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/mm^3 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), was 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/mm^3 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 (Moake, 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

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nature of TTP-HUS, plasmapheresis with fresh frozen plasma replacement (plasma exchange) is initiated to improve the patient's hematologic status, increase the platelet count, and reduce hemolysis (George, 2010; Humphreys et al., 2004; Izzedine et al., 2006); however, others have stressed that it is more important to stop the gemcitabine therapy (Gore et al., 2009). Plasma exchange may be done in the presence of more significant disease (Gore et al., 2009). Renal dialysis is required to improve renal function and reduce uremic toxicity. The use of plasmapheresis and dialysis together appear to produce a better outcome in significant disease when stopping gemcitabine alone is not adequate therapy (Zupancic et al., 2007).

In the presence of hypertension, antihypertensive medications are initiated and the doses titrated as needed (Zupancic et al., 2007). Steroids may be used, such as prednisone (1 mg/kg daily orally) if there is minimal response to plasmapheresis (Kaplan & George, 2013). Platelet count and LDH are monitored daily to evaluate the patient's response to plasma exchange (George, 2010), which is continued until the platelet count and LDH return to normal. Anemia is managed with pRBC administration. Platelet transfusions may be administered with caution to treat bleeding or used preprocedure (George, 2010; Kaplan & George, 2013). Rituximab 375 mg/m^2 IV weekly may be administered for its immune-suppressant effect. Tun and Villani (2012) found that rituximab was tolerated and effective in a study of patients with acute refractory or chronic relapsing nonfamilial TTP.

The patient's response to therapy aids and guides the need for additional interventions. After the completion of therapy, patients are monitored for relapse. The management of gemcitabine-induced TTP-HUS continues to be controversial, and much more research is needed for a standard of care to be determined.

- Abnormal urine analysis–hematuria, proteinuria
- Acute renal failure, elevated creatinine
- Elevated indirect bilirubin
- Elevated lactase dehydrogenase (from tissue ischemia and hemolysis)
- Elevated reticulocyte count
- Low serum haptoglobin
- Microangiopathic hemolytic anemia
- Schistocytes (fragmented red blood cells) on peripheral smear
- Thrombocytopenia

Figure 1. Laboratory Abnormalities Associated With Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

Note. Based on information from Cohen et al., 1998; Humphreys et al., 2004; Izzedine et al., 2006.

Nursing Management

Early identification has the potential to be beneficial in reducing the toxicity of gemcitabine-associated TTP-HUS. Nurses should check the blood pressure of patients on therapy prior to each dose of gemcitabine and periodically after therapy to monitor for the new onset of hypertension or exacerbation of existing hypertension (Humphreys et al., 2004). Hypertension may precede the diagnosis of TTP-HUS by weeks (Humphreys et al., 2004). In addition, patients on gemcitabine therapy for longer than three months may benefit from monthly monitoring of renal function, haptoglobin, and the presence of schistocytes (Humphreys et al., 2004).

Nurses play a critical role in the assessment, management, and treatment of patients with TTP-HUS. Because of the formation of clots, ischemia may develop; therefore, it is crucial that nurses assess and monitor the central nervous, cardiac, renal, skin, and mucous membranes for dysfunction (Myers, 2002). Signs and symptoms to monitor include new or worsening hypertension (may develop prior to diagnosis); hematuria; dyspnea, pallor, and tachycardia associated with anemia; peripheral edema; fever; bleeding; and a change in mental status (Cohen, Brecher, & Bandarenko, 1998; Humphreys et al., 2004; Izzedine et al., 2006).

Nurses should report any abnormalities in assessments and laboratory results to the licensed independent practitioner. Prescribed therapies should

Clinical Highlights

Nursing Assessment of Gemcitabine-Related Side Effects

- Monitor blood pressure prior to each dose of gemcitabine and periodically after therapy for new onset of hypertension or exacerbation of preexisting hypertension.
- Patients on gemcitabine therapy longer than three months may benefit from monitoring of renal function and haptoglobin, as well as for the presence of schistocytes.
- Early signs of gemcitabine-associated thrombotic thrombocytopenic purpura (TTP) with hemolytic uremic syndrome (HUS) include onset or exacerbation of hypertension, hematuria, and renal insufficiency. TTP-HUS is diagnosed based on the low platelet count and presence of microangiopathic hemolytic anemia.
- Gemcitabine is discontinued. Treatment options consist of plasmapheresis (plasma exchange), renal dialysis, antihypertensive medications, transfusions, prednisone, and rituximab.
- Platelet counts and lactic dehydrogenase are monitored daily to evaluate response to therapy.
- Critical nursing assessments are required for renal, cardiac, and central nervous systems because of ischemia and clotting.

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be administered following established guidelines and standards. Antihypertensive medications may need to be added or the doses adjusted based on the patient's response to therapy. In addition, the prescribed medications should be administered in collaboration with the pheresis nurse and dialysis nurse as well as the timing of plasmapheresis and dialysis. Packed red blood cells may be administered to manage anemia. Platelets are not administered prophylactically.

TTP-HUS is a serious life-threatening complication of gemcitabine administration. Prompt recognition of the presenting symptoms and abnormalities seen on complete blood count or platelet count in addition to monitoring blood pressure are important, as is timely treatment, to reduce the risk of death.

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