Thrombocytopenia: Optimizing Approaches in Cancer Patients

April 15, 2015 | Oncology Journal [1]
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In this issue of ONCOLOGY, Dr. Kuter insightfully summarizes the differential diagnosis and management of thrombocytopenia in cancer patients.[1] Chemotherapy-induced thrombocytopenia causes nearly two-thirds of cases of thrombocytopenia in the cancer setting.[2] In patients receiving chemotherapy, thrombocytopenia leads to dose reductions in 15% of treatment cycles and chemotherapy delays in 6% of cycles.

Thrombocytopenia complicated by bleeding occurs in 9% of cycles. Bleeding complications are more common with a prior bleeding history; baseline platelet count < 75,000/µL; bone marrow metastases; poor performance status; or administration of cisplatin, carboplatin, carmustine, or lomustine.[3] Thrombocytopenia-associated healthcare costs may be considerable even in the absence of bleeding, due to prophylactic transfusions, additional clinic visits, and frequent laboratory monitoring.[4] Ultimately, myelosuppression resulting in an inability to administer the optimal dose of chemotherapy may lead to inferior treatment outcomes.[5]

While chemotherapy-induced thrombocytopenia is the most common type of thrombocytopenia in cancer patients, the clinical scenario of an individual patient may suggest other causes—such as drug-induced thrombocytopenia or sepsis—as the most likely etiology. In some cases, the cause of thrombocytopenia cannot be ascertained based on history alone, and additional evaluation is necessary. Here, we will discuss our clinical approach to thrombocytopenia in cancer patients when chemotherapy and radiation therapy are not the likely explanation. Typical laboratory evaluation in such cases includes complete blood cell count, coagulation studies, evaluation of fibrinogen and D-dimer levels, and assessment for the presence of fibrinogen degradation products. If thrombotic microangiopathy (TMA) is a consideration, then levels of creatinine, bilirubin, and lactate dehydrogenase (LDH) should also be obtained. Review of the peripheral blood smear is essential in diagnostic evaluation of TMA and disseminated intravascular coagulation (DIC). Peripheral blood smear findings are important in determining whether a bone marrow biopsy is warranted; biopsy may be used to evaluate for suspected bone marrow metastases or treatment-related acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS).[6,7]

TMAs are characterized by microvascular thrombosis, red blood cell (RBC) destruction, and platelet consumption. Chemotherapy-related hemolytic uremic syndrome (HUS) is a form of TMA. It is characterized by hemolytic anemia, the presence of schistocytes on a peripheral blood smear, thrombocytopenia, renal insufficiency, elevated LDH, and normal serum levels of the metalloprotease ADAMTS13.[8-11] It is most commonly seen in patients treated with mitomycin C or gemcitabine, but HUS has also been reported with targeted agents, such as bevacizumab or sunitinib.[12] Bevacizumab-induced HUS is proposed to be the result of inhibition of vascular endothelial growth factor signaling in the kidney.[12] HUS induced by mitomycin C and gemcitabine is thought to be the result of direct endothelial cell injury and is dose-dependent.[13] The onset of mitomycin-induced HUS has been described with a cumulative dose greater than 40 mg/m².[8] In one report, the cumulative dose with gemcitabine-induced HUS ranged from 2,450 to 48,000 mg/m², and the median duration of gemcitabine treatment was 5.8 months.[14] Based on the limited case reports of HUS with targeted therapy, there does not appear to be a clear correlation between the onset of HUS and the cumulative chemotherapy treatment dose.[11] DIC is observed in approximately 7% of patients. While it is more common with advanced disease, it portends a poor prognosis regardless of cancer stage.[15] Cancer patients with DIC may present with thrombosis (procoagulant form), bleeding (hyperfibrinolytic form), or laboratory abnormalities in the absence of clinical manifestations (subclinical form of DIC). The procoagulant form of DIC results from excess thrombin generation and is seen predominantly in adenocarcinomas or pancreatic cancer. Hyperfibrinolytic DIC, which occurs in acute promyelocytic leukemia and metastatic prostate cancer,
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Published on Cancer Network (http://www.cancernetwork.com)

Thrombocytopenia manifests with widespread bruising and bleeding. Subclinical DIC may be found in a variety of solid tumors and is typically revealed by a laboratory diagnosis. Diagnosis of DIC in cancer patients may be challenging. Although prolongation of the prothrombin time (PT) is part of the International Society on Thrombosis and Haemostasis diagnostic scoring system for DIC, only 60% of cancer patients with DIC have a prolonged PT. Fragmented RBCs are seen in about two-thirds of patients with DIC. The most common coagulation abnormalities in cancer patients with DIC are thrombocytopenia (median platelet count, 5,777,000/µL), hypofibrinogenemia, elevated D-dimer level, and elevated levels of fibrinogen degradation products. Monitoring for changes in platelet count and fibrinogen and D-dimer levels may be useful in monitoring patients at risk for DIC or with suspected DIC. Frequently, thrombocytopenia in cancer patients is accompanied by anemia or leukopenia. Pancytopenia in the setting of recent chemotherapy or radiation therapy typically may be managed with supportive care. If there is prolonged pancytopenia or pancytopenia in the absence of recent treatment, a bone marrow biopsy may be indicated to evaluate for bone marrow metastases or therapy-related AML or MDS. Almost all cancers may metastasize to the bone marrow, but bone marrow metastases are most common in breast, prostate, and lung cancers. Bone marrow infiltration by metastatic carcinoma leads to extramedullary hematopoiesis, predominantly from the spleen. This, in turn, may lead to premature release of hematopoietic cells from the spleen into the peripheral blood, which is termed a leukoerythroblastic reaction. Leukoerythroblastic changes in the peripheral blood include nucleated RBCs, teardrop RBCs, and immature myeloid cells. While the absence of leukoerythroblastic changes does not preclude the possibility of bone marrow metastases, the presence of such changes supports obtaining a bone marrow biopsy. Of 39 patients with metastatic gastric cancer, 44% reported bone pain, and 21% had active bleeding when diagnosed with bone marrow involvement. Thrombocytopenia was the most common indication of bone marrow biopsy (69% of cases), followed by DIC, leukoerythroblastic reaction, and anemia. As Kuter nicely describes, thrombocytopenia is a common finding in patients with malignant diseases. In the clinical approach to thrombocytopenia in the setting of cancer, it is critical to look for other causes of low platelet count, including infectious causes, coagulopathy, drugs, immune thrombocytopenia, post-transfusion purpura, and thrombotic microangiopathy. Typically, we consider performing bone marrow aspiration and biopsy in patients with unexplained thrombocytopenia or pancytopenia, particularly when a leukoerythroblastic reaction or pathologic features of dysplasia are noted on peripheral blood smear.

Financial Disclosure: The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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