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Treating Chemotherapy-Induced Thrombocytopenia: Is It Time for Oncologists to Use Thrombopoietin Agonists?

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Given the availability of new US Food and Drug Administration (FDA)-approved thrombopoietic agents, it is timely and of great interest to discuss how they might be used in the management of thrombocytopenia in cancer patients. Dr. Kuter's review accurately summarizes the ontogeny of thrombocytes and the role of thrombopoietin in enhancing megakaryocyte development and differentiation.[1] While his article appropriately acknowledges that thrombocytopenia in cancer patients can be caused by a variety of factors, such as immune thrombocytopenia, infections, and coagulopathy, the most common cause of thrombocytopenia in this setting is chemotherapy-induced thrombocytopenia. Thrombocytopenia is a major concern in cancer patients; not only does it result in an increased risk of bleeding, but importantly it can also lead to reduction in chemotherapy dose and frequency.

For cancer patients receiving chemotherapy with curative intent, dose reductions due to chemotherapy-induced thrombocytopenia may compromise their long-term disease-free survival. In published series, the incidence of grade IV thrombocytopenia (platelet counts < 250,000/ μ L) is 3% to 4%, with less than 3% of chemotherapy-treated patients receiving platelet transfusions. [2] Nevertheless, while severe thrombocytopenia requiring platelet transfusions is relatively rare, dose reductions by the oncologists treating these patients are common; such dose reductions support the clinical need for effective thrombopoietic agents that could be used prophylactically to prevent chemotherapy-induced thrombocytopenia, and they allow maintenance of chemotherapy dose density and intensity.

Since the time required for thrombopoietic agents to differentiate hematopoietic progenitors to megakaryocytes that produce platelets is 10–14 days,[3] these agents must be used prophylactically, before thrombocytopenia develops, if they are going to have practical clinical application in preventing chemotherapy-induced thrombocytopenia. Dr. Kuter presents his own anecdotal experience in using these agents prophylactically in cancer patients receiving chemotherapy, as well as results from small randomized phase II clinical trials. These clinical studies demonstrate a role of thrombopoietin agonists in improving compliance with cytotoxic regimens in cancer patients whose chemotherapy was delayed due to thrombocytopenia,[4] and they suggest that prophylactic use of eltrombopag or romiplostin might reduce the degree and duration of chemotherapy-induced

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thrombocytopenia. However, the long-term effect on survival among patients with cancer has not been established. Since guidelines pertaining to prevention and treatment of chemotherapy-induced thrombocytopenia are lacking, there is an urgent need for further studies of the benefit of thrombopoietin receptor agonists compared to other therapies used in thrombocytopenic patients.

It is important to note that past experience with the use of other hematopoietic growth factors has not been without significant long-term safety concerns. The use of recombinant thrombopoietin proteins to prevent chemotherapy-induced thrombocytopenia was marred by patients' development of autoantibodies to thrombopoietin that exacerbated their thrombocytopenia,[5] and, in the case of normal volunteer subjects, led to prolonged thrombocytopenia lasting weeks to months.[6,7] The clinical perspective on the role of hematopoietic growth factors in patients with cancer has been shaped most recently by negative clinical data related to use of recombinant erythropoietic agents in patients with solid tumor malignancies.[8] In spite of very aggressive promotional efforts by the pharmaceutical companies that marketed these agents, enthusiasm for their integration into the management of chemotherapy-induced anemia waned dramatically when they were shown to be associated with an increased risk of deep-vein thrombosis and decreased survival due to tumor progression among erythropoietin-treated patients.[9] Current concerns about previously unanticipated clinical effects with the newer thrombopoietin receptor agonists, including the induction of marrow fibrosis,[10] and the theoretical concern that a cytokine that promotes hematopoietic stem cell self-renewal might promote growth or survival of malignant cells, have limited the widespread clinical adoption of these new thrombopoietin-mimetics in the setting of cancer patients receiving chemotherapy.

An aspect of these drugs that is only briefly touched upon by Dr. Kuter is their potential use as radioprotective agents and their physiological role in maintaining the hematopoietic stem cell compartment. While most endogenous thrombopoietin is made in the liver, local production of thrombopoietin by bone marrow stroma has been demonstrated[11] and may be critical to the ability of marrow stromal cells to maintain a self-renewing population of hematopoietic stem cells.[12]

Additional long-term risks that must be considered in the setting of chemotherapy-induced thrombocytopenia, given the increased risk of secondary myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) associated with use of chemotherapy, are that chronic use of exogenous thrombopoietic agents could promote the development of these diseases; however, secondary development of MDS and AML has not been observed to date in clinical trials of these agents.[13]

Current success of thrombopoietic agents in treating immune thrombocytopenic purpura and aplastic anemia demonstrates the therapeutic abilities of these agents. Therefore, further investigation into their usefulness in other hematologic pathologies, such as chemotherapy-induced thrombocytopenia, is warranted. Dr. Kuter appropriately stresses the need for prospective, placebo-controlled, double-blinded clinical trials of the new thrombopoietin receptor agonist drugs in the management of chemotherapy-induced thrombocytopenia, to address concerns about the safety and practical efficacy of these expensive new drugs before

we accept them as standard therapies for prevention of thrombocytopenia associated with chemotherapy in our patients.

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