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Case Report

Successful Treatment with Continuous High-dose 5-Fluorouracil Infusion, Followed by Oral Capecitabine in a Patient with Advanced Gastric Cancer with Bone Marrow Metastasis and Microangiopathic Hemolytic Anemia

Hsiu-Tzu Wang, Su-Peng Yeh*

Division of Hematology and Oncology, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan

Abstract

A 61-year-old male with a history of Stage 1A gastric body adenocarcinoma and s/p radical subtotal gastrectomy + B-II reconstruction 5 years previously presented with general malaise and bone pain. A hemogram revealed severe anemia and thrombocytopenia, which were refractory to blood transfusion. A peripheral blood smear showed marked thrombocytopenia with numerous fragmented red blood cells and normoblasts. A bone marrow biopsy showed metastatic adenocarcinoma of gastric origin. Therefore, he was diagnosed with cancer-associated microangiopathic hemolytic anemia (MAHA). In addition to aggressive transfusion support, high-dose continuous 5-fluorouracil infusion was administered, and the MAHA and thrombocytopenia dramatically resolved. Capecitabine was subsequently administered orally at the outpatient clinic, and his disease was well controlled without the recurrence of MAHA or thrombocytopenia for 1 year. Although most chemotherapies may aggravate cytopenia, our case illustrates that effective chemotherapy can not only control cancer-associated MAHA but also restore cytopenia to normal.

Keywords: 5-fluorouracil, advanced gastric cancer, capecitabine, microangiopathic hemolytic anemia

Introduction

Few patients with both gastric cancer and microangiopathic hemolytic anemia (MAHA) have been reported, and their prognosis is extremely poor, with a survival time of usually <1 month despite aggressive supportive care.[1] Treatment of cancer-associated MAHA is very difficult. Although chemotherapy with 5-fluorouracil (5-FU) and cisplatin has been widely used in patients with advanced gastric cancer with a response rate of 35%–50%,[2,3] the use of such chemotherapy in patients with MAHA may further aggravate cytopenia due to bone marrow toxicity and increase the risk of life-threatening

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Address for correspondence: Dr. Su-Peng Yeh, Division of Hematology and Oncology, Department of Internal Medicine, China Medical University Hospital, No. 2, Yuh-Der Road, Taichung 40447, Taiwan.
E-mail: supengyeh@gmail.com

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hemorrhage. Infusion of 5-FU is an effective regimen for advanced gastric cancer with negligible myelosuppression; thus, it may be a favorable choice as an initial therapy for such patients. Here, we report a case of recurrent gastric cancer with bone marrow metastasis with severe MAHA and thrombocytopenia successfully treated with high-dose 5-FU infusion followed by capecitabine.

Case Report

This patient was a 61-year-old male with a history of gastric adenocarcinoma diagnosed in August 2013 and s/p radical subtotal gastrectomy + B-II reconstruction in August 2013, pT1bN0, cM0, Stage IA. In March 2018, he presented with general malaise and bone pain. Blood tests showed a typical presentation of hemolytic anemia including a hemoglobin (Hb) level of 6.8 g/dL, reticulocyte percentage of 6.65%, haptoglobin level of <5.83 mg/dL, total bilirubin level of 2.2 mg/dL, lactate dehydrogenase level of 544 IU/L, thrombocytopenia of 16 × 10^3/uL, and elevated alkaline phosphatase level of 1416 IU/L. A peripheral blood smear showed fragmented red blood cells 2+ (1–2/100 × 10 field), numerous normoblasts, and true thrombocytopenia. We immediately performed a bone marrow examination, which revealed numerous tumor nests. Because of his prior history of gastric cancer, cancer-associated MAHA was considered instead of thrombotic thrombocytopenic purpura or hemolytic uremic syndrome. Esophagogastroduodenoscopy showed a gastric ulcer over the B-II anastomosis site. The pathology of the biopsy revealed no malignancy. A bone marrow biopsy yielded diffuse infiltration of polygonal, signet-ring tumor cells with hyperchromatic nuclei, and vacuolated cytoplasm arranged in nests. Immunohistochemical analysis showed cytokeratin (+), thyroid transcription factor-1 (−), CDX-2 (+, focal and weak), and human epidermal growth factor receptor-2 (−, score 0). Overall, the findings suggested metastatic adenocarcinoma of gastric origin. He was then treated with a 48-h infusion of high-dose 5-FU (2400 mg/m^2) and leucovorin (LV) (400 mg/m^2). Ten days later, we also administered low-dose oral capecitabine (1500 mg/day) as maintenance therapy. Two weeks after starting chemotherapy, his Hb level increased to 8.9 g/dL, and platelet count increased to 46 × 10^3/uL without transfusion support. Six weeks later, his blood cell count became normal. Oral capecitabine (1500–1600 mg/day) was continued for 1 year, and his complete blood cell count remained normal during this period. However, gastric cancer progressed with the recurrence of MAHA afterward, and he is now under platinum-based salvage chemotherapy.

Discussion

MAHA is a rare but severe complication of gastric cancer. Effective chemotherapy for the underlying malignancy may be the only way to control MAHA. However, the myelosuppressive effect of most combination chemotherapies may prevent their use in the clinical setting of MAHA.

On reviewing the literature, mainly from Japan, patients with gastric cancer with MAHA and thrombocytopenia have been reported to be successfully treated using 5-FU-containing regimens.[4,5] Yeh,[4] Hung,[6] and Noda *et al*.[7] reported a successful initial treatment of patients with gastric cancer, MAHA, and thrombocytopenia with aggressive chemotherapy [Table 1]. A retrospective study of 19 patients with advanced gastric cancer with MAHA and thrombocytopenia as the predominant feature confirmed that high-dose 5-FU/LV, a nonmyelosuppressive dosing schedule of 5-FU, is a safe and effective first-line therapy.[6] In addition, Tokar *et al*.[8] used a continuous infusion of 5-FU (200 mg/m^2/day), another nonmyelosuppressive dosing schedule of 5-FU, as the initial treatment for patients with advanced gastric cancer presenting with MAHA.

According to previous retrospective studies, the response induced by a protracted infusion of 5-FU is usually short and persists for only a few weeks. Therefore, once the MAHA and thrombocytopenia symptoms are controlled, the addition of newer cytotoxic drugs may be necessary to consolidate the remission.[8] Initially, we planned to first administer high-dose 5-FU infusion, followed by combination chemotherapy if the MAHA and thrombocytopenia resolved, and the patient developed tolerance. However, because the subsequent subdural hematoma caused a relatively poor performance status, we only administered oral capecitabine as maintenance therapy. Unexpectedly, his cancer-associated MAHA and thrombocytopenia resolved without the recurrence for nearly 1 year [Figures 1 and 2].

Conclusion

Cancer-associated MAHA and thrombocytopenia associated with advanced gastric cancer respond to initial treatment with a high dose of 5-FU/LV, which may persist under control with oral capecitabine maintenance therapy.

Declaration of patient consent

We obtained the appropriate patient consent forms. In the form, the patient provided his consent for his clinical information to be reported in the journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

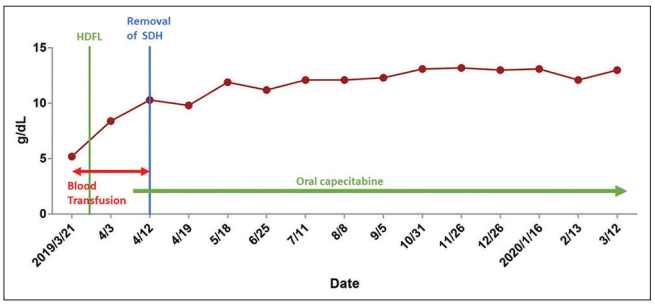

Figure 1: Clinical response of the hemoglobin serum level of the patient
HDFL = High dose of 5-FU/leucovorin, SDH = Subdural hematoma

Table 1: Different treatments and modalities for patients with advanced gastric cancer and microangiopathic hemolytic anemia

	Number of patients with AGC and MAHA	Gastric cancer metastasis	Regimen	Recovery from MAHA
Yeh and Cheng (1998)[4]	5	4 bone marrow, 3 liver, 3 lung, 3 bone, 1 adrenal gland metastasis	HDFL Weekly 5-FU 2600mg/m^2, 24h infusion and leucovorin 300mg/m^2	5 Most resolved within 2 doses of weekly HDFL
Chao *et al*. (2000)[5]	6	5 peritoneum, 3 bone, 2 lung, 2 liver metastasis	EEPFL Weekly etoposide 40 mg/m^2, i.v.d ≥30 min, epirubicin 10 mg/m^2, i. v. d ≥5 minutes, cisplatin 25 mg/m^2, 5-FU 2200 mg/m^2, and leucovorin 120 mg/m^2, given simultaneously 24h infusion	6 Most resolved within 6 doses of weekly EEPFL
Hironaka *et al*. (2000)[9]	9	Unknown	Weekly MTX 1000 mg/m^2, i.v. bolus, followed 3h later by 5-FU 600 mg/m^2, i.v. bolus	8 The median time to recovery from MAHA: 10 days (6-34)
Tokar *et al*. (2006)[8]	6	Unknown	5-FU 200 mg/m^2/day	5 The clinical status improved dramatically within 2 weeks
Huang *et al*. (2008)[6]	19	14 bone marrow, 13 bone, 3 liver, 2 lung, 3 ovary	HDFL Weekly 5-FU 2600 mg/m^2, leucovorin 300 mg/m^2, 24h infusion	14 After the median of 4 weeks of HDFL, the MAHA was resolved

AGC=Advanced gastric cancer, MAHA=Microangiopathic hemolytic anemia, 5-FU=5-fluorouracil, HDFL=High-dose 5-fluorouracil/leucovorin, MAHA=Microangiopathic hemolytic anemia, IV=Intravenous

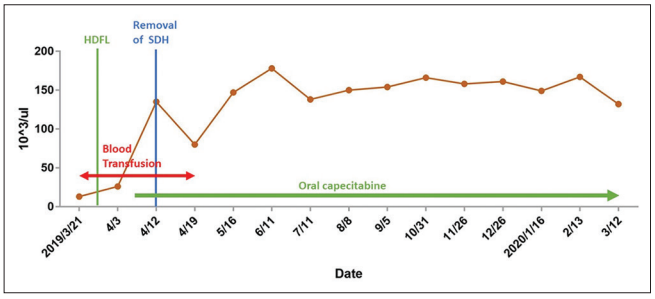

Figure 2: Clinical response of the platelet count of the patient . HDFL = High dose of 5-FU/leucovorin, SDH = Subdural hematoma

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Nil.

Conflicts of interest

There are no conflicts of interest.

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