

Eltrombopag Use in Thrombocytopenia for Endoscopic Submucosal Dissection of a Gastric Carcinoid

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Abstract

Severe thrombocytopenia is a contraindication for therapeutic endoscopy due to the risk of bleeding. Platelet transfusions can temporarily increase platelet count, but are difficult to administer in the 2 weeks following endoscopic resection, during which the patient is at high risk for delayed bleeding. We present the use of a novel thrombopoietin receptor agonist, eltrombopag, to sustain platelet levels for the safe and complete endoscopic submucosal dissection of a gastric carcinoid in a patient with severe thrombocytopenia due to cirrhosis and idiopathic thrombocytopenic purpura. We performed complete and safe endoscopic removal of a gastric carcinoid after correcting the thrombocytopenia.

Introduction

Current guidelines recommend platelet counts greater than $50 \times 10^9/L$ in the absence of coagulation abnormalities as the threshold to safely perform invasive procedures.¹ Patients with thrombocytopenia are often unable to undergo therapeutic endoscopy such as endoscopic submucosal dissection (ESD) due to the risk of bleeding. Pre-procedure platelet transfusions are often given; however, their effect is transient. Transfusions lead to a rapid rise (within the first hour), but also a rapid fall (within 72 hours) in platelet counts; thus, repeated transfusions are needed to sustain adequate levels.

Case Report

A 65-year-old male with decompensated alcoholic cirrhosis (Child-Pugh Class A, MELD 10) with prior variceal bleeds (grade II varices and portal hypertensive gastropathy) and chronic idiopathic thrombocytopenic purpura (ITP) was referred for a gastric subepithelial lesion. He reported a 35-year drinking history, with his last drink 4 years prior. Physical examination revealed no scleral icterus, asterixis, or hepatosplenomegaly. His abdomen was soft, nontender, and nondistended. His laboratories were significant for thrombocytopenia at $30 \times 10^9/L$, white blood cell count $4.8 \text{ cells}/\mu\text{L}$, hemoglobin 13.3 g/dL , hematocrit 38.9%, creatinine 0.92 mg/dL , bilirubin 1.1 mg/dL , prothrombin time 16.3, and international normalized ratio 1.29.

On endoscopy, a 1.5-cm sessile subepithelial lesion was found in the posterior wall of the proximal gastric body (Figure 1A). On endoscopic ultrasound (EUS), the lesion was hypoechoic and limited to the submucosa. There were no abnormal lymph nodes. Biopsy of the lesion revealed a well-differentiated neuroendo-

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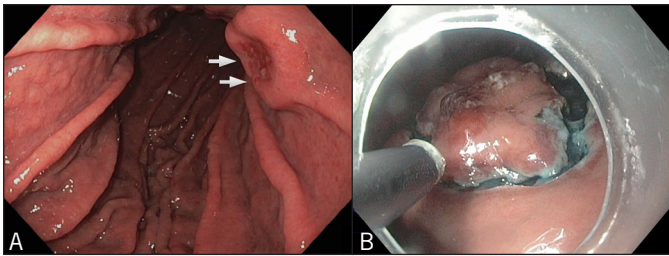


Figure 1. (A) Endoscopic image of gastric carcinoid on the posterior wall on the lesser curvature in the gastric body, and (B) endoscopic submucosal dissection using the IT-knife.

crine tumor (NET) of the stomach (gastric carcinoid), type III (sporadic), characterized by <2 mitotic figures per 10 high-power fields. The Ki-67 index was 2% and the WHO grade was 1.² Immunohistochemical stains for synaptophysin and chromogranin were positive.

A positron emission computed tomography (PET CT) and somatostatin-receptor-scintigraphy showed no regional or metastatic disease. A bone marrow biopsy showed increased megakaryocytes and a normal immunophenotype consistent with chronic ITP. CT showed no portal vein thrombosis (PVT). Doppler ultrasound was not done, however it was likely warranted to rule out PVT prior to initiating eltrombopag.

We initiated eltrombopag 50 mg oral daily and achieved a platelet count of $80 \times 10^9/L$ after 2 weeks. We chose the low dose in order to prevent portal vein thrombosis. We performed endoscopic submucosal dissection of the gastric lesion (Figure 1B) using a mixture of indigo carmine and saline, and performed a complete circumferential incision using a combination of dual knife and IT-knife (Olympus America, Center Valley, PA). Finally, we snared the lesion and removed it en bloc. Minor bleeding occurred but was easily treated using coagulation and hot biopsy forceps. Pathology confirmed a completely resected submucosal well-differentiated NET, WHO grade 1, measuring 1.4 cm in greatest dimension and 0.4 cm in maximum depth (Figure 2). The tumor was T2 based on size, stage IIa. The adjacent mucosa was normal and *Helicobacter pylori* testing was negative.

There was no bleeding or complications after the procedure or from eltrombopag. Omeprazole 20 mg twice daily was given for 2 months. Etrombopag was continued for 4 weeks since ESD-induced ulcers can take up to 2 months to resolve and bleeding in patients with cirrhosis has significant morbidity and mortality (Figure 3). On repeat endoscopy, a scar was noted at the prior resection site without endoscopic or endosonographic evidence of local recurrence, and no bleeding was present. A PET-CT at 4 months and 15 months later showed no signs of recurrent

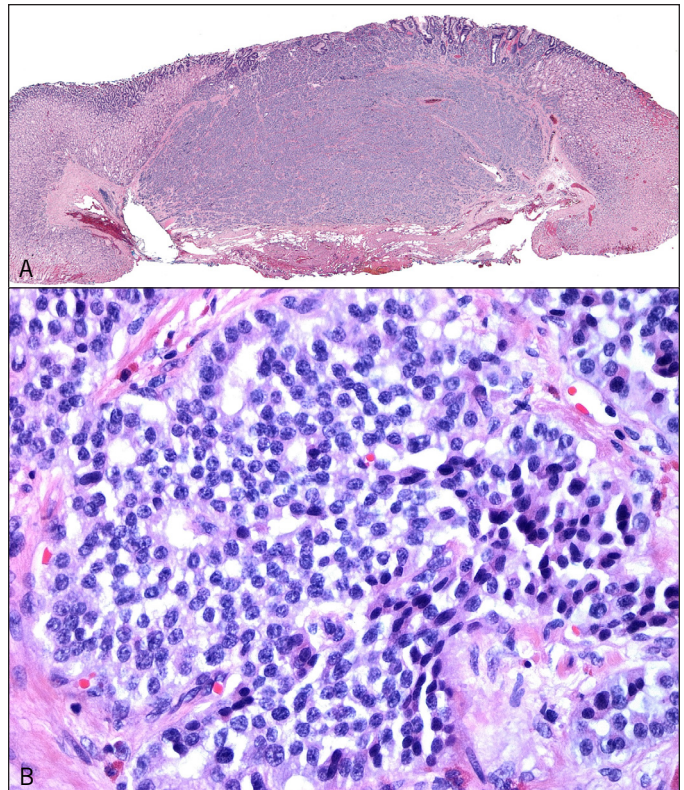


Figure 2. (A) Low-power histopathologic view showing a circumscribed but unencapsulated nodule extending from the deep mucosa into and expanding the submucosa. The deep cauterized edge and the peripheral margins do not show involvement by neoplasm. (B) High-power view of H&E stain demonstrating typical features of well-differentiated neuroendocrine tumor.

malignancy or metastases, and no portal vein thrombosis. At 6 months, the patient developed massive ascites attributed to progression of his liver disease.

Discussion

We present a case of successful periprocedure platelet management with eltrombopag in a thrombocytopenic patient who underwent ESD of a 1.4-cm gastric carcinoid. Eltrombopag (Promacta®) and romiplostim (Nplate®) are novel thrombopoietic growth factors that activate a signal cascade leading to megakaryocyte proliferation, differentiation, and

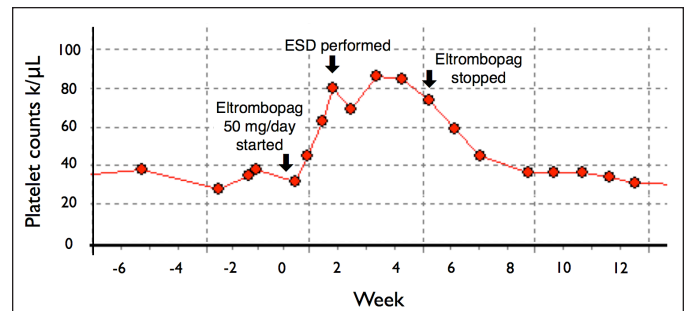


Figure 3. Platelet count relative to eltrombopag use.

platelet production.³ Eltrombopag is a small receptor-stimulating molecule administered orally once daily. In contrast, romiplostim is a peptide given in weekly subcutaneous injections. In clinical trials, eltrombopag exhibited a dose-dependent increase in platelets in relapsed or refractory ITP, and romiplostim achieved a durable platelet response $>50 \times 10^9/L$ in patients with chronic ITP.^{4,5}

Novel thrombopoietin agents can medically optimize patients and obviate the need for platelet transfusion prior to invasive procedures. Eltrombopag 75 mg daily for 14 days reduced the need for platelet transfusions in cirrhotic patients undergoing elective invasive procedures.⁶ Similarly, preoperative administration of romiplostim 1 $\mu\text{g}/\text{kg}$ weekly in patients with hepatitis C, cirrhosis, and thrombocytopenia increased platelet counts in 33 of 35 patients to levels eligible for surgery with no additional thrombotic complications or postoperative bleeding.⁶

Serious adverse effects of thrombopoietic agents include liver function test abnormalities, bone marrow fibrosis, thrombotic/thromboembolic complications, and hemorrhage after drug discontinuation. Dose optimization is critical. The trial of eltrombopag for periprocedure platelet management was stopped early due to portal vein thrombosis, possibly due to thrombosis at study entry or over targeting platelet counts. A post hoc analysis found that platelet counts $>200 \times 10^9/L$ were associated with an increased risk for thrombotic events.⁷ Although there are no published guidelines, abdominal ultrasound to evaluate the portal vein prior to initiating therapy with thrombopoietic factors is often pursued.

These agents offer a lower-cost alternative for the treatment of thrombocytopenia. Platelet transfusions cost approximately \$600.00 to \$1000.00 per unit. Adult transfusions are on average 4–6 units and raise the platelets by approximately $30 \times 10^9/L$. Costs increase quickly, especially with repeated transfusions. The average wholesale cost for 30 50-mg and 75-mg tablets of eltrombopag is \$6,803.29 and \$10,204.94, respectively.⁸ A 250- μg and 500- μg vial of romiplostim costs \$1,615.80 and \$3,231.60, respectively.⁸

Given our patient's comorbidities, which placed him at increased risk perioperatively, and the characteristics of his type III gastric carcinoid (1–2 cm, limited to the submucosa on EUS with negative nodes/metastatic work-up), ESD was preferred to surgery.^{9,10} Typically, type III gastric carcinoids

should be treated as gastric adenocarcinomas, requiring partial or total gastrectomy with local lymph node dissection, given their aggressive growth rate, mortality rate of 25–30%, and metastatic rate of 50–100%.⁹ To prevent excessive bleeding during ESD, we administered eltrombopag 50 mg for 14 days prior to intervention, which is in line with current guidelines. This allowed complete and safe endoscopic removal of the gastric carcinoid after correcting the thrombocytopenia.

Disclosures

Author Contributions: All authors contributed equally to the design, drafting, revision and approval of the article, and to the generation and interpretation of the data. JM Kolb is the article guarantor.

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Informed consent was obtained for this case report.

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