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Thrombotic Thrombocytopenic Purpura and Gemcitabine

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Key Words

Thrombotic thrombocytopenic purpura · Gemcitabine · Non-small cell lung cancer ·

Abstract

Thrombotic thrombocytopenic purpura (TTP) is a rare and life-threatening complication of gemcitabine treatment. Since the approval of this nucleoside analog for the treatment of pancreatic cancer by the FDA in 1996, reported incidence varies from 0.015 to 1.4%. The classic ‘pentad’ describing the disease process (fever, hemolytic anemia, thrombocytopenia, neurological complications and renal impairment) is not always present to the same extent in every patient. Here, we present a rare case of TTP associated specifically with gemcitabine treatment, and further, we briefly discuss the manifestations, treatment options and outcomes related to the complication. In our opinion, it is important to realize that as the indications for the use of gemcitabine increase and its use becomes more widespread, TTP and other disorders on the spectrum of thrombotic microangiopathies are important considerations to remember in patients with worsening anemia and thrombocytopenia. New onset or exacerbation of underlying hypertension may provide a clue to diagnose the disease entity earlier in this subgroup of patients.

Background

Thrombotic thrombocytopenic purpura (TTP) is a rare but life-threatening condition with significant morbidity and mortality associated with the disease [1]. Prior to the 1960s, the mortality numbers reporting TTP were as high as 77% [2]. The classic ‘pentad’ describing the disease process (fever, hemolytic anemia, thrombocytopenia, neurological complications and renal impairment) is not always present to the same extent in every patient. Of the causes associated with TTP, drugs, especially chemotherapeutic agents, are one of them. Early identification of TTP in such circumstances is essential in improving survival and instituting early treatment. Here, we present a rare case of TTP associated specifically with gemcitabine treatment, and further, we briefly discuss the manifestations, treatment options and outcomes related to the complication.

Case Report

A 68-year-old woman with a past medical history significant for stage IIIB non-small cell lung cancer diagnosed 2 years ago presented to the Emergency Department with complaints of fever and headache 3 days after receiving a cycle of chemotherapy.

With respect to her oncological history, she was originally treated with carboplatin, taxol (paclitaxel) and avastin (bevacizumab). In 2009, she showed progression of disease and was started on tarceva (erlotinib), and then switched to Alimta. However, following 8 cycles of Alimta (pemetrexed), a follow-up computed tomography (CT) scan showed progression of disease, which is being treated with gemcitabine (Gemzar) since July 2010, showing no major complications and a stable malignancy.

Apparently, after the cycles of chemotherapy, she used to have mild headaches and occasionally fever lasting for one or two days; however, symptoms related to her last cycle of chemotherapy 3 days ago were different. She described the pain as diffuse, sudden in onset, aching in nature and as the ‘worst’ headache she had ever had. Associated symptoms included fever (38.4°C, 101.1°F) on presentation, some neck pain/stiffness and eye discomfort/photophobia. Her vital signs otherwise were stable on presentation except for a systolic and diastolic blood pressure of 145–185 and 75–94 mm Hg, respectively. Of note, the patient was not hypertensive prior to admission and her only medical problems were mild depression and cervical cancer for which she had undergone curative surgery 40 years ago.

Initially, suspecting a possible viral versus bacterial meningitis, a lumbar puncture was instantly performed. However, the results were not suggestive of meningitis, and CSF parameters were within normal limits. The patient’s hemoglobin/hematocrit levels were noted to have trended down from a baseline of 9.3 g/dl (28.5%) to 8.4 g/dl (25.8%). Thrombocytopenia worsened from 144 × 10⁹/l on presentation to 107 × 10⁹/l on day 2 of admission.

A literature review of side effects associated with gemcitabine showed that gemcitabine has the potential, though rarely, to cause microvascular angiopathy leading to hemolytic uremic syndrome (HUS), TTP, malignant hypertension and other related diseases.

Given concerns for hemolysis and possible TTP in our patient, a peripheral smear was examined, which did show presence of schistocytes. Hemolysis laboratories also confirmed intravascular hemolysis (a high LDH of 437 IU/l and haptoglobin <4 mg/dl), for which the hematology department was promptly consulted. The patient was urgently started on plasmapheresis the same day and is undergoing daily plasmapheresis with monitoring of LDH, haptoglobin, hemoglobin, hematocrit and platelet counts along with her renal function. [Table 1](#) highlights some of the typical findings reported in patients with gemcitabine-associated TTP and the findings seen in our patient.

Discussion

TTP is a rare and life-threatening complication of gemcitabine treatment. Since the approval of this nucleoside analog for the treatment of pancreatic cancer by the FDA in 1996, reported incidence varies from 0.015 to 1.4% [3]. Endothelial cell injury is thought to be the postulated mechanism behind gemcitabine-induced TTP. The downstream effects from the endothelial dysfunction, including release of nitric oxide and von Willebrand factor, and increased levels of tissue plasminogen activator, thrombomodulin, and plasminogen activator inhibitor, are described to promote the development of TTP [4]. With the use of this drug becoming more common, gemcitabine-induced thrombotic microangiopathy (TMA) is increasingly being recognized, and TTP and HUS are considered disorders on the same spectrum of the disease process [5]. As is known, renal dysfunction tends to be the hallmark of HUS, whereas neurological complications tend to dominate in TTP [6].

According to the excellent review by Zupancic et al. [3] on gemcitabine-associated TTP, the complication appears to be dose related and is seen more in individuals with a cumulative dose of 20,000 mg/m² and when the number of doses exceeds 18. A review of our patient's chemotherapy records revealed that she had received 13 doses of gemcitabine prior to presentation and that she was in the 8th month of therapy. Usually, the complication is rarely seen before the 7th month of therapy [7]. Of note, however, TTP can be seen earlier in individuals who are on multiple other chemotherapeutic agents associated with the development of the complication. While mitomycin and cisplatin have been classically implicated with TTP, other chemotherapeutic agents are also associated with this complication [8]. **Table 2** outlines some of the chemotherapeutic and other classes of drugs associated with the development of TTP.

A very interesting observation seen in patients who develop TTP specifically due to gemcitabine is either the development of new hypertension or difficulty in controlling blood pressure and/or increment in the number of antihypertensive medications in patients who have already been diagnosed with hypertension [9]. In a review of all cases with gemcitabine-associated TMA diagnosed at Partners Healthcare System (Boston, Mass., USA) between January 1997 and February 2002, apparently the patients' blood pressure readings were noted to increase at least one week prior to symptoms onset. Moreover, 3 out of 9 patients had symptoms onset 6–10 weeks after the detection of the elevated blood pressures [9]. Thus, patients on gemcitabine should be frequently monitored for any changes in their blood pressure from baseline, since it may be a predictor of potentially dramatic microvascular complications in the near future. Moreover, in some series, the development of hypertension was also a marker for poor prognosis/outcome [5].

Treatment options employed and outcomes highlighted in the series of case reports have been variable and range from discontinuation of gemcitabine to only the employment of plasmapheresis and use of steroids along with control of blood pressure with antihypertensive medications. Some case reports have also highlighted a potential role of the anti-CD20 antibody rituximab in the treatment of TTP/HUS [8]. Plasmapheresis, however, appears to be the mainstay along with drug cessation in the treatment of gemcitabine-induced TTP, with most patients requiring at least 8–12 treatments. Complications associated with the procedure itself, including line sepsis and hemorrhage from line insertion, thrombosis and mortality documented in patients receiving plasmapheresis should always be kept in mind [10].

Conclusions

As the indications for the use of gemcitabine increase and its use becomes more widespread, TTP and other disorders on the spectrum of TMAs are important considerations to remember in patients with worsening anemia and thrombocytopenia. New onset or exacerbation of underlying hypertension may provide a clue to diagnose the disease entity earlier in this subgroup of patients.

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Table 1. Comparison of findings noted in our patient and findings of patients with gemcitabine-induced TTP

Findings in gemcitabine-induced TTP	Findings in our patient
New onset or worsening of hypertension noted specifically with gemcitabine-induced TTP; it is thought to represent underlining renal microvascular disease/damage and heralds the onset of TTP in patients treated with gemcitabine	Patient did not have any diagnosis of hypertension; noted to have blood pressures as high as 185/94 mm Hg on presentation, which increased to 204/100 mm Hg later during her hospital course, requiring multiple anti-hypertensives
Fever	Fever
Neurological symptoms	Severe headache and photophobia on presentation
<i>Microangiopathic hemolytic anemia</i> Schistocytes present on peripheral smear Increased LDH Decreased haptoglobin	<i>Microangiopathic hemolytic anemia</i> Schistocytes present on peripheral smear: 1+ 1–5%/hpf Increased LDH: 437 IU/l, increased to 706 IU/l later Decreased haptoglobin: <4 mg/dl
Thrombocytopenia	Patient's platelet number increased to $266 \times 10^9/l$ in January, and rapidly decreased from $144 \rightarrow 107 \rightarrow 99 \times 10^9/l$ prior to the start of plasmapheresis. The lowest platelet number decreased to $37 \times 10^9/l$
<i>Some degree of renal dysfunction</i> Increased BUN/Cr	<i>Some degree of renal dysfunction</i> BUN increased from 8 $\rightarrow$ 10 $\rightarrow$ 15 mg/dl despite i.v. boluses and continued hydration; Creatinine level is 1.1 mg/dl; GFR decreased from 55 to 49 ml/min/1.73 m ² . Creatinine worsened to 1.9 mg/dl during her hospital course
Mild proteinuria Mild hematuria	2+ (~100 mg/dl or 0.5–1 g/day) protein on dipstick 2+ (positive) blood on dipstick; 15–20 red blood cells/hpf on microscopy
PT/PTT normal	Normal
Fibrinogen normal	Normal
Reticulocyte count (unreliable in setting of chemotherapy-induced TTP; most commonly low)	Reticulocyte count 0.4%; absolute reticulocyte count $0.010 \times 10^{12}/l$; low
Increased premature precursors	High nucleated red blood cells; 94.4% neutrophils
Deficiencies of ADAMTS-13 (noted only in 13% of patients, thereby, representing a different mechanism)	94% (normal >68%)
Pulmonary symptoms	Not present in our patient initially; however, when she received packed red blood cells for her worsening anemia, she developed pulmonary edema (which is also seen in patients with TTP when they receive transfusions. Transfusion-related acute lung injury and acute respiratory distress syndrome may also develop; therefore, patients receiving transfusions need to be closely monitored).

Table 2. Drugs associated with the development of TTP

Chemotherapeutic drugs commonly associated with TTP	Chemotherapeutic drugs less commonly associated with TTP/case reports	Other drugs associated with TTP
Mitomycin C (4–15%) Cisplatin (2–6%)	<i>Fluorouracil</i> <i>Dacarbazine</i> <i>Doxorubicin</i> <i>Carboplatin</i> <i>Oxaliplatin</i> <i>Lomustine</i> <i>Bleomycin</i> <i>Vinblastine</i> <i>Medroxyprogesterone</i> <i>Tamoxifen</i> <i>Chlorozotocin</i> <i>Zinostatin</i> <i>Carmustine</i> <i>Tretinoin</i> <i>Pentostatin</i> <i>Estramustine</i> <i>Cytarabine</i> <i>Daunorubicin</i>	Quinine Estrogen-containing oral contraceptives Immunosuppressive agents – Cyclosporine – Tacrolimus – Sirolimus Antiplatelet drugs – Ticlopidine – Clopidogrel Antiviral agents – Valacyclovir

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