Published in final edited form as:

Med Oncol. 2013 ; 30(2): 568. doi:10.1007/s12032-013-0568-x.

Thrombotic microangiopathy during docetaxel, trastuzumab, and carboplatin chemotherapy for early-stage HER2+ breast cancer: a case report

Wade Iams,

Department of Internal Medicine, Vanderbilt University Medical Center, D-3100 Medical Center North, Nashville, TN 37232-2358, USA

Kathryn Eby Beckermann,

Department of Internal Medicine, Vanderbilt University Medical Center, D-3100 Medical Center North, Nashville, TN 37232-2358, USA

Anne T. Neff,

Department of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN, USA

Ingrid A. Mayer, and

Department of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN, USA

Vandana Gupta Abramson

Department of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN, USA

Wade Iams: wade.t.iams@vanderbilt.edu

Abstract

Chemotherapy-induced thrombotic microangiopathy is a severe illness that has occurred in a small number of patients treated with carboplatin and combination of docetaxel and trastuzumab chemotherapy. We describe herein the case of a patient with stage IIB breast cancer who developed thrombotic microangiopathy after five cycles of carboplatin, docetaxel, and trastuzumab.

Keywords

Thrombotic microangiopathy; Docetaxel; Trastuzumab; Carboplatin

Introduction

Thrombotic microangiopathy (TMA) is a potentially fatal syndrome characterized by microangiopathic hemolytic anemia, thrombocytopenia, and variable end-organ damage due to thrombi in the microcirculation [1]. It was first described in 1952 by Symmers as a shortened version of thrombotic microangiopathic hemolytic anemia [2, 3]. The term TMA is currently used to describe cases of non-idiopathic hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), and clinically indistinguishable cases of HUS/TTP [4].

Hemolytic uremic syndrome is classically described in association with *Escherichia coli* O157:H7 diarrheal infections in children, but it is also a congenital illness and can be associated with pneumococcal infection [5]. TTP is typically caused by decreased ADAMTS13 activity, which leads to unusually large von Willebrand factor multimers and systemic thrombi formation. The decreased ADAMTS13 activity can be inherited or acquired [6]. Mixed disorders of HUS/TTP that are described as TMA can occur in association with solid organ transplant, bone marrow transplant, pregnancy, disseminated malignancy, and medications, including chemotherapy [5, 6].

Thrombotic microangiopathy associated with disseminated malignancy, also known as cancer-related microangiopathic hemolytic anemia (CR-MAHA), is most commonly observed in patients with metastatic gastric, breast, prostate, and lung cancer [7]. Case reports have also described TMA in association with chemotherapeutic agents such as gemcitabine, cisplatin, carboplatin, mitomycin, and bleomycin [3, 8, 9]. Recently, a case of TMA following the administration of docetaxel and trastuzumab in a patient with stage II breast cancer has been described [3].

Herein, we describe the case of a 57-year-old woman with stage IIB breast cancer who developed TMA following five cycles of adjuvant carboplatin, docetaxel, and trastuzumab.

Case report

A 57-year-old woman self-palpated a left-sided breast mass and was eventually found to have estrogen receptor/progesterone receptor (ER/PR)-positive, human epidermal growth factor receptor 2 (HER2)-positive breast cancer. She underwent a modified radical mastectomy with axillary lymph node dissection; pathology revealed a 4.5-cm high-grade invasive mammary carcinoma of no special type with an intermediate proliferation rate. Three of 11 axillary lymph nodes were positive for malignancy, with one lymph node showing extranodal extension. Staging CT scans did not identify any distant metastases, and the patient was classified as having stage IIB breast cancer. Four weeks after resection, she began adjuvant treatment with intravenous (IV) carboplatin at an AUC of five, docetaxel 75 mg/m² IV, and trastuzumab 6 mg/kg IV, all administered every 3 weeks.

After four cycles of carboplatin, docetaxel, and trastuzumab, the patient presented with fatigue and dyspnea with exertion. Her hemoglobin level was 8.3 g/dL, and she received two units of packed red blood cells. Her platelet count, lactate dehydrogenase (LDH), and total bilirubin levels were within normal limits, and a red blood cell type and screen was negative for red blood cell autoantibodies.

Two weeks after receiving her fifth cycle of carboplatin, docetaxel, and trastuzumab, the patient presented with dyspnea on exertion, fatigue, dark urine, and jaundice. She was found to have a hemoglobin level of 7.2 g/dL, platelet count of 47,000, total bilirubin of 1.5 mg/dL, LDH of 799 Units/L, haptoglobin of less than 10 mg/dL, and creatinine of 0.85 mg/dL. Her blood was again negative for red blood cell autoantibodies, and she received two units of packed red blood cells.

Three days after this second red blood cell transfusion, the patient returned with refractory dyspnea on exertion, fatigue, dark urine, and jaundice. Her hemoglobin level was 6.8 g/dL, platelet count was 101,000, total bilirubin was 1.9 mg/dL, LDH was 2,187 Units/L, haptoglobin was 0 mg/dL, and creatinine was 1.56 mg/dL. A urinalysis showed a large amount of blood, urine microscopy showed two red blood cells, her reticulocyte count was 18 %, and a red blood cell direct antiglobulin test was negative for immunoglobulin G (IgG) and complement factor 3 (C3). These findings were consistent with a hemolytic process, thrombocytopenia, and acute renal failure. There was no evidence of decreased ADAMTS13

activity, viral bone marrow suppression, or disseminated intravascular coagulation (DIC). The patient's ADAMTS13 activity was 91 %, parvovirus and cytomegalovirus testing was negative, a few schistocytes and many microspherocytes were seen on a red blood cell smear, and the patient's fibrinogen level, prothrombin time, and partial thromboplastin time were within normal limits. The patient was admitted to the intensive care unit with a diagnosis of chemotherapy-induced TMA.

The patient rapidly recovered with 5 days of daily plasmapheresis, prednisone 80 milligrams daily, and red blood cell transfusions. She was discharged from the hospital after an 8-day stay with a hemoglobin of 8.1 g/dL, platelet count of 281,000, total bilirubin of 1.0 mg/dL, LDH of 370 Units/L, and a creatinine of 1.28 mg/dL.

As an outpatient, she completed a 2-week prednisone taper, and her renal function and markers of hemolysis slowly improved. She has been managed supportively, but did require a two unit red blood cell transfusion 3 weeks after discharge for a hemoglobin of 7.7 g/dL, LDH of 250 Units/L, and haptoglobin <10 mg/dL. Her creatinine returned to baseline 5 weeks after discharge, her LDH remained elevated until 6 weeks after discharge, and her haptoglobin level did not increase to the normal range until 9 weeks after discharge. She remains anemic with a hemoglobin of approximately 10 g/dL, but has not had a recurrence of TMA. She did not receive her final intended carboplatin and docetaxel, and she continues trastuzumab monotherapy every 3 weeks.

Discussion

In oncology patients presenting with TMA, practitioners must differentiate CR-MAHA from medication-induced TMA. In our case, the patient had known stage II disease with no radiographic evidence of metastasis, and the time course coincided with carboplatin, docetaxel, and trastuzumab therapy. As greater than 90 % of patients with CR-MAHA have metastatic disease [7] and the time course suggested medication-induced TMA, we concluded that the patient had chemotherapy-induced TMA.

Thrombotic microangiopathy is pathologically characterized by the deposition of platelet microaggregates within the renal vasculature, and it is clinically characterized by microangiopathic hemolytic anemia and thrombocytopenia [2]. Other components of TMA that can be seen but are not required for diagnosis include acute renal failure, neurological deficits, cardiovascular dysfunction, pulmonary dysfunction, and reduced ADAMTS13 activity [4, 10, 11]. The patient in our case demonstrated hemolysis, thrombocytopenia, and acute renal failure, but did not exhibit neurological, cardiovascular, or pulmonary deficits or decreased ADAMTS13 activity. This is unique from the previously reported case of docetaxel and trastuzumab-induced TMA in a patient with stage II breast cancer [3], as their patient exhibited neurological deficits and reduced ADAMTS13 activity. These differences suggest that chemotherapy-induced TMA varies in manifestations and severity.

There are two speculated pathophysiologic pathways underlying chemotherapy-induced TMA. One is that TMA develops after immune complex formation and deposition within the renal vasculature. This model has been validated in conjunction with mitomycin therapy, where the median time to onset of TMA after mitomycin initiation is 8 months [4, 12]. The second pathophysiologic model of TMA involves direct chemotherapy-induced endothelial toxicity. In this model, TMA is caused by decreased tissue plasminogen activator and increased plasminogen activator inhibitor, resulting in defective fibrinolysis and micro-thrombi deposition [4, 10]. Whereas the previous case of TMA in early-stage breast cancer occurred 1 day after the first administration of docetaxel and trastuzumab, likely by the latter mechanism [3], our case occurred after 4 months of carboplatin, docetaxel, and trastuzumab,

likely by the former mechanism. Our patient received trastuzumab after her episode of TMA without any further sequelae, indicating that the inciting drugs were likely carboplatin or docetaxel, or the combination of those drugs with trastuzumab.

The treatment of chemotherapy-induced TMA has been difficult historically, and the illness has a 2-month mortality rate of 50 % [4]. Previous literature has shown that only 20 % of patients with chemotherapy-induced TMA respond to corticosteroids and plasmapheresis [3, 4]. If these treatments fail, there are several other lines of therapy that have been documented to be effective in the treatment of chemotherapy-induced TMA. These include extracorporeal immunoadsorption therapy with staphylococcal protein A columns (PROSORBA), which showed a 45.4 % response rate in patients with chemotherapy-induced TMA [13]. Also, immunomodulatory therapies such as azathioprine, cyclophosphamide, and vincristine have been anecdotally reported to be effective [3], and rituximab has been shown to induce remission in mitomycin-induced TMA [14]. Fortunately, our patient responded to first-line therapy and had a rapid, full recovery.

In summary, chemotherapy-induced TMA is an important hematological condition to consider in oncology patients who present with anemia and thrombocytopenia. The current case report suggests that chemotherapy-induced TMA may be more common than previously described in patients with early-stage breast cancer treated with carboplatin, docetaxel, and trastuzumab.

References

1. Pisoni R, Ruggerenti P, Remuzzi G. Drug-induced thrombotic microangiopathy; incidence, prevention, and management. *Drug Saf.* 2001; 24(7):491–501. [PubMed: 11444722]
2. Symmers W. Thrombotic microangiopathic haemolytic anaemia (thrombotic microangiopathy). *Br Med J.* 1952; 2:897–903. [PubMed: 12978378]
3. Siau K, Varughese M. Thrombotic microangiopathy following docetaxel and trastuzumab chemotherapy: a case report. *Med Oncol.* 2010; 27:1057–1059. [PubMed: 19847680]
4. Murgo, AJ. Cancer- and chemotherapy-associated thrombotic microangiopathy. In: Kaplan, BS.; Trompeter, RS.; Moake, JL., editors. *Hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura*, (kidney disease S v. 10). Vol. vol. 22. New York: Marcel Dekker Ltd; 1992. p. 271-295.
5. Rahdi M, Carpenter SL. Thrombotic microangiopathies. *ISRN Hematol.* 2012
6. Moake JL. Thrombotic microangiopathies. *NEJM.* 2002; 347(8):589–600. [PubMed: 12192020]
7. Lechner K, Obermeier HL. Cancer-related microangiopathic hemolytic anemia. *Medicine.* 2012; 91:195–205. [PubMed: 22732949]
8. Walker RW, Rosenblum MK, Kempin SJ, Christian MC. Carboplatin-associated thrombotic microangiopathic hemolytic anemia. *Cancer.* 1989; 64(5):1017–1020. [PubMed: 2667747]
9. Fisher DC, Sherrill GB, Hussein A, Rubin P, Vredenburgh JJ, Elkordy M, Ross M, Petros W, Peters WP. Thrombotic micro-angiopathy as a complication of high-dose chemotherapy for breast cancer. *Bone Marrow Transpl.* 1996; 18(1):193–198.
10. Dlott JS, Danielson CFM, Blue-Hnidy DE, McCarthy LJ. Drug induced thrombotic thrombocytopenic purpura/haemolytic uremic syndrome: a concise review. *Ther Apher Dial.* 2004; 8(2):102–111. [PubMed: 15255125]
11. Fields SM, Lindley CM. Thrombotic microangiopathy associated with chemotherapy: case report and review of the literature. *DICP.* 1989; 23(7–8):582–588. [PubMed: 2669373]
12. Cantrell JE Jr, Phillips TM, Schein PS. Carcinoma-associated hemolytic-uremic syndrome: a complication of mitomycin C chemotherapy. *J Clin Oncol.* 1985; 3(5):723–734. [PubMed: 3923162]
13. Snyder HW Jr, Mittelman A, Oral A, Messerschmidt GL, et al. Treatment of cancer chemotherapy-associated thrombotic thrombocytopenic purpura/hemolytic uremic syndrome by protein A immunoadsorption of plasma. *Cancer.* 1993; 71(5):1882–1892. [PubMed: 8448753]

14. Onitilo AA, Engel JM, Clouse LH, Gerndt KM. Successful treatment of mitomycin-induced thrombotic thrombocytopenic purpura with rituximab. *Vasc Interv Radiol*. 2009; 20(2):275–276.