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Case Report

Use of Eltrombopag Among Patients with Liver Cirrhosis: A Case Series

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Abstract

Background: Thrombocytopenia is commonly found among patients with liver cirrhosis. It complicates treatment of patients requiring an invasive procedure as part of their routine clinical care. An important clinical question is whether there is a need for a platelet-stimulating growth factor or thrombopoietin receptor agonist among patients with liver cirrhosis who have thrombocytopenia.

Case Summary: This paper discusses the profile of three patients with thrombocytopenia and liver cirrhosis who received Eltrombopag prior to invasive procedures and one patient in the control of hemorrhagic stroke expansion. Eltrombopag was given at doses of 25 mg to 50 mg daily for two to three weeks, except one patient who was maintained for more than a year. Bleeding complications were prevented in all patients, with no adverse events seen during and post treatment.

Conclusion: Treatment with eltrombopag is an effective and safe approach to increase platelet counts in thrombocytopenic cirrhotic patients

Keywords: Case Series; Eltrombopag; Liver Cirrhosis; Thrombocytopenia; Platelet Transfusion

Introduction

Thrombocytopenia is frequently observed in patients with chronic liver disease, where it is considered a marker for hepatic fibrosis and cirrhosis severity. It is defined as a reduction in platelet count to <150,000. Thrombocytopenia in these patients is due to both reduced hepatocellular mass available for constitutive production of thrombopoietin (TPO) as well as to increase portal hypertension resulting in splenomegaly, and splenic sequestration of circulating platelets [1]. Furthermore, the development of antiplatelet antibodies (alloimmunization) can cause refractory thrombocytopenia in up to half of patients who receive multiple transfusions like patients with liver cirrhosis [2].

Data on the incidence of liver cirrhosis in the Philippines is limited. Liver diseases are more common in countries where hepatitis B virus carriers are prevalent, such as the Philippines [3]. According to the latest World Health Organization (WHO) data published in 2018, liver disease-related deaths in the Philippines reached 7,492 or 1.23% of total deaths. Complications arising from these chronic liver diseases, including cirrhosis and liver cancer, are therefore emerging threats in the Asia–Pacific region [4].

Treatment options in liver cirrhosis target slowing down fibrosis and addressing its complications [5]. Thrombocytopenia complicates the treatment of patients with chronic liver disease. An important clinical question is whether there is a need for a platelet-stimulating growth factor or thrombopoetin receptor agonist among liver cirrhotic patients with thrombocytopenia [6]. As of writing, there is no available data on the use of Eltrombopag among patients with liver cirrhosis in the Philippines.

Oral thrombopoietin-receptor agonist, like Eltrombopag is approved for use in patients with chronic immune thrombocytopenia [7]. An article published in The New England Journal of Medicine reports the results of the Eltrombopag Evaluated for Its Ability to Overcome Thrombocytopenia and Enable Procedures (ELEVATE) study — a double-blind, placebo-controlled trial that evaluated the ability of eltrombopag to increase platelet counts and reduce the need for platelet transfusions in patients with thrombocytopenia and chronic liver disease who were undergoing an elective invasive procedure.

The objective of this paper is to discuss a series of patients with liver cirrhosis who received Eltrombopag instead of multiple platelet transfusions before undergoing elective invasive procedures, and to determine if eltrombopag is a safe and effective mean to elevate platelet counts in chronic liver disease patients with thrombocytopenia in the Philippines.

Case Presentation

Case 1: 54 yr old cirrhotic female admitted due to left sided body weakness

Patient developed liver cirrhosis secondary to NASH with Grade II esophageal varices. She had been stable for many years on maintenance medication. Suddenly, she presented with sudden onset of inability to move the left side of her body associated with slurred speech and facial asymmetry. Patient was brought to local hospital where CT scan showed intracranial bleed of 10mL thus admitted (Figure 1) (Table 1).

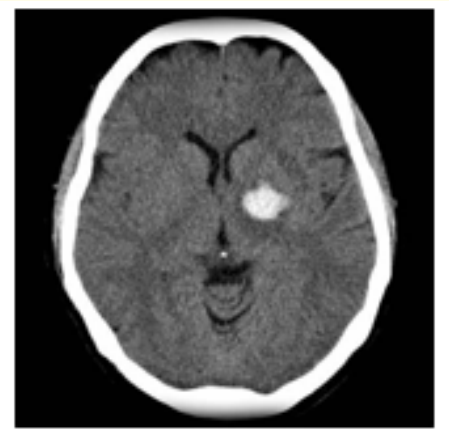

Figure 1: Cranial CT scan image done on a 54year-old female patient showing 10mL intracranial bleed.

	Age	Sex	Child Pugh Score	Indication for Eltrombopag use
Patient 1	54	Female	A (Score of 6)	Intracranial hemorrhage bleeding control
Patient 2	56	Female	A (Score of 6)	ERCP with CBD stone extraction and lap cholecystectomy
Patient 3	66	Male	B (Score of 7)	Coronary angiography, and CABG
Patient 4	68	Male	C (Score of 10)	ICD Placement

Table 1: Patient Demographics.

Patient was initially transfused with 6 units of platelet concentrate with noted increase of platelet from baseline of 33 g/L to 45 g/L. At this point, Eltrombopag 25 mg/tab 1 tablet daily was started 2 hours before breakfast. Platelet trends while admitted: 66g/L (Day 2 Eltrombopag), 70 g/L (Day 3 Eltrombopag), 74 g/L (Day 5 Eltrombopag), 55 g/L (Day 7 Eltrombopag). 1 week after starting the medication, Eltrombopag dose was increased to 2 tablets daily (50 mg a day dose). Subsequent platelet trend: 68 g/L (Day 10 Eltrombopag) to 79 g/L (Day 14 Eltrombopag). Patient was then discharged improved neurologically with Eltrombopag 25 mg 2 tablets daily as part of her medication. This dosage was maintained for 6 months then titrated down to 25 mg per day for the next 6 months. All through out the follow up period, no CVD bleed observed, and no signs of portal vein or mesenteric vascular thrombosis on regular abdominal ultrasound and CT scan.

Case 2: 56 year old cirrhotic female for gallbladder surgery

Patient is a known patient with liver cirrhosis maintained on Eltrombopag 25 mg 1 tablet once a week for more than a year due to a previous cerebrovascular event. She was admitted this time due to severe abdominal pain. Abdominal CT-scan revealed bile duct ectasia secondary to suspicious common bile duct stone (CBD) and cholecystitis. She eventually had endoscopic retrograde cholangiopancreatography (ERCP) with CBD stone extraction and later followed by laparoscopic cholecystectomy.

Initial CBC on admission showed platelets of 92 g/L. Eltrombopag 25 mg/ tab at 2 tablets daily was restarted 5 days before the ERCP. Platelet trends while admitted: 61 g/L (Day 3 Eltrombopag) to 69 g/L (Day 6 Eltrombopag) to 75 g/L (Day 9 Eltrombopag). Patient underwent laparoscopic cholecystectomy on day 12 Eltrombopag with no bleeding complications noted post surgery. She was eventually discharged with Eltrombopag at 25 mg a day.

Case 3: 66 year old cirrhotic male admitted for chest heaviness

Patient was managed for ST-elevation myocardial infarction (STEMI) and underwent coronary angiogram showing 3-vessel disease. Eventually had 3-vessel coronary artery bypass graft operation (CABG) within the same hospitalization.

Initial CBC on admission showed platelet count of 90 g/L. Patient was started on Eltrombopag 25 mg/tab 1 tab every day. Had the following platelet trend thereafter: 35 g/L (Day 3 Eltrombopag). Because of the urgency of the procedure, he was transfused with 6 units platelet concentrates on Day 3 of Eltrombopag and had coronary angiogram. Platelet trends were then 74 g/L (Day 6 Eltrombopag) and increased further to 90 g/L (Day 14 Eltrombopag). He was eventually cleared to undergo CABG, but still required 6 units platelet transfusion before the major cardiac revascularization surgery as advised by hematology service. Two days post CABG, Eltrombopag was maintained at 25 mg every other day up to hospital discharge (Day 22 Eltrombopag). Despite the platelet count not reaching to more than 100 g/L and given the nature of the invasiveness of the CABG, the patient had no bleeding complications post surgery.

Case 4: 68 year old cirrhotic male with chief complaint of dyspnea

Patient is a known case of 3-vessel coronary artery disease presenting with chest heaviness, shortness of breath and dyspnea. Upon consult, he was noted to have cardiac dysrhythmia thus admitted. He was referred to the Gastroenterology service due to cardiac cirrhosis.

Patient was scheduled for Implantable Cardioverter Defibrillator (ICD) implantation, however his work-ups showed thrombocytopenia. He was started on Eltrombopag 25 mg/ tab 1 tab every other day. Had the following platelet trend while on Eltrombopag: 80 g/L (Day 3 Eltrombopag), 106 g/L (Day 6 Eltrombopag), 124 g/L (Day 10 Eltrombopag). Patient was eventually cleared for ICD implantation. Post-operative events were unremarkable. Eltrombopag was discontinued on Day 20 of Eltrombopag administration with platelet count of 324 g/L (Figure 2) (Table 2).

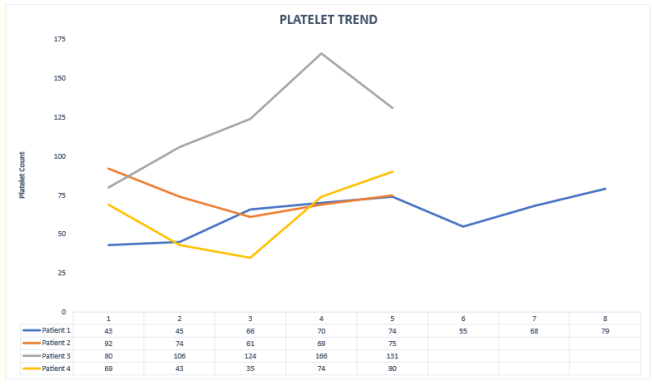

Figure 2: Platelet trend of patients.

	Baseline Platelet Count (g/L)	Final Platelet Count (g/L)	% increase in Platelet count
Patient 1	43	79	84%
Patient 2	75	92	23%
Patient 3	80	131	64%
Patient 4	69	324	369%

Table 2: Summary of the increase in platelet count in percentage.

Discussion

Thrombocytopenia is the most common hematological abnormality encountered in patients with chronic liver disease. In addition to being an indicator of advanced disease and poor prognosis, it frequently hinders crucial interventions. Over the past years, there have been significant advances in the understanding of thrombopoiesis, which, in turn, has led to an improved understanding of thrombocytopenia in cirrhosis [8].

Hepatic production of thrombopoietin (TPO) plays a pivotal role in thrombopoiesis [9]. The liver secretes TPO at a constant rate

into the circulation, where it binds to ligands on both platelets and megakaryocytes stimulating platelet production. In patients with chronic liver disease, circulating TPO levels are decreased due to impaired production and secretion, and increased degradation by platelets sequestered in the spleen [8]. Reduced TPO levels result in decreased megakaryocyte stimulation and platelet production.

Eltrombopag is an oral thrombopoietin-receptor agonist. The ELEVATE study published in the New England Journal of Medicine evaluated the efficacy of eltrombopag for increasing platelet counts and reducing the need for platelet transfusions in patients with thrombocytopenia and chronic liver disease. In this study, patients with Child Pugh Score (CP) Score of 6-12 who will undergo an elective invasive procedure were included and were given the drug at 75 mg daily.

Treatment with Eltrombopag increased the platelet counts in all of our patients with a percentage increase from 23% to 369% from baseline count. This is consistent with the findings of the ELEVATE trial where a significant number of the enrolled liver patients treated with Eltrombopag had a platelet count increase up to Day 14 of the trial. The need for repetitive platelet transfusion was avoided in our patients, except for one patient who needed to have an urgent coronary angiography and eventual CABG, wherein platelet blood products were transfused immediately prior to the procedure, but none thereafter. Likewise, the patient with CVD hemorrhage with platelet count of 33 g/L on admission was given platelet concentrate transfusion, but no further blood transfusion thereafter. It is worthy to say that. no bleeding episodes were noted in all our patients. Remarkably, the patient who suffered an intracranial bleed did not have further hemorrhage extension or recurrence when the drug was initiated and maintained for several months.

The most common adverse events, occurring in more than 3% of patients in the ELEVATE trial were headache, pyrexia, abdominal pain, diarrhea, nausea, and hepatic encephalopathy. Of note, thromboembolic events involving the portal venous system (portal, upper mesenteric, and splenic vein) is noted to be the most severe of these events [7]. These important adverse embolic events were however noted to be infrequent even in a more prolonged treatment period as shown in the EXTEND study.

In the encountered studies, the dose of Eltrombopag is normally at 75mg daily, however, some studies have dose adjustments. In the EXTEND study, the starting dose was 50 mg daily and was titrated to as low as 25 mg daily or less often if platelet counts were too high, and to as high as 75 mg daily if platelet counts were too low. Likewise, repeated short courses of Eltrombopag were also employed in some ITP patients (REPEAT), with the same good platelet response. In the RAISE trial, 50 mg daily dose for ITP patients were employed for 6 months. In our patients, we employed a more lowered dose from 25 mg to 50 mg daily. This is in consideration that our patients had coexisting cerebrovascular and very active cardiac problems, hence, the risk of embolic events is higher in these patients compared to patients in the existing literature. Despite the lowered dose in our case series, the platelet count increased to levels that prevented bleeding complications. More importantly, no further worsening of the MI and thrombotic compromise of the grafted vessels post CABG occurred to our 2 patients. One patient received Eltrombopag continuously for more than 2 years, but of varying doses and interval between dosing, and no significant adverse events occurred on those period [10-14].

Conclusion/Recommendation

In conclusion, treatment with eltrombopag reduced the need for multiple platelet transfusions in our patients with chronic liver disease and thrombocytopenia who were undergoing invasive procedures. Platelet counts were increased during treatment with Eltrombopag in all of our four patients. No significant adverse events were seen in all of the abovementioned patients. Hopefully, we can extend the utility of this medication to a much larger number of thrombocytopenic cirrhotic patients, especially those with the same clinical scenarios mentioned above and those who will undergo surgical and invasive procedures. However, we should always balance the benefits and the risks inherent with the drug administration.

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Conflict of Interest

None.

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