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SHORT COMMUNICATION

Rapid and complete resolution of chemotherapy-induced thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) with rituximab

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Abstract
Purpose Gemcitabine-induced thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) is a well described, albeit rare, complication, which is associated with a high morbidity and mortality. Treatment with standard TTP/HUS therapies such as plasma exchange, and cessation of gemcitabine is often unsuccessful. The purpose of this report is to describe the successful treatment of gemcitabine-induced TTP/HUS with rituximab, a CD20 monoclonal antibody that has been used for the treatment of refractory idiopathic TTP/HUS.
Methods We describe the clinical course and follow-up of a patient who developed gemcitabine-induced TTP/HUS, did not respond to cessation of gemcitabine, administration of plasma exchanges, and intravenous glucocorticoids, but responded to rituximab.
Results TTP/HUS responded rapidly and resolved completely with two courses (8 doses) of intravenous rituximab. In three of four reported cases (including the current report), rituximab was rapidly effective in resolving chemotherapy-induced TTP/HUS that was refractory to plasma exchanges and glucocorticoids.
Conclusions Rituximab may be indicated for early treatment of chemotherapy-induced TTP/HUS, particularly when plasma exchange is not rapidly effective.

Keywords ADAMTS-13 protein, human · Gemcitabine · Non-small cell lung carcinoma · Rituximab · Thrombotic thrombocytopenic purpura

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Introduction

Gemcitabine-induced thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) is well-recognized, with an incidence ranging from 0.008 to 2.2% [4, 6, 9, 13, 18], and is associated with a mortality of 40–90% [10]. The pathogenesis of gemcitabine-induced TTP/HUS remains unclear, and successful treatment is difficult as it rarely responds to standard treatments for TTP/HUS [18]. Rituximab, an anti-CD20 monoclonal antibody, has been used to treat refractory idiopathic TTP/HUS [2] and was found to be remarkably effective in the treatment of our patient.

Case report

A 48-year-old man with progressive intermittent multiple sclerosis and controlled hypertension (HTN) underwent evaluation of a persistent cough, when a right peri-hilar mass was discovered. Bronchoscopy revealed a non-small cell lung carcinoma, clinical stage IIIA (T3N1M0). The patient received neo-adjuvant chemotherapy with carboplatin (dosed to area under the curve = 5, IV on day 1) and gemcitabine (1,000 mg/m^2 IV on days 1 and 8) every 3 weeks. After cycle four, including a total of 6,934 mg/m^2 of

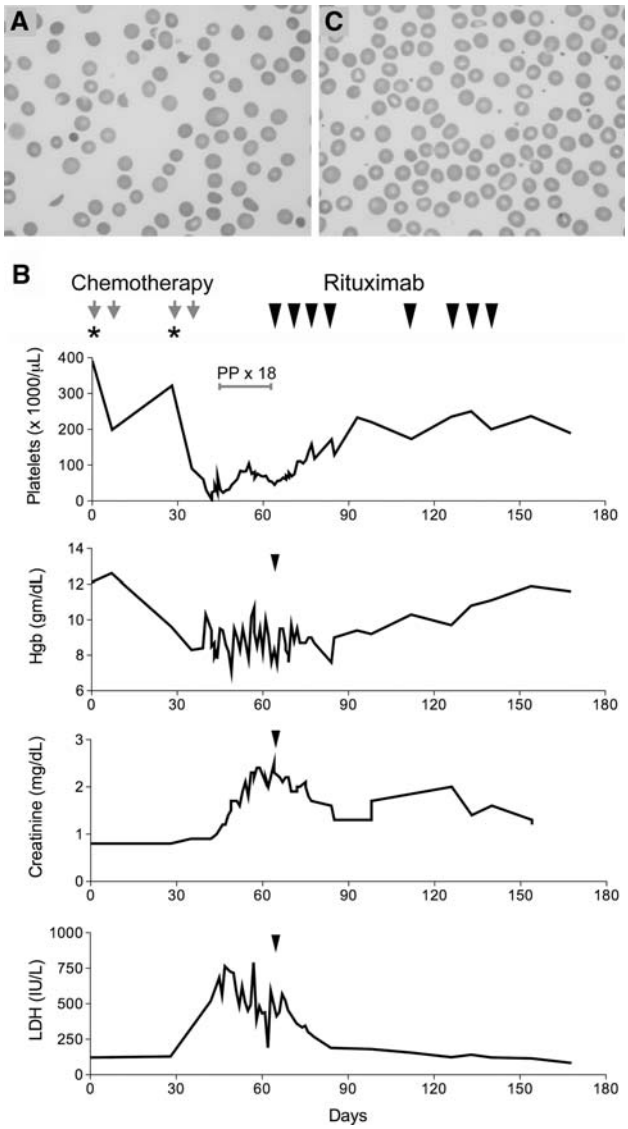

Fig. 1 **a** Peripheral blood smear before rituximab, showing marked thrombocytopenia, increased polychromasia, and numerous red cell fragments (schistocytes, microspherocytes, helmet cells), indicative of microangiopathic hemolysis. Wright & Giemsa stain, ×40 magnification. **b** Graphical representation of the effect of treatments on the patient's platelet count, hemoglobin, creatinine, and LDH. Day 0 is the beginning of the third cycle of chemotherapy. Gemcitabine (*grey arrows*) and carboplatin (*asterisks*) administration. Plasmapheresis therapy duration (PP). Rituximab administration (*black arrowheads*), with initiation of rituximab in the subsequent graphs indicated by a single small black arrowhead. **c** Peripheral blood smear after rituximab showing resolution of microangiopathic features. Wright & Giemsa stain, ×40 magnification

gemcitabine, the patient was admitted with mucocutaneous bleeding, a growing subungual hematoma, exacerbation of HTN and severe thrombocytopenia (platelet count 3,000/μL, 1 week after the last dose of gemcitabine). Platelet transfusions did not achieve a sustained increase in platelet counts. On hospital day (HD) three, the blood smear showed microangiopathic hemolysis (Fig. 1a). The laboratory data showed: decreased platelets (31,000/μL) and haptoglobin (8.4 mg/dL); normal PT (10.8 s), APTT (27.7 s), fibrinogen (311 mg/dL), and a disintegrin and metalloproteinase with a thrombospondin type 1 motif (ADAMTS)-13 level (80%); negative Coombs test and bacterial cultures; elevated LDH (684 IU/L); and creatinine above his baseline. The patient's laboratory parameters and response to therapy are shown in Fig. 1b. Initial therapy comprised of daily plasmapheresis. The patient developed urticaria during the first run of plasmapheresis; therefore, hydrocortisone (100 mg IV) was added before subsequent plasmapheresis runs. After 18 plasmapheresis and continued hydrocortisone (100 mg IV before each plasmapheresis), there was no improvement in TTP/HUS, kidney function declined further, and HTN (up to 187/138 mm Hg) remained difficult to control. The patient developed bilateral upper extremity catheter-related deep vein thrombi (DVT), a calf hematoma from anticoagulation for the DVTs, and steroid-induced hyperglycemia. Plasmapheresis were discontinued and intravenous hydrocortisone replaced by oral prednisone. On HD 23, four weekly intravenous injections of rituximab (375 mg/m^2) were started. After the second dose of rituximab, the patient's platelet count and kidney function began to improve rapidly, and he was discharged on five antihypertensive agents, oral prednisone (tapering by 5 mg every week), and the remainder of the rituximab course. After completion of the 4 weeks course of rituximab, platelets peaked at 233,000/μL and creatinine declined to 1.3 mg/dL (upper limit of normal, 1.2 mg/dL). However, TTP/HUS activity (evidenced by decline in platelet count by 60,000/μL and increase in creatinine to 2.0 mg/dL) recurred within 4 weeks of completion of the first course of rituximab. A second course of four weekly rituximab (375 mg/m^2) injections was therefore administered, resulting in complete resolution of TTP/HUS (Fig. 1c). The patient remains on slowly tapering doses of prednisone (currently 10 mg/day orally), with normal kidney function (creatinine 1.0 mg/dL), platelet counts (271,000/μL), bilirubin (0.3 mg/dL), and LDH (96 IU/L), nearly 5 months after completion of the second course of rituximab.

Discussion

Chemotherapy-induced TTP/HUS usually presents with a combination of uremia, thrombocytopenia, and microangiopathic hemolytic anemia [14]. While mitomycin and cisplatin have been the best described causes of such TTP/HUS, multiple other agents have been implicated, including gemcitabine, fluorouracil, carboplatin, oxalipatin, and bleomycin [18].

The risk of TTP/HUS associated with gemcitabine sharply increases after the total dose exceeds 20,000 mg/m^2

Table 1 Chemotherapy-induced TTP/HUS treated with rituximab

Study	Malignancy	Chemotherapy	Number of plasma exchanges	Gluco-corticoids given with plasma exchanges	ADAMTS-13/VWFcp level	Resolution with rituximab	Number of rituximab doses given (375 mg/m^2)
Onitilo et al. [14]	Adenocarcinoma, primary not identified	Mitomycin-C* daunorubicin cisplatin	8	Yes	38%	Yes	4
Kasper et al. [11]	Breast cancer	Mitomycin-C* vinorelbine	>120	Yes	46%	No	8
Bharthua et al. [1]	Pancreatic adenocarcinoma	Gemcitabine* capecitabine bevacizumab	>13	Yes	Reported as "normal"	Yes	2
Gourley et al. (current report)	Non-small cell lung carcinoma	Gemcitabine* carboplatin	18	Yes	80%	Yes	8

* Drug believed to have caused TTP/HUS

[17, 18]. There is, however, one report of TTP/HUS occurring after the initial dose of 2,000 mg [3]. The threshold for the development of TTP/HUS may be lower than 20,000 mg/m^2 when patients have been treated with other agents known to cause TTP/HUS, mitomycin in particular [18]. Our patient received 6,934 mg/m^2 of gemcitabine in combination with carboplatin, which may have lowered the threshold or even contributed to the development of TTP/HUS. In the literature, TTP/HUS has been reported to occur in up to 2.2% patients [4] receiving gemcitabine, whereas carboplatin has been reported to cause TTP/HUS in only a few patients (one who received carboplatin as a single agent [16] and two who concurrently received either gemcitabine [7] or cyclophosphamide and thiotepa [15]). We therefore believe that it is more likely that gemcitabine was the predominant cause of TTP/HUS in our patient, although attribution to carboplatin cannot be excluded.

Cessation of gemcitabine and supportive care is effective in reversing TTP/HUS in a proportion of patients; the disease follows a relentless course in the majority, with morbidities such as renal failure, prolonged hospitalizations and multiple invasive procedures, and considerable mortality [10, 17, 18].

The pathophysiology of gemcitabine-induced TTP/HUS is unclear [6]. Some have attributed the cause to be related to chemotherapy-induced endothelial cell damage leading to capillary endothelial cell swelling, separation of capillary endothelium, and neoformation of a thick sub-endothelial basement membrane seen on electron microscopy [5, 18]. Other proposed causes of chemotherapy-induced TTP/HUS have included an immune response [14], either from immune complexes as seen in heparin-induced thrombocytopenia or from self-antigen "confusion" after endothelial damage.

Rituximab is a novel and apparently effective treatment for chemotherapy-induced TTP/HUS. A review of the literature revealed only three case reports of chemotherapy-induced TTP/HUS treated with rituximab (Table 1). Two of these episodes of TTP/HUS were attributed to mitomycin [11, 14], and the third to gemcitabine [1]. ADAMTS-13/VWFcp levels were low in both patients who received mitomycin and normal in the patient who received gemcitabine. Plasma exchanges and glucocorticoids were unsuccessful in all cases. Two of the three cases resolved with rituximab treatment. In the case that did not resolve [11], rituximab was given late in the course, six and a half months after onset of TTP/HUS.

ADAMTS-13 level/activity suppression is a typical feature of classic TTP, but is not usually seen in HUS. However, both conditions seem to respond to plasma exchange, suggesting that TTP and HUS are clinical scenarios along the same molecular signaling pathway [12]. Gemcitabine-induced TTP/HUS frequently has a normal ADAMTS-13 level/activity. As seen in our patient, plasma exchange has limited success [8, 18]. The efficacy of rituximab in our patient and in TTP/HUS induced by other chemotherapy drugs in two other case reports lends support to the hypothesis of an immune (B-cell)-mediated pathogenesis, which bypasses ADAMTS-13/von Willebrand cascade or interacts in a manner that is not affected by replacement of factors by plasma exchange.

The efficacy of rituximab has been established in idiopathic TTP/HUS and recurrent/relapsing TTP/HUS [2]. In three of four reported cases (including the current report), rituximab was highly effective in resolving chemotherapy-induced TTP/HUS refractory to plasma exchange. Therefore, rituximab may be indicated for early treatment of chemotherapy-induced TTP/HUS, particularly in cases where plasma exchange is not rapidly effective.

Conflict of interest statement The authors declare that they have no conflict of interest.

References

1. Bharthuar A, Egloff L, Becker J, George M, Lohr JW, Deeb G, Iyer RV (2009) Rituximab-based therapy for gemcitabine-induced hemolytic uremic syndrome in a patient with metastatic pancreatic adenocarcinoma: a case report. Cancer Chemother Pharmacol 64:177–181
2. Cataland SR, Wu HM (2005) Immunotherapy for thrombotic thrombocytopenic purpura. Curr Opin Hematol 12:359–363
3. De Smet D, Jochmans K, Neyns B (2008) Development of thrombotic thrombocytopenic purpura after a single dose of gemcitabine. Ann Hematol 87:495–496
4. Desrame J, Duvic C, Bredin C, Bechade D, Artru P, Brezault C, Defuentes G, Poirier JM, Dourthe LM, Coutant G, Chaussade S, de Gramont A, Algayres JP (2005) Hemolytic uremic syndrome as a complication of gemcitabine treatment: report of six cases and review of the literature. Rev Med Interne 26:179–188
5. Flombaum CD, Mouradian JA, Casper ES, Erlandson RA, Benedetti F (1999) Thrombotic microangiopathy as a complication of long-term therapy with gemcitabine. Am J Kidney Dis 33:555–562
6. Fung MC, Storniolo AM, Nguyen B, Arning M, Brookfield W, Vigil J (1999) A review of hemolytic uremic syndrome in patients treated with gemcitabine therapy. Cancer 85:2023–2032
7. Gross M, Hiesse C, Kriaa F, Goldwasser F (1999) Severe hemolytic uremic syndrome in an advanced ovarian cancer patient treated with carboplatin and gemcitabine. Anticancer Drugs 10:533–536
8. Hovinga JA, Studt JD, Alberio L, Lammle B (2004) von Willebrand factor-cleaving protease (ADAMTS-13) activity determination in the diagnosis of thrombotic microangiopathies: the Swiss experience. Semin Hematol 41:75–82
9. Humphreys BD, Sharman JP, Henderson JM, Clark JW, Marks PW, Rennke HG, Zhu AX, Magee CC (2004) Gemcitabine-associated thrombotic microangiopathy. Cancer 100:2664–2670
10. Izzedine H, Isnard-Bagnis C, Launay-Vacher V, Mercadal L, Tostivint I, Rixe O, Brocheriou I, Bourry E, Karie S, Saeb S, Casimir N, Billemont B, Deray G (2006) Gemcitabine-induced thrombotic microangiopathy: a systematic review. Nephrol Dial Transplant 21:3038–3045
11. Kasper S, Neurath MF, Huber C, Theobald M, Scharrer I (2007) Protein A immunoadsorption therapy for refractory, mitomycin C-associated thrombotic microangiopathy. Transfusion 47:1263–1267
12. Moake JL (2002) Thrombotic microangiopathies. N Engl J Med 347:589–600
13. Muller S, Schutt P, Bojko P, Nowrousian MR, Hense J, Seeber S, Moritz T (2005) Hemolytic uremic syndrome following prolonged gemcitabine therapy: report of four cases from a single institution. Ann Hematol 84:110–114
14. Onitilo AA, Engel JM, Clouse LH, Gerndt KM (2009) Successful treatment of mitomycin-induced thrombotic thrombocytopenic purpura with rituximab. J Vasc Interv Radiol 20:275–276
15. Rodenhuis S, Westermann A, Holtkamp MJ, Nooijen WJ, Baars JW, van der Wall E, Slaper-Cortenbach IC, Schornagel JH (1996) Feasibility of multiple courses of high-dose cyclophosphamide, thiotepa, and carboplatin for breast cancer or germ cell cancer. J Clin Oncol 14:1473–1483
16. Walker RW, Rosenblum MK, Kempin SJ, Christian MC (1989) Carboplatin-associated thrombotic microangiopathic hemolytic anemia. Cancer 64:1017–1020
17. Walter RB, Joerger M, Pestalozzi BC (2002) Gemcitabine-associated hemolytic-uremic syndrome. Am J Kidney Dis 40:E16
18. Zupancic M, Shah PC, Shah-Khan F (2007) Gemcitabine-associated thrombotic thrombocytopenic purpura. Lancet Oncol 8:634–641