THROMBOPOIETIC FACTORS

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ABSTRACT

Over the past two decades, there have been major advances in the therapy of malignancies. One of the major obstacles to the delivery of effective doses of chemotherapeutic agents is the hematopoietic toxicity associated with certain agents. Chemotherapy dose modification, administration of antibiotics and red cell and platelet transfusions have constituted the major means for coping with the hematologic side effects of cancer treatment. Despite the considerable success of these supportive care efforts, myelosuppression is still an important problem both for health care workers and patients. After the successful use of granulocyte colony stimulating factor (G-CSF) as prophylaxis against neutrophilic complications of chemotherapy, attention has shifted to thrombocytopenia and encouraged the clinical investigation of several agents with the ability to stimulate thrombocytosis.

Among the variety of thrombopoietic molecules, five agents have now been tested clinically. These are interleukin 1 (IL-1), IL-3, IL-4, IL-11 and IL-3 and GM-CSF fusion protein (PIXY321). Two other molecules IL-3 mimetic (SC55494) and thrombopoietin (TPO) are poised to enter clinical trials. Current information about these molecules are largely confined to toxicity data and very limited efficacy results from phase I investigations.

IL-1

IL-1 is a broad acting cytokine which plays an important role as a regulator of hematopoiesis by inducing a variety of hematopoietically active cytokines and by synergizing with these cytokines to amplify the hematopoietic response. It is also a prominent component of the inflammatory response to sepsis. IL-1 has two different forms: IL-1 alpha and IL-1 beta which are structurally different but have same biologic actions. Animal studies with IL-1 suggest that it can act either as a myelostimulatory drug when given after chemotherapy or as a myeloprotector when administered prior to a cytotoxic agent.

This agent has now undergone phasa I/II testing in the setting of chemotherapy-induced cytopenia and high dose chemotherapy and stem cell transplantation.

Phase I testing of the cytokine alone has shown that mild thrombocytopenia and anemia can occur during IL-1 treatment, but this is followed by a late thrombocytosis that peaks two to three weeks after IL-1 initiation. IL-1 can induce a modest neutrophilia coincident with the transient induction of increases in serum G-CSF levels. IL-6 is also briefly produced (1,2).

Clinical administration of IL-1 alpha prior to chemotherapy has revealed contradictory evidence of hematologic protection. One trial showed no benefit resulting from prechemotherapy administration, but another study indicated that neutrophil and platelet recovery may be marginally enhanced when IL-1 alpha is given prior to high dose chemotherapy and autologous bone marrow transplantation (ABMT) (3,4).

Trials of IL-1 after chemotherapy have also produced inconsistent results. Two phase I studies indicated that a short course of IL-1 after carboplatin will significantly increase platelet number to levels more than 50.000/ml.(3,5). However improved platelet and neutrophil recovery was not achieved when IL-1 alpha was given after a carboplatin, cisplatin, cyclophosphamide combination for ovarian cancer, nor when it was administered two days after 5-fluorouracil therapy (6,7). In another trial, intermittent treatment with IL-1 beta following nitrosureas has been claimed to improve both neutrophil and platelet nadirs (8). Enhanced eutrophil recovery was not seen in any of these trials.

In patients undergoing autologous progenitor cell transplantation in support of intensive chemotherapy, IL-1 therapy resulted in hastened neutrophil recovery. One of these trials showed that IL-1 might lessen the duration of thrombocytopenia and anemia, thereby decreasing hospitalization and transplant related costs (9).

Common side effects of both IL-1 alpha and beta include fever, chills, myalgias, headache and nausea. Dose limiting toxicities have been hypotension, pulmonary adema and renal dysfunction (1,4).

IL-3

IL-3 is also known as multi-CSF and it is a multilineage hematopoietic growth factor which regulates early and intermediate stages of hematopoiesis. It promotes proliferation and differentiation of multipotential and committed progenitor cells of the myeloid, erythroid and megakaryocytic cell lineages. The function of mature monocytes and eosinophils are effected by IL-3, but it has no effect on the function of mature neutrophils. Clinical trials of this molecule have focused on its use following bone marrow transplantation, as a peripheral blood progenitor-mobilizing agent with G-CSF or with GM-CSF.

Administration of IL-3 in the clinic provokes late and moderate thrombocytosis. It can also stimulate a leukocytosis, but this effect is modest in proportion to the vigorous increases in granulocyte counts that can occur with G-CSF or GM-CSF.

A number of phase I trials of IL-3 have been performed in conjunction with chemotherapy and have included control groups to give preliminary assessments of efficacy. The most optimistic of these trials have suggested a speeding of both platelet and neutrophil recovery and occasional improvements in on-time administration of chemotherapy, but other protocols have documented little improvement in these end points (10,11). Phase I evaluation of IL-3 alone after ABMT has suggested the potential for more rapid myeloid and platelet recovery, but other experience may not bolster these claims (12).

IL-3 has also a modest effect on neutrophil generation, so combined administration of IL-3 and GM-CSF has been tried. When given without chemotherapy, treatment with a sequence of IL-3 followed by GM-CSF demonstrates an equivalent thrombocytosis but a greater leukocytosis than IL-3 alone (13). Clinical trials have shown conflicting results. One trial indicated improved platelet and neutrophil restoration and less toxicity with sequential IL-3 and GM-CSF administration, but another advocated concurrent administration of the cytokines (14,15). Phase I trials examining the combined and sequential use of IL-3 and G-CSF have not demonstrated significantly enhanced platelet recovery, either in patients receiving outpatient chemotherapy or ABMT (15,16).

Common toxicities seen with IL-3 administration have consisted of fever, flu like symptoms, facial flushing, headache, conjunctival inflammation, bone pain, local injection site reactions, rashes, tachycardia, dyspnea, edema and pericardial effusions (17).

PIXY321

Based on clinical data supporting use of IL-3 and GM-CSF in combination, investigators at Immunex developed a fusion protein combining GM-CSF and IL-3 into a single molecule, designated PIXY321. Clinical trials assessing the myelorestorative potential of PIXY321 have documented significant neutrophil restorative activity that may be comparable to that of G or GM-CSF. Improved platelet counts have been noted in some trials, but the results have not been consistently significant (18,19).

The most common side effects of PIXY321 are injection site reactions and constitutional flu like symptoms. The maximum tolerated dose of PIXY321 has not been determined yet.

IL-6

This multifunctional cytokine has effects on T cells, myeloid cell differentiation, regulation of acute phase reactants and the development and maturation of megakaryocytes. Its administration to humans in early phase I trials has been shown to double platelet counts, with the peak thrombocytosis occurring in two weeks (20). Changes in neutrophil are unusual, but many patients develop a transient anemia that reverses promptly upon cessation of IL-6. Administration of IL-6 and GM-CSF together results in the expected GM-CSF induced leukocytosis and a thrombocytosis comparable to that seen with IL-6 alone (21). IL-6 toxicities are fever, chills, fatique, myalgias, headache, bone pach, anorexia, nausea and erythema at subcutaneous injection sites. Increases in liver function tests and serum creatinine are not uncommon (22).

IL-11

IL-11 enhances the growth of IL-3 dependent megakaryocytic colony formation, promotes maturation of late human megakaryocytic

progenitors, and induces production of acute phase proteins. In monkeys it can double platelet counts two weeks after initiation of treatment. Similar two fold platelet count increments are observed in cancer patients receiving IL-11 alone. Peak platelet levels occur between days 13 and 19. Like with IL-6 transient anemia has been observed. It has no effect on white blood cell counts (23, 24).

Toxic reactions to IL-11 include peripheral edema, nasal congestion, fatigue, myalgias, arthralgias and injection site reactions. IL-11 is the only thrombopoietic agent that has not induced febrile responses.

THROMBOPOIETIN (TPO)

In the past several years a murine oncogene has been characterized as an orphan cytokine receptor with a potential influence on thrombopoiesis. Attempts to isolate the true thrombopoietin were initiated, culminating in the identification of a cytokine that appeared to be a highly active and specific platelet-lineage growth factor.

In animal studies it has been shown that platelet recovery was substantially enhanced with this new cytokine. No information regarding toxicity or thrombotic complications arising out of TPO administration or excessive thrombocytosis has been described (25, 26). It is expected that clinical trials of this new agent will begin shortly.

CONCLUSION

As these new agents enter clinical trials, it is important that clinicians focus on the endpoints of benefit that will be used to decide the clinical merits of any of these agents. Because death or serious bleeding are rarely a complication of chemotherapy administration, it is unlikely that length of life can be improved by use of a thrombopoietic agent. So to ensure appropriate clinical application of thrombopoietic agents, careful attention must be paid to the patient's need and drug toxicity.

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