significant thrombocytopenia could possibly limit the benefits of modern cancer therapy for potentially curable malignancies by preventing appropriate administration of drugs at the optimal doses and schedule.

Although platelet transfusions remain the “gold-standard” for the acute management of severe thrombocytopenia, there are many resource issues and possible complications associated with their use [1]. Consequently, the oncology community is engaged in an ongoing evaluation of the absolute risks of thrombocytopenic bleeding, indications for platelet transfusions, and a search for alternative therapeutic interventions to raise platelet counts. Recombinant human interleukin-11 (rHuIL-11, Oprelvekin, Neumega®) was the first commercially available thrombopoietic cytokine [2]. It is licensed for the prevention of severe thrombocytopenia and the reduction of the need for platelet transfusion following myelosuppressive chemotherapy in patients with...
nonmyeloid malignancies that are at high risk of severe thrombocytopenia. However, rHuIL-11 has significant side effects and demonstrates only modest efficacy. Therefore, optimizing the management of cancer-related thrombocytopenia remains a significant unmet need for a subset of patients with this condition [2].

The search for more targeted and specific stimulation of thrombopoiesis has been fostered by research into the molecular regulation of hematopoietic stem cells, megakaryocytes, and platelet production. Sequence analysis of c-Mpl (the cellular homologue of the murine myeloproliferative leukemia retrovirus oncogene, v-Mpl), suggested that the protein product of this gene, MPL, was a member of the family of hematopoietic growth factor receptor genes [3]. Subsequently, the c-Mpl ligand was identified as thrombopoietin (TPO) [4]. Therefore, c-Mpl has become an attractive candidate for targeted drug therapy. This review describes conventional management strategies for thrombocytopenia and discusses the overall biology of thrombopoietic growth factors. Following a review of the literature on rHuIL-11 and the limitations of this molecular pathway, it provides an update on the status of targeted therapy to prevent cancer-related thrombocytopenia with c-Mpl ligands including full-length recombinant human TPO (rHuTPO).

**IMPLICATIONS OF CONVENTIONAL MANAGEMENT STRATEGIES FOR THROMBOCYTOPENIA**

At this time, platelet transfusions are the most effective means of controlling bleeding and the acute risks of severe thrombocytopenia associated with the treatment of hematologic malignancies and solid tumors [5]. However, there are a number of issues related to platelet transfusion therapy that support the need for alternate strategies to reduce or eliminate the need for this blood product. These include availability, cost, refractoriness, transfusion reactions and disease transmission [5].

Blood products, including platelets, are a limited resource. While packed red blood cells can be stored for 42 days, platelets must be discarded after only 5 days. This short shelf life contributes to a chronic restriction of the supply of usable platelets [6]. Another factor that severely limits platelet availability is the relative shortage of blood donors. While the demand for blood as a source of platelets, red blood cells, and other blood products is growing at a rate of 1% annually, donations are falling by approximately the same percentage [7]. This has created routine shortages during some holidays and is expected to result in more widespread shortages in the near future. The growing problems with supply may be further complicated by the attempt by the Food and Drug Administration (FDA) to prevent the transmission of bovine spongiform encephalopathy; the most recent action in this regard has been to impose a ban on blood donations by potential donors who have lived in or visited the United Kingdom for a cumulative period of 6 months or more from 1980 to 1996 [8].

Although platelets are harvested from voluntary donors, platelet transfusions are among the most expensive supportive measures in the field of hematology and oncology [9]. In one study, platelet transfusion costs ranged from $389 (merged units of random platelet donors) to $661 (for a specially processed single donor apheresis) [5, 10]. Associated costs include disposable materials (processing and administration), storage, management of inventory, outdating, wastage, HLA typing, record keeping, and nursing time to administer and evaluate potential reactions [5]. Refractoriness to platelet transfusions is associated with significantly greater inpatient costs and length of stay [11]. Efforts have been made to control costs and increase efficiency of transfusion practices by utilizing lower-dose single-donor platelet transfusions, but this practice may actually increase overall hospital transfusion costs [12].

Patients refractory to platelet transfusions will fail to achieve an adequate platelet count increment following transfusion, and this can be a significant clinical risk. Refractoriness is identified in 15% to 40% of patients who receive multiple platelet transfusions over time [5]. An inadequate increment in platelet numbers following transfusion is most often due to alloimmunization. It can also result from drug-related antibodies, hypersplenism, severe disseminated intravascular coagulation, or massive hemorrhage [13]. Refractory patients are difficult to manage and require platelet transfusions from donors who are HLA-A and HLA-B selected. In some instances, platelet cross-matching may be necessary to find suitable donors [13].

Approximately 5% to 30% of platelet transfusions are associated with a reaction, usually of the febrile, non-hemolytic type [5]. Reactions may be due to recipient HLA antibodies reacting with donor leukocytes or to cytokines in the donor plasma [14, 15]. Steps to decrease the incidence of reactions include leukocyte depletion, platelet washing, or infusion of platelets stored for 3 days or less [16, 17]. Transfusion-associated infections are another risk of platelet administration. Platelet transfusions can transmit the same infections as a unit of whole blood. Intensive donor screening, serologic tests, and nucleic acid testing on the unit have significantly reduced the risk of transfusion-associated infection. Transmissible diseases, however, remain a concern [5]. Although the risk of transfusion-associated infection of a single-donor platelet pack is limited to that of the donor, the risk of pooled products (or multiple single-donor platelets) is increased by the number of different donors.
Septic reactions are the most common serious risk of platelet transfusion. Compared with platelet concentrates, the use of single-donor platelets can significantly reduce the incidence of these reactions [18].

Costs and complications associated with platelets indicate that alternatives to platelet transfusions are a reasonable therapeutic goal. The search for pharmacologic interventions to raise platelet counts has been helped by advances in the understanding of hematopoiesis and thrombopoiesis.

**Biology of Thrombopoietic Growth Factors**

Megakaryocyte development can be conceptually divided into three stages: the development of early stage progenitor cells, subsequent expansion and differentiation into promegakaryoblasts, and mature megakaryocytes [19]. Uncommitted stem cells give rise to megakaryocyte progenitor cells, primitive cells upon which ultimately rests the expansion of later-stage megakaryocyte numbers. Like progenitor cells of other lineages, these elements lose proliferative potential as they develop [19]. Promegakaryoblasts are transitional elements that link the progenitor cells with the more mature, postmitotic population. Mature megakaryocytes exist in three maturational stages: megakaryoblast, promegakaryocyte, and granular megakaryocyte [19]. Megakaryoblasts possess morphologic features of other myeloid blasts but can often be recognized by their enlarged size. Promegakaryocytes are larger cells with increased amounts of cytoplasm containing platelet-specific granules. Granular megakaryocytes are the largest myeloid elements in the bone marrow. Each of these polyploid cells has large amounts of granular cytoplasm that has been estimated to be responsible for the production of several thousand platelets [19].

The control of hematopoiesis involves a complex interaction among hematopoietic elements, bone marrow stromal cells, and soluble cytokines and hematopoietic growth factors [20]. Cytokines and hematopoietic growth factors are regulatory proteins that may act in an autocrine, paracrine, or endocrine fashion. They exert their effect by binding to high-affinity receptors expressed on the cell surface of responsive elements. Many cytokines and hematopoietic growth factors influence megakaryocytopenesis by increasing the number of committed progenitor cells, decreasing cycling time, and increasing the number of cycles per progenitor. Early-acting cytokines include stem cell factor (kit ligand), IL-3, IL-6, IL-11, GM-CSF, and erythropoietin (Epo). While these growth factors may increase lineage-specific differentiation of primitive elements, this biological activity may not translate directly into the ability to increase platelet production, a role that the more specific actions of TPO may support optimally.

**Cytokines with Thrombopoietic Potential**

Although TPO, the c-Mpl ligand, is the primary endogenous regulator of thrombopoiesis, clinical studies have been conducted on a number of early-acting cytokines to fully evaluate their thrombopoietic potential (Table 1) [2]. In particular, preclinical studies have indicated that IL-1, IL-3, IL-6, GM-CSF, and IL-11 can stimulate megakaryocyte growth and platelet production [2, 21].

**IL-1**

IL-1 is an important agent for megakaryocytopenesis. In vitro culture systems, the combination of IL-1 and megakaryocyte growth and development factor (MGDF), a biotechnology-derived version of the endogenous c-Mpl ligand, was superior to other cytokine combinations (i.e., IL-3, IL-6, IL-11, stem cell factor, MGDF) in optimizing the number of megakaryocytes and megakaryocyte progenitor cells in a liquid culture system [22]. In human studies, administration of IL-1β increased platelet counts [23]. Unfortunately, IL-1 has significant proinflammatory properties, inducing fever, hypotension, fluid retention, and supraventricular arrhythmias, all of which combine to eliminate its therapeutic utility as a thrombopoietic agent [24, 25].

**IL-3**

Megakaryocytic cell lines express the IL-3 receptor. In vitro, IL-3 induces both proliferation and the early differentiation of murine megakaryocytic progenitors [26, 27]. An early study of recombinant human IL-3 for the treatment of chemotherapy-induced thrombocytopenia suggested modest efficacy [28]. Toxicities related to IL-3 include a flu-like syndrome and other abnormalities related to the release of inflammatory mediators such as leukotriene C4 [29]. These side effects, as well as the marginal efficacy, have limited...
the clinical utility of IL-3 in the treatment of thrombocytopenia. Consequently, efforts have been made to develop synthetic IL-3 agonists having increased hematopoietic activity without an increased side-effect profile. One of these, dubbed “synthokine,” significantly reduced the duration of thrombocytopenia and enhanced platelet recovery compared with controls in a nonhuman model of radiation-induced bone marrow aplasia [30]. However, the activity of this agent, as yet, has not been confirmed in appropriately powered human clinical trials.

IL-6

IL-6 has potent thrombopoietic activity and stimulates platelet production in an in vivo murine model [26]. Clinical trials of recombinant IL-6 have reported side effects of fever, headache, myalgias, hyperbilirubinemia, rapid development of anemia, and fatigue with only modest thrombopoietic activity [31-34]. This agent is no longer in active clinical development either.

GM-CSF

In nonhuman primate models, GM-CSF increases megakaryocyte volume and ploidy with variable increases in platelet counts [35]. Low doses of GM-CSF have a thrombopoietic effect in approximately one-third of patients with transfusion-dependent thrombocytopenia [36]. Genetic engineering has been used to link the IL-3 and GM-CSF gene products. The resultant chimeric protein, PIXY321, has failed to provide significant benefits in patients with thrombocytopenia [37].

The above studies indicate that although IL-1, IL-3, IL-6, and GM-CSF act upon early hematopoietic elements, their theoretical potential has not been achieved in clinical trials. Patients treated with these cytokines have experienced significant side effects without evidence of clinically significant biologic activity. Even with genetic engineering to increase this activity, synthetic IL-3 and IL-3/GM-CSF have failed to provide clinical benefit. In addition, the activity of early-acting cytokines on primitive hematopoietic elements has raised concerns that they might increase the number of blasts in thrombocytopenic patients with myelodysplasia or treated acute leukemia. These factors have all led to the discontinuation of clinical investigation of these agents and an ongoing search for safe and effective alternatives.

rHuIL-11

IL-11 is a protein product of bone marrow stromal cells [38]. It can enhance the growth of early hematopoietic progenitor cells, and it stimulates both megakaryocytopoiesis and erythropoiesis. Administration of recombinant IL-11 to myelosuppressed animals accelerates the recovery of multilineage blood elements, including platelets.

In phase I studies of women with advanced breast cancer receiving aggressive doses of combination chemotherapy, administration of recombinant human IL-11 produced a dose-dependent increase in bone marrow progenitor cells, megakaryocytes, cycling megakaryocytes, and mean platelet counts, and it also decreased the anticipated incidence of severe thrombocytopenia [39, 40]. Adverse events accompanying rHuIL-11 included anemia, fatigue, myalgias, dependent edema, and cardiovascular events. Administration of the recombinant cytokine produced dose-dependent increases in mean platelet counts and bone marrow megakaryocyte and progenitor cell counts [40]. Compared with expectations, patients receiving rHuIL-11 experienced a reduced incidence of severe thrombocytopenia. The efficacy of rHuIL-11 (25 µg/kg and 50 µg/kg) to prevent the need for platelet transfusions in cancer patients with severe thrombocytopenia due to chemotherapy was only evaluated in 16 patients from this trial, however. The marginal activity of IL-11 to decrease the risks of thrombocytopenia was confirmed in a small randomized, placebo-controlled study of rHuIL-11 to prevent chemotherapy-induced thrombocytopenia. This trial tested only 77 women with breast cancer treated with dose-intensive chemotherapy [41]. IL-11-associated toxicities reported in these studies included fatigue, myalgias, arthralgias, and fluid retention with weight gain [40, 41].

The efficacy of rHuIL-11 in preventing the need for platelet transfusions, compared with placebo, was also studied in 93 cancer patients receiving chemotherapy who had a previously documented need for platelet transfusion support [42]. These patients had required platelet transfusions in the chemotherapy cycle immediately preceding entry into the study. Among the patients receiving placebo along with the chemotherapy, 96% again experienced thrombocytopenia requiring platelet transfusion. In contrast, a 50-µg/kg dose of rHuIL-11 modestly reduced the platelet transfusion requirements to 70% (p < 0.05) [42]. Based upon these results, as well as the lack of any other available therapies besides transfusional support, the FDA approved rHuIL-11 for the treatment of severe chemotherapy-induced thrombocytopenia. Treatment-associated toxicities from the randomized study were the same as those reported in prior studies and confirmed that the use of IL-11 is frequently associated with unacceptably severe side effects. These IL-11-induced toxicities included a low incidence of atrial arrhythmias and syncope, as well as more common problems with edema and fluid retention. Despite these results with conventional chemotherapy regimens, a randomized trial of rHuIL-11 in the autologous bone marrow transplantation setting failed to demonstrate significant
efficacy in decreasing platelet transfusion requirements [43]. Given its modest activity and nontrivial side-effect profile, rHuIL-11 must be viewed as one possible therapeutic option, but it is clear that more effective and tolerable alternatives would still be welcomed by clinicians and patients. IL-11 has simply not satisfied the unmet needs for a thrombopoietic agent that can provide a safe and effective alternative to platelet transfusions.

**c-Mpl-Targeted Therapies**

Despite extensive investigations, early-acting cytokines and rHuIL-11 have not provided clinicians with an optimal or reliable thrombopoietic agent that can be viewed as fully safe and effective. However, as with vascular endothelial growth factor and its receptor, advances in molecular biology have provided us with tools to characterize more fully the hematopoietic cytokines, identify their targets, and improve the therapeutic potential for their signaling pathways. The search for TPO, a lineage-specific growth factor specific for platelet development, began in the 1950s [44]. For the next 40 years, investigators attempted to identify and purify the elusive hematopoietic growth factor from a variety of sources including plasma and serum of patients with thrombocytopenia.

The myeloproliferative leukemia virus (MPLV) is a leukemogenic murine retrovirus that infects hematopoietic progenitors. Following infection, progenitor cells acquire independence from hematopoietic growth factor-induced proliferation and terminal differentiation [3]. The first major advance in the search for TPO occurred in 1992 with identification of c-Mpl, the cellular homologue of the MPLV-derived oncogene, v-Mpl [3]. Sequence analysis of the extracellular domain of human MPL indicates that it shares structural and amino acid homology with members of the hematopoietic growth factor receptor superfamily [3].

c-Mpl is present on multilineage myeloid progenitor cells, and its expression is sustained in lineage-restricted megakaryocyte/erythroid precursors; however, the receptor is lost with granulocyte/monocyte or lymphoid lineage commitment [45]. c-Mpl knockout mice are viable but demonstrate a reduction in platelet count of approximately 90% compared with controls [46]. This is a result of a reduction in the number of progenitor cells and a decrease in megakaryocyte ploidy. Since the platelets and megakaryocytes in c-Mpl knockout animals are morphologically and functionally normal, the function of c-Mpl appears to be controlling the numbers rather than the maturation of the megakaryocyte population [46, 47]. In 1994, four groups reported cloning the gene for the c-Mpl ligand [48-51].

The identification of the c-Mpl ligand as TPO was confirmed with the observation that all of the platelet- and megakaryocyte-stimulating activity of thrombocytopenic plasma could be removed by binding the factor to recombinant c-Mpl [4]. TPO is now established as the primary endogenous and physiologic regulator of platelet levels. Two variant forms of human thrombopoietin were developed to target c-Mpl: megakaryocyte growth and development factor (PEG-rHuMGDF), a truncated and pegylated derivative of the molecule produced in E. coli (Amgen Inc.; Thousand Oaks, CA), and rHuTPO, the full-length, glycosylated molecule produced in a mammalian cell line (Genentech, Inc.; San Francisco, CA and Pharmacia Corp.; Peapack, NJ). In addition, synthetic c-Mpl ligands have also been developed subsequently.

**MGDF**

rHuMGDF is a potent stimulator of megakaryocytopoiesis and platelet production and is highly selective for cells bearing the Mpl receptor. Studies of PEG-rHuMGDF indicated that it produced a dose-related enhancement of platelet recovery after myelosuppressive chemotherapy and that it could help to mobilize peripheral blood progenitor cells. Unfortunately, the molecule proved immunogenic when administered via a subcutaneous route of administration. A subset of both cancer patients and normal platelet-donor volunteers developed neutralizing antibodies following treatment with PEG-rHuMGDF. Consequently, the molecule was withdrawn from clinical development in 1998 [52]. Interestingly, it remains unclear how much of the immunogenicity might have been due to the subcutaneous route of administration versus the substantial modification of the molecule itself as a variant from normal physiology.

**rHuTPO**

Injection of a single dose of intravenous rHuTPO, increased platelet counts 61% to 213% (p = 0.002) in a dose-dependent fashion [53]. Platelet counts began to rise approximately on day 4 following injection of the recombinant c-Mpl ligand and peaked on a median of day 12. Platelets were morphologically normal and demonstrated a physiologic response to a variety of platelet agonists. Following injection, the bone marrow showed a dose-related increase in megakaryocytes as well as expansion of the progenitor pool of multipotential, megakaryocyte, myeloid, and erythroid lineages. In addition, there was a 5.7- to 10-fold mobilization of progenitors of multiple lineages into the peripheral blood. Patients receiving rHuTPO tolerated the treatment well and experienced no adverse events [53].

The efficacy and safety of rHuTPO administered before chemotherapy and after a second cycle of chemotherapy was evaluated in a phase I/II study of 29 patients with gynecologic cancer treated with carboplatin [54]. Treatment with
1.2 µg/kg body weight of rHuTPO, the optimal biologic dose of the c-Mpl ligand, after chemotherapy significantly reduced the degree and duration of thrombocytopenia and enhanced platelet recovery (Table 2) [54]. The mean platelet count nadir in cycle 2 (carboplatin plus rHuTPO) in this group was higher (44 × 10⁹/l versus 20 × 10⁹/l; p = 0.002) and the number of days with a platelet count <20 × 10⁹/l was shorter (4 versus 7 days; p = 0.006) than in cycle 1 (carboplatin only). In addition, platelet transfusion requirements were reduced from 75% of the patients in cycle 1 to only 25% of patients in cycle 2 (p = 0.013) [54]. Therapy with rHuTPO is well tolerated, without malaise or fever. Patients treated with this hematopoietic growth factor showed no thrombotic events [54]. Importantly, in contrast to the experience with MGDF, no neutralizing antibodies have been detected in humans receiving rHuTPO.

**SYNTHETIC MPL LIGANDS**

Synthetic peptides can be designed to target MPL. These small-molecular-weight substances lack homology with the endogenous physiologic MPL ligand. One example, GW395058, is a pegylated peptide being studied for the treatment of chemotherapy-induced thrombocytopenia [55]. In a canine model of chemotherapy-induced thrombocytopenia, GW395058 reduced the thrombocytopenic effects of carboplatin without causing drug-related adverse events [56]. Although it has the potential to induce the formation of neutralizing antibodies, experimental studies indicate that the risk is low. Genetic engineering techniques have been used to construct promegapoietin, a chimeric growth factor with binding activity for both the IL-3 and MPL receptors [57]. However, due to concerns about antibody development, clinical development of the molecule was discontinued in 1998 [2].

**STATE OF THE ART OF MPL-TARGETED THERAPIES**

Development of MGDF and promegapoietin has been suspended. Peptide mimetics of the MPL ligand are currently being studied in preclinical trials [2]. TPO is the natural MPL ligand. rHuTPO has been shown to be safe and effective without the side effects of the early-acting cytokines on thrombopoiesis (Table 3). Although MGDF therapy was associated with the development of neutralizing antibodies, rHuTPO has not been shown to be significantly immunogenic, as noted above [2]. There is certainly sufficient rationale to continue the clinical development of rHuTPO. The aim of ongoing clinical investigation of this novel hematopoietic growth factor will be to demonstrate that the excellent safety and tolerability profile will also be supported with definitive evidence of efficacy in appropriately powered clinical trials. By doing this, investigators will hopefully clarify dosing schedules in relationship to various chemotherapy protocols, establish its efficacy at consistently raising platelet counts in a diverse set of patients, and document that treatment with MPL-targeted therapy can improve clinical outcomes.

Clinical studies are under way to evaluate targeted MPL therapy with rHuTPO in a number of diseases. These include immune thrombocytopenic purpura, aplastic anemia, myelodysplasia, the thrombocytopenia with absent radii syndrome, HIV-induced thrombocytopenia, and drug-induced thrombocytopenia. Studies are also evaluating rHuTPO in the medical oncology population as both primary and secondary prophylaxis for the prevention or treatment of chemotherapy-induced thrombocytopenia requiring platelet transfusions. Study populations include sarcoma patients treated with dose-intensive regimens of doxorubicin and ifosfamide, patients with refractory or recurrent non-Hodgkin’s lymphoma treated with combination chemotherapy, as well as multiple myeloma patients. Studies are also under way in the pediatric population in patients with recurrent solid tumors treated with ifosfamide, carboplatin, and etoposide chemotherapy.

**CONCLUSIONS**

Management of severe thrombocytopenia remains a significant challenge to practicing hematologists and oncologists. Although platelet transfusions remain the standard of care for acute management of this disorder, administration of platelets is associated with a number of problems including availability, cost, immunogenicity, and
transmission of infection. Additionally, there is good reason to suspect that prevention will be a preferable option to therapy, much as is true in many other areas of medical practice. Therefore, since currently available means for treating chemotherapy-induced thrombocytopenia are inadequate, investigators are actively developing rationally targeted pharmacologic interventions for this problem. Despite the somewhat naïve hopes that primitive-acting cytokines might be effective therapy for this disorder, several candidate molecules in this regard have failed to fulfill this promise. rHuIL-11 is the only therapeutic agent currently approved for this problem. However, treatment with rHuIL-11 is associated with significant risk of side effects and only modest efficacy. At this time, MPL-targeted therapy offers the best hope for the future. rHuTPO is a potent ligand for MPL. Phase I/II studies indicate that this agent is well tolerated. Additionally, preliminary efficacy data from these studies will need to be confirmed by prospective randomized trials that show that this agent may reduce the need for platelet transfusions, thereby optimizing the supportive care for patients with thrombocytopenic disorders, including those resulting from anticancer chemotherapy.

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