Gemcitabine-Associated Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

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A patient being treated for metastatic adenocarcinoma of the pancreas presents to the clinic for a routine appointment. A complete blood count reveals hemoglobin of 6.5 g/dl and a platelet count of 30,000 K/mm³ thought to be from the last of many doses of gemcitabine. On assessment, the only complaint was fatigue with no evidence of bleeding or other abnormal physical findings other than pallor. Past medical history includes hypertension managed with three antihypertensive agents. Additional laboratory tests reveal elevated blood urea nitrogen (69 mg/dl), creatinine (2.76 mg/dl), and lactic dehydrogenase (LDH), as well as indirect bilirubin (2.1 mg/dl). The patient is admitted and transfused with packed red blood cells (pRBCs). The next day, the platelet count drops to 9,000 K/mm³ and the hemoglobin increases, appropriately, to 8.9 g/dl. Urinalysis is positive for hemoglobin (+ 3). The peripheral blood smear is positive for schistocytes (fragmented RBCs). A pheresis catheter is placed after the patient was evaluated by a hematologist and a nephrologist. A presumptive diagnosis of thrombotic thrombocytopenic purpura (TTP) with hemolytic uremic syndrome (HUS) was made.

The patient was started on plasmapheresis and dialysis because anuria promptly ensued. Daily plasmapheresis along with dialysis was performed for three weeks, and then dialysis was reduced to three times per week. At this time, rituximab was administered weekly for two weeks. Throughout the course of hospitalization, the patient’s hypertension was very labile and required medication changes and dose adjustments. After a month is the hospital, the patient was stable and discharged to a skilled nursing facility for rehabilitation and ongoing dialysis because renal function did not normalize.

Definitions

TTP is a condition characterized by the presence of thrombocytopenia and microangiopathic hemolytic anemia not caused by another etiology (George, 2013). TTP is a rare but serious complication of gemcitabine therapy, which may develop during or after the completion of therapy (Izzedine et al., 2006). HUS is the presence of hematuria related to hemolytic anemia, thrombocytopenia, and impaired renal function (Blackall & Marques, 2004). TTP and HUS are considered types of thrombotic microangiopathy (Izzedine et al., 2006). The presenting signs and symptoms are similar even when the etiologies are not, which explains the use of TTP-HUS terminology (George, 2006, 2013).

Pathophysiology

Although the exact etiology of gemcitabine-induced HUS has not been clearly elucidated, damage to the renal (glomerular) endothelial microvasculature related to gemcitabine is seen in affected patients (Zupancic, Shah, & Shah-Khan, 2007). There also may be damage or dysregulation of the complement system that may play a role in this process (Tsai, 2013). The problem appears to be drug-dose dependent (George, 2010). The damage produces an inflammatory response followed by clotting in the small blood vessels (Blackall & Marques, 2004; Furlan & Lammle, 2001). The type of HUS associated with gemcitabine is classified as atypical and has been seen in patients with cancer and in patients receiving chemotherapy (Maoke, 2002). As platelets and RBCs pass through the damaged endothelium, platelet aggregation occurs and RBCs fragment to produce a picture of thrombocytopenia and microangiopathic hemolytic anemia (Humphreys et al., 2004; Zupancic et al., 2007). The end result of the renal microvasculature endothelial damage and clot formation is renal failure.

Laboratory Studies

Diagnostic workup of the patient with suspected TTP-HUS includes a complete blood count, platelet count, renal function tests, LDH, haptoglobin, bilirubin, urinalysis, and evaluation of a peripheral blood smear for schistocytes. Coagulation studies are conducted, including partial thromboplastin time, prothrombin time with international normalized ratio, and fibrin degradation products and fibrinogen. A special test that may be performed is ADAMTS 13, which is a normal metalloprotease that cleaves von Willebrand factor. The test result would not be severely reduced with atypical HUS, and it may not be reduced in TTP seen in patients with cancer and in patients receiving chemotherapy (Hovinga, Studt, Alberio, & Lammle, 2004; Tsai, 2013; Zupancic et al., 2007). Figure 1 contains a listing of laboratory abnormalities associated with TTP-HUS.

Interventions and Treatment

As soon as TTP-HUS is identified, gemcitabine therapy is discontinued (George, 2006; Gore, Jones, & Marques, 2009). Because of the life-threatening