Duke Cancer Network
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Practice Alert:

Gemcitabine and Thrombotic Microangiopathy

PRACTICE RECOMMENDATION

Monitor patients receiving Gemcitabine for emerging Microangiopathic Hemolytic Anemia, often signaled by anemia and/or thrombocytopenia out of proportion to the underlying treatment.

CASE REPORT

A 54-year-old woman presented with a cystic mass in the tail of her pancreas five years ago. Biopsy of the mass confirmed adenocarcinoma and she underwent Whipple's procedure. She received no additional anti-cancer therapy and was then lost to follow-up for 2 years. She subsequently presented with shortness of breath. A CT of the chest showed bilateral pulmonary nodules. Biopsy of the nodules confirmed metastatic adenocarcinoma. She was started on chemotherapy with gemcitabine and protein-bound paclitaxel (Abraxane™). The patient tolerated therapy relatively well until routine laboratory evaluation obtained about 1 year after the start of the combination therapy revealed significant abnormalities. The lab results are shown in the adjacent Table:

Hemoglobin	7.0 mg/dL
Hematocrit	20.9%
WBC	11.2
Platelets	246,000/mm^3
BUN	19 mg/dL
Creatinine	1.3 mg/dL

The patient was transfused with 2 units of packed red blood cells and her chemotherapy was held.

Follow-up laboratory values are in the Table below:

Hemoglobin	5.6 mg/dL
Hematocrit	16.7 %
WBC	15.7
Platelets	331,000/mm^3
BUN	35 mg/dL
Creatinine	2.3 mg/dL

Evaluation included review of the peripheral blood smear that revealed the presence of schistocytes and fragmented red cells.

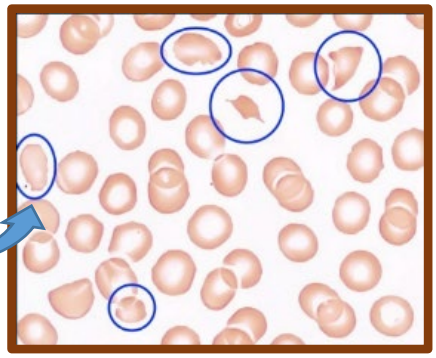

Figure 1 Source: Wikipedia

Additional blood work included:

LDH	1677	Iron Studies	Normal
Haptoglobin	Undetectable	Vitamin B12	Normal
Reticulocyte	8%	Folate	Normal
Coombs'	Negative	SPEP	Normal
PT/INR	Normal	ADAMTS 13	Normal
PTT	Normal		

The patient was diagnosed with Drug-induced (Gemcitabine) Thrombotic Microangiopathic Hemolytic Anemia (GITMA).

BACKGROUND

Gemcitabine is commonly used to treat several malignancies including pancreatic cancer. Adverse effects of gemcitabine are well described with myelotoxicity, increased vascular permeability and peripheral edema reported most frequently. Another, more insidious adverse event occurs less frequently but with potentially more lethal effects. **Acute renal failure** has been reported with hemolytic uremic syndrome (HUS) the underlying process. Clinicians must have a high index of suspicion to detect, diagnose and manage the syndrome effectively. HUS is characterized by progressive renal failure associated with microangiopathic hemolytic anemia, thrombocytopenia proteinuria and hematuria. The primary event appears to be endothelial cell injury and thrombotic microangiopathy (TMA) is the histopathological lesion. Although damage to the renal microvasculature is a hallmark of this condition, damage to the microvasculature in the central nervous, cardiovascular system and other organs has been described. [i]

Microangiopathic hemolytic anemia is a descriptive term for non-immune hemolysis characterized by intravascular red blood cell fragmentation showing up as **schistocytes** on the peripheral blood smear. Other features include **elevated reticulocyte count**, **negative direct antiglobulin (Coombs) test**, **increased lactate dehydrogenase (LDH**), **increased indirect (unconjugated) bilirubin** and **low haptoglobin**. Microangiopathic hemolytic anemia may be directly related to the cancer or to chemotherapy used to treat the cancer. The presence of microangiopathic hemolytic anemia and thrombocytopenia defines the syndrome of Thrombotic Microangiopathy (TMA). Diagnosis of chemotherapy-induced TMA is crucial, as the **treatment is to remove the inciting agent** and to prevent renal damage.

Gemcitabine-Induced TMA is **cumulative dose and duration dependent**. Median duration of therapy is 6 to 7 months and median cumulative dose 18 to 22 g/m^2. Mechanism of gemcitabine induced thrombotic microangiopathic hemolytic anemia (GITMA) is unknown but proposed mechanisms include endothelial damage, intravascular thrombosis, mechanical damage of red blood cell, and alternative complement pathway activation. Rapid control of TMA is paramount to prevent irreversible kidney damage.
Optimal treatment strategy GITMA beyond the discontinuation of gemcitabine is unknown. Treatment used in other causes of microangiopathic hemolytic anemias - such as plasma exchange, fresh frozen plasma infusion, and glucocorticoids - may not be effective in GITMA.

There are a number of reports for the efficacy of anticomplement therapy in the management of drug-induced TMA, particularly when the mechanism is dose-dependent as in the case of our patient receiving Gemcitabine. **Eculizumab**, a recombinant humanized monoclonal antibody inhibits the cleavage of complement C5 protein, preventing the generation of the inflammatory peptide C5a and the cytotoxic membrane-attack complex C5b. Eculizumab has demonstrated activity with a single dose, associated with rapid improvement of gemcitabine-associate thrombotic microangiopathy[ii].

Prepared by Drs. Maddhu Chaudhry and Linda Sutton

[i] Cidon EU, et al. Gemcitabine-induced haemolytic uremic syndrome, although infrequent can it be prevented: A case report and review of the literature. *World J Clin Cases* 6(12):531-537, 2018.
[ii] Burns ST, et al. Rapid improvement in gemcitabine-associated thrombotic microangiopathy after a single dose of eculizumab; case report and review of the literature. *Anticancer Res* 40(7):3995-4000, 2020.