RhIL-11 for the Prevention of Dose-Limiting Chemotherapy-Induced Thrombocytopenia

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In order to derive maximum benefit from treatment with chemotherapeutic agents, adherence to the established chemotherapy dose and schedule is imperative.

Improving Outcomes by Optimizing Platelet Support

Although granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) and granulocyte-macrophage colony-stimulating factor (GM-CSF, molgramostim [Leucomax]) are capable of ameliorating the risk of neutropenic infections, they do not address the problem of thrombocytopenia. In fact, they may actually aggravate thrombocytopenia by permitting the use of more highly myelotoxic agents or more dose-intensive oncology regimens.[7,8] As a result, thrombocytopenia induced by anticancer therapy has emerged as the major dose-limiting hematologic toxicity among patients with cancer.

The standard practice of reducing drug doses or delaying the next cycle of chemotherapy in patients with low platelet counts may be acceptable for patients receiving palliative chemotherapy. However, because of the reduced likelihood of cure or disease remission, this reactive style of toxicity management is less acceptable for patients receiving aggressive chemotherapy with a curative intent. Perhaps a more proactive approach should be considered now that the availability of platelet growth factors has provided clinicians with a means of supporting platelet homeostasis during chemotherapy. This approach presents the possibility of enabling cancer patients to receive full doses of chemotherapy without interruption, potentially improving tumor control and, ultimately, survival.

Epidemiologic data indicate that approximately one-quarter of the patients undergoing chemotherapy for nonmyeloid malignancies can expect reductions in platelet counts to nadirs ≤ 50,000/µL.[9,10] For these patients, the standard management strategy has been to continue chemotherapy using reduced drug doses if platelets are at ≤ 50,000/µL,[8] or to delay administering the next cycle until platelets have recovered to ≥ 100,000/µL.[7] Therefore, the probability of cure may be compromised because of slow platelet recovery.

RhIL-11 Therapy

With the increasing knowledge of the diverse regulatory role of cytokines and growth factors in biological systems and the rapid development of human recombinant forms, the development of a clinically useful platelet growth factor was inevitable. Recombinant human interleukin-11 (rhIL-11, also known as oprelvekin [Neumega]) is currently the only drug approved by the US Food and Drug Administration for the prevention of chemotherapy-induced thrombocytopenia in patients with nonmyeloid malignancies. This multifunctional cytokine is defined as a [thrombopoietic (platelet) growth factor] with efficacy established in controlled clinical trials.

Both adult and pediatric patients with solid tumors or lymphomas have been safely treated with rhIL-11. Adults have benefited from rhIL-11 therapy in terms of preventing the development of platelet nadirs < 20,000/µL, accelerating platelet recovery, and/or subsequently reducing the
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requirement for platelet transfusions. Positive trends have been seen in children as well, but no definitive controlled pediatric trials have been performed. rhIL-11 is generally well tolerated, with little cause for discontinuation in controlled clinical trials. Edema is the most frequently reported adverse event, but it is usually easily managed and reversible.

Prophylactic therapy with rhIL-11 must be started within 24 hours after the last dose of chemotherapy and continued for 10 to 21 days until platelet counts of ≥ 50,000/µL are achieved. Early initiation of therapy takes into account the stimulatory role of rhIL-11 throughout both early and later stages of megakaryocytopoiesis, providing for the release of newly formed platelets into circulation at approximately the same time as the expected postchemotherapy platelet nadir. Bearing in mind the maturation time of megakaryocytes, it is clear that rhIL-11 is not designed to function as rescue therapy once patients have become severely thrombocytopenic (platelet count < 20,000/µL).

For the purpose of supporting the delivery of unmodified chemotherapy regimens, rhIL-11 therapy should be initiated prophylactically, when there is a high probability that platelet reductions resulting in dose reduction and/or delay will occur (platelet counts of ≤ 50,000 or even ≤ 70,000/µL). During myelosuppressive chemotherapy, the administration of subsequent cycles is routinely delayed until the platelet count has recovered to 100,000/µL as mandated by almost all protocols for investigations of chemotherapeutic regimens.[7,11-16]

A demonstrated ancillary benefit of rhIL-11 therapy's thrombopoietic effect is avoidance of platelet transfusions. Considering the numerous transfusion-related complications, this would be welcomed by both clinicians and patients. For example, the recently and highly publicized risk of contracting bacterial and viral infections from transfused blood products is undoubtedly a major concern. Among patients with cancer who are already immunosuppressed, contracting infections from treatments intended to support their well-being is an irony they can ill afford. Furthermore, the development of refractoriness to repeated platelet transfusions is a significant risk.

In summary, when used appropriately, rhIL-11 enhances platelet recovery and, thus, facilitates the maintenance of aggressive chemotherapy regimens without dose modification, thereby enabling the best possible outcome in patients with nonmyeloid malignancies.

References:
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