Title

Chemotherapy Associated Thrombotic Microangiopathy: A Case of Indolent Thrombotic Thrombocytopenia Purpura After Gemcitabine Treatment

Journal

Proceedings of the UCLA Department of Medicine, 15(1)

Authors

Itagaki, Brandon K.
Ra, Seong
Hajmomenian, Hamid

Publication Date

2011-03-31

CLINICAL VIGNETTE

Chemotherapy Associated Thrombotic Microangiopathy: A Case of Indolent Thrombotic Thrombocytopenia Purpura After Gemcitabine Treatment

Brandon K. Itagaki, M.D., Seong Ra, M.D. and Hamid Hajmomenian, M.D.

Case Report

A 52-year-old female was admitted to the hospital with slowly worsening renal function over the course of 7 months. Her medical history is significant for pancreatic cancer, diagnosed 17 months earlier. The patient underwent 6 cycles of gemcitabine plus radiation therapy prior to undergoing a pancreaticoduodenectomy (Whipple procedure). This was followed by 5 additional cycles of adjuvant gemcitabine for a total dose of 49.2 g/m^2 over 17 months. Although the patient had no prior history of hypertension, she was noted to have slowly rising blood pressure and was treated with hydrochlorothiazide/ triamterene (37.5/25 mg daily), amlodipine (5 mg daily) and clonidine (0.1 mg tid). She also required a total of 6 units of packed red blood cells and one unit of single-donor platelets for anemia and thrombocytopenia. The patient had no history of renal, cardiac, neurological or liver disease. Renal function and blood chemistries were normal seven months earlier.

Physical exam on admission revealed a temperature or 36.9° C, pulse 64 per minute and regular, blood pressure of 188/87 mmHg in the sitting position and respirations of 20 per minute. Lungs were clear to auscultation and percussion. Heart examination revealed no murmurs or gallops. Abdominal exam was negative for any tenderness or masses. There was trace lower extremity edema bilaterally. She was alert and responsive without any focal neurological signs.

Pertinent laboratories are summarized in Table 1 and include the following: WBC 6.34 x 10^3/ul, Hgb 7.8 g/dl, Hct 22.4%, Platelet count 88,000/ul, Na 133 mmol/l, K 4.7 mmol/l, Cl 107 mmol/l, CO2 19 mmol/l, BUN 50 mg/dl, Cr 2.0 mg/dl, glucose 144 mg/dl, PT 10.3 sec, APTT 29.9 sec, INR 1.1. LDH was elevated at 625 u/l and haptoglobin was < 8 mg/dl. A peripheral smear revealed occasional schistocytes and spherocytes. Urinalysis was positive for protein, 5-10 RBC/hpf, 6-12 WBC/hpf and negative for crystals. Random urine sodium was 32 mmol/l and urine eosinophils were negative. A renal ultrasound and renal artery duplex evaluation revealed normal sized kidneys with no evidence of renal artery stenosis.

The patient underwent a renal biopsy, which demonstrated acute and chronic thrombotic microangiopathy. Gemcitabine therapy was discontinued and the patient was started on plasmapheresis and steroids. Her renal function improved one month after completion of plasmapheresis, although it has not returned to baseline.

Discussion

First described in 1924, thrombotic thrombocytopenic purpura or TTP is a condition characterized by microangiopathic hemolytic anemia, thrombocytopenia, neurologic and renal abnormalities and fever[1,2]. Pathologically, TTP manifests with hyaline thrombi and platelet aggregation in terminal arterioles and capillaries in the

kidney, brain, heart, spleen, pancreas and adrenal gland[3]. Acquired forms of TTP have been associated with pregnancy, autoimmune disorders, infections, hematopoietic stem cell transplantation and various drugs and medications[4]. Cancer chemotherapeutic agents associated with TTP include mitomycin, bleomycin, and cisplatin[5-7].

Gemcitabine was first approved in 1996 for the treatment of unresectable pancreatic cancer. Indications for its use have since expanded to include non-small cell lung cancer, lymphoma, breast and ovarian cancer. Adverse effects of this nucleoside analog include myelosuppression, flu-like symptoms and rarely TTP[8]. The first case of gemcitabine induced TTP was described by Casper and colleagues in 1994[9]. Since then, TTP has been infrequently reported in the literature, with the manufacturer estimating a 0.015-0.28% incidence of TTP[10-11]. A case series by Humphreys and colleagues, which looked at 2586 patients taking gemcitabine found a 0.31% incidence of TTP[12]. In this study, the median cumulative gemcitabine dose was 19.2 g/m^2 (range 9-56 g/m^2) and the median time to development of TTP was 8 months (range 3-18 months).

Our patient was first treated with gemcitabine 17 months before her presentation and received a total dose of 49.2 g/m^2. Because anemia and thrombocytopenia are common adverse effects of gemcitabine, diagnosing TTP caused by this chemotherapeutic agent is challenging. Our patient developed both anemia and thrombocytopenia, which required blood and platelet transfusions prior to her diagnosis of TTP.

Due to the difficulty in diagnosing gemcitabine associated TTP based on laboratory findings, Humphreys et al recommended using the development or the exacerbation of existing hypertension to aid in the diagnosis[12]. In their case series, 7 of 9 patients who developed gemcitabine associated TTP had a systolic blood pressure (SBP) $\geq$ 170 mmHg or an increase of $\geq$ 20 mmHg relative to baseline. Our patient was noted to have gradually increasing blood pressure over the course of 8 months. Prior to the initiation of gemcitabine, her blood pressure was 116/68 mmHg and she was on no antihypertensive medications. Once gemcitabine was started, our patient's blood pressure continued to rise despite the eventual addition of three antihypertensive medications and was noted to be 188/87 mmHg on the day of admission.

Conclusion

Gemcitabine associated TTP is infrequently reported, with an estimated incidence of 0.015-0.31%. Due to the high mortality associated with this condition, early diagnosis and initiation of plasmapheresis is vital. We report a case of indolent TTP that presented 17 months after initiation of treatment with gemcitabine. Our patient presented with anemia and thrombocytopenia initially felt secondary to the myelosuppressive effects of gemcitabine. Additional symptoms including slowly progressive renal failure and exacerbation of hypertension is therefore important to aid in the diagnosis of gemcitabine associated TTP.

Table 1. Laboratory Studies

Test	Prior to Gemcitabine Treatment[1]	Admission	Completion of Plasmapheresis[2]
WBC ($x10^3/\mu l$)	4.82	6.34	4.55
Hgb (g/dl)	12.0	7.8	9.8
Hct (%)	36.4	22.4	28.6
Plt ($x10^3/\mu l$)	291	88	183
Na (mEq/l)	141	133	138
K (mEq/l)	4.1	4.7	4.4
Cl (mEq/l)	106	107	110
CO2 (mEq/l)	26	19	19
BUN (mg/dl)	12	50	32
Cr (mg/dl)	0.8	2.0	1.4

[1] 17 months prior to admission. [2] 5 months after admission.

REFERENCES

1. **Amorosi EL, Ultmann JE**. Thrombotic thrombocytopenic purpura: report of 16 cases and review of the literature. *Medicine* 1966; 45:139-59.
2. **Moschocowitz E**. Hyaline thrombosis of the terminal arterioles and capillaries: A hitherto undescribed disease. *Proc NY Pathol Soc* 1924; 24:21-4.
3. **Tsai HM**. Current concepts in thrombotic thrombocytopenic purpura. *Annu Rev Med*. 2006;57:419-36. Review. PubMed PMID: 16409158; PubMed Central PMCID:PMC2426955.
4. **George JN**. Clinical practice. Thrombotic thrombocytopenic purpura. *N Engl J Med*. 2006 May 4;354(18):1927-35. Review. PubMed PMID: 16672704.
5. **Snyder HW Jr, Mittelman A, Oral A, Messerschmidt GL, Henry DH, Korec S, Bertram JH, Guthrie TH Jr, Ciavarella D, Wuest D, et al**. Treatment of cancer chemotherapy-associated thrombotic thrombocytopenic purpura/hemolytic uremic syndrome by protein A immunoadsorption of plasma. *Cancer*. 1993 Mar 1;71(5):1882-92. PubMed PMID: 8448753.
6. **Lesesne JB, Rothschild N, Erickson B, Korec S, Sisk R, Keller J, Arbus M, Woolley PV, Chiazze L, Schein PS, et al**. Cancer-associated hemolytic-uremic syndrome: analysis of 85 cases from a national registry. *J Clin Oncol*. 1989 Jun;7(6):781-9. Review. PubMed PMID: 2497229.
7. **Watson PR, Guthrie TH Jr, Caruana RJ**. Cisplatin-associated hemolytic-uremic syndrome. Successful treatment with a staphylococcal protein A column. *Cancer*. 1989 Oct 1;64(7):1400-3. PubMed PMID: 2528403.
8. **Green MR**. Gemcitabine safety overview. *Semin Oncol*. 1996 Oct;23(5 Suppl 10):32-5. Review. PubMed PMID: 8893879.
9. **Casper ES, Green MR, Kelsen DP, Heelan RT, Brown TD, Flombaum CD, Trochanowski B, Tarassoff PG**. Phase II trial of gemcitabine (2,2'-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. *Invest New Drugs*. 1994;12(1):29-34. PubMed PMID: 7960602.
10. **Fung MC, Storniolo AM, Nguyen B, Arning M, Brookfield W, Vigil J**. A review of hemolytic uremic syndrome in patients treated with gemcitabine therapy. *Cancer* 1999 May 1;85(9):2023-32. PubMed PMID: 10223245.
11. **Eli Lilly and Company**: Gemzar^{Ò} [product label]. Indianapolis: Eli Lilly, 2003
12. **Humphreys BD, Sharman JP, Henderson JM, Clark JW, Marks PW, Rennke HG, Zhu AX, Magee CC**. Gemcitabine-associated thrombotic microangiopathy. *Cancer*. 2004 Jun 15;100(12):2664-70. PubMed PMID: 15197810.

Submitted on March 31, 2011