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Short Communication

Efficacy and safety of repeated use of lusutrombopag prior to radiofrequency ablation in patients with recurrent hepatocellular carcinoma and thrombocytopenia

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Aims: Thrombocytopenia is often associated with chronic liver disease. Lusutrombopag is a small molecule thrombopoietin receptor agonist designed to temporarily increase the platelet count in patients with chronic liver disease for whom elective invasive procedures are planned. In the present study, the efficacy and safety of repeated use of lusutrombopag prior to radiofrequency ablation (RFA) for recurrent hepatocellular carcinoma were examined.

Methods: Eight patients with hepatocellular carcinoma who had a platelet count <50 000/μL prior to both initial and repeat RFA at the time of recurrence received lusutrombopag (3 mg/day) orally for 7 days between March 2016 and August 2018. The following were compared: the effect of lusutrombopag to increase the platelet count as determined by the platelet count after the initial and repeated use of lusutrombopag, the rate of avoiding platelet transfusion, and the presence of any complications.

Results: The platelet count increased to 103 100 ± 22 800/μL 14 days after the first treatment and to 110 700 ± 17 800/μL 14 days after the repeated use. None of the patients required platelet transfusion. None of the patients developed clinical symptoms such as thrombosis, fever, rash, portal vein thrombosis, bleeding, or any other serious adverse events.

Conclusions: Repeated use of lusutrombopag increased the platelet count. It did not cause any serious adverse events and led to avoidance of platelet transfusion. Radiofrequency ablation was carried out safely in all patients. Future studies with more cases of repeated use are needed to examine the long-term efficacy and safety of lusutrombopag.

Key words: chronic liver disease, hepatocellular carcinoma, lusutrombopag, radiofrequency ablation, thrombocytopenia, thrombopoietin receptor agonist

INTRODUCTION

MULTIPLE FACTORS CONTRIBUTE to thrombocytopenia in patients with chronic liver disease.[1–3] When patients with chronic liver disease have thrombocytopenia, platelet transfusion is generally carried out to lower the risk of bleeding prior to undertaking invasive procedures.[4] However, platelet transfusion has several clinical limitations and potential complications.[5–8] Side-effects of platelet transfusion include serious adverse reactions such as anaphylactic shock, anaphylaxis, hypotension, dyspnea, transfusion-associated circulatory overload, and transfusion-related acute lung injury, and non-serious adverse reactions such as urticaria and fever. There are also risks of infectious diseases and platelet transfusion refractoriness due to repeated transfusion.[5–8]

Lusutrombopag, an active small molecule human thrombopoietin (TPO) receptor agonist discovered and developed by Shionogi & Co., Ltd (Osaka, Japan) that became available in September 2015,[9] is effective for improving thrombocytopenia in patients with chronic liver disease for whom elective invasive procedures are planned. Multiple invasive procedures are often carried out within a short period of time to treat patients with chronic liver

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disease. In particular, radiofrequency ablation (RFA) is often carried out repeatedly for patients with recurrent hepatocellular carcinoma.[10–12] No studies to date have examined the safety of repeated use of lusutrombopag and its effectiveness in terms of increasing the platelet count. In the present study, the treatment effect and safety of repeated use lusutrombopag at the time of repeated RFA were investigated in patients with recurrent hepatocellular carcinoma and thrombocytopenia.

METHODS

AMONG 661 PATIENTS with cirrhosis who underwent RFA for hepatocellular carcinoma at our hospital from March 2016 to August 2018, 66 patients had thrombocytopenia (platelet count <50 000/μL). All 66 patients received lusutrombopag. Among the 66 patients, eight (six men and two women) who received repeated treatment with lusutrombopag between March 2016 and August 2018 were included in this study. Lusutrombopag (3 mg/day) was given orally for 7 days before the first and second RFA for recurrent hepatocellular carcinoma.

The following were compared: (i) the effect of lusutrombopag on the platelet count, as determined by the platelet count after the first and second treatment with lusutrombopag; (ii) the rate of avoiding platelet transfusion; and (iii) the presence of any complications.

To diagnose the portal vein thrombosis, contrast-enhanced computed tomography was undertaken at the screening after RFA. In addition, ultrasonography was carried out after the initiation of study treatment and immediately before the RFA procedure.

Data are expressed as the mean and standard deviation. Two-way repeated ANOVA was used to compare the platelet count between the first and second lusutrombopag treatments. A *P*-value less than 0.05 was considered to indicate statistical significance. All statistical analyses were undertaken using Easy R (EZR) version 1.29 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[13]

RESULTS

THE MEAN AGE of the patients (six men and two women) was 68.75 ± 10.64 years. Three patients were positive for hepatitis C virus, two had non-alcoholic steatohepatitis, and three had alcoholic liver disease. The mean Child–Pugh score was 6.63 ± 0.51 (Table 1). The median tumor diameter at RFA was 25.0 mm (range, 20.0–30.0 mm), and the median interval of repeated use of lusutrombopag was 193 days (range, 68–329 days).

Prior to RFA, the platelet count was 42 500 ± 5200/μL when lusutrombopag was first given and 43 800 ± 6000/μL when lusutrombopag was re-administered. The platelet count increased to 103 100 ± 22 800/μL 14 days after the first treatment and to 110 700 ± 17 800/μL 14 days after the treatment was repeated ($P = 0.113$) (Fig. 1). There was no difference in the change in platelet counts between first and repeated use of lusutrombopag.

None of the patients required platelet transfusion.

One patient had procedural nausea at initial and repeated use of lusutrombopag. However, none of the patients developed clinical symptoms such as thrombosis, fever, rash, portal vein thrombosis, bleeding, or any other serious adverse event. No patient discontinued the study drug because of adverse events.

DISCUSSION

THROMBOCYTOPENIA IS COMMON in cirrhosis patients, with approximately 76% of patients having platelet counts <150 000/μL and approximately 13% having platelet counts between 50 000 and 75 000/μL.[1–3] Patients with chronic liver disease often require invasive procedures as part of their treatment for hepatocellular

Table 1 Clinical characteristics of patients enrolled in this study

Characteristics	Number or mean ± SD	Median (range)
Gender, male/female	6/2	
Age, years	68.75 ± 10.64	73.50 (46–78)
Etiology, HCV/NASH/alcohol	3/2/3	
Child–Pugh score	6.63 ± 0.51	7 (6–7)
Baseline platelet count, $\times 10^4/\mu L$	4.27 ± 0.52	4.30 (3.60–4.90)
Interval time of repeated use, days	189.12 ± 91.84	193 (68–329)
Tumor number	2.00 ± 0.53	2 (1–3)
Tumor size, mm	24.66 ± 4.81	25.0 (20.0–30.0)
Tumor location, unilobar/bilobar	5/3	

HCV, hepatitis C virus, NASH, non-alcoholic steatohepatitis; SD, standard deviation.

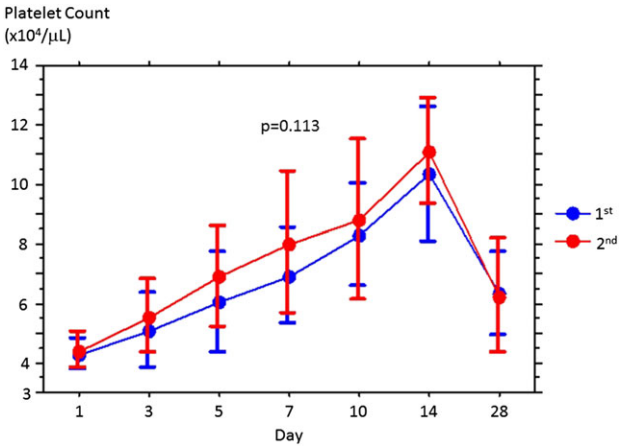

Figure 1 Time course of platelet count of patients with recurrent hepatocellular carcinoma and thrombocytopenia undergoing repeated radiofrequency ablation and treatments with lusutrombopag. Error bars indicate standard deviation. [Color figure can be viewed at wileyonlinelibrary.com]

carcinoma, as well as for esophageal and gastric varices. However, procedures could be delayed or sometimes canceled due to the risk of bleeding in patients who also have thrombocytopenia. Therefore, thrombocytopenia is a major issue in patients with chronic liver disease. Although platelet transfusion has been the only effective strategy to date, it is associated with limitations because it is not effective in some patients and can also cause side-effects.[5–8]

Lusutrombopag (Shionogi & Co., Ltd., Osaka, Japan) has been approved in Japan for the improvement of chronic liver disease-associated thrombocytopenia in patients scheduled to undergo invasive procedures.[9] It is a chemically synthesized, orally active, small molecule human TPO receptor agonist that activates the signal transduction pathway in the same fashion as endogenous TPO and induces platelet production.[9]

A Japanese phase III trial examined the effect of lusutrombopag prior to invasive procedures in Japanese patients with chronic liver disease, and it showed that lusutrombopag treatment resulted in avoidance of platelet transfusion in a significantly higher proportion of patients than in those on placebo (79.2% and 12.5%, respectively).

Phase II and phase III trials reported that the platelet count was maintained at ≥50 000/μL for a median of 21.0 and 22.1 days, respectively, in patients who were on lusutrombopag and did not require platelet transfusion.[9,14,15]

This suggests that lusutrombopag treatment should be repeated after this time period.

Studies indicated that romiplostim, which has the same pharmacological action as lusutrombopag, led to production of neutralizing antibody when continuously administered for a long period, and it was associated with the risk of thromboembolism due to increased platelet counts when overdosed.[16,17]

Similarly, treatment with lusutrombopag could also lead to production of neutralizing antibodies, thus reducing the overall effect to increase platelet counts at the time of re-administration. Furthermore, retreatment might increase the platelet count excessively, thus increasing the risk of thromboembolism, as found with eltrombopag in the ELEVATE study.[18]

In the present study, repeated use of lusutrombopag at the time of repeated RFA in patients with recurrent hepatocellular carcinoma and thrombocytopenia showed that the platelet count not excessively but similarly increased following both the first and repeated treatment. The effect on the platelet count did not decrease after repeated use.

One patient had procedural nausea at the initial and repeated use of lusutrombopag. However, none of the patients developed clinical symptoms such as thrombosis, fever, rash, portal vein thrombosis, bleeding, or any other serious adverse events. No patient discontinued the study drug because of adverse events. Radiofrequency ablation was carried out safely in all patients.

In the case where repeated invasive treatments, such as RFA, are carried out, as in this study, splenectomy or embolization of splenic artery which provides permanent or prolonged restoration of platelet counts is considered to be one of the options for treatment of thrombocytopenia.[3] However, these procedures are invasive, which have a risk of postoperative pain, severe infection, or splenic abscess after procedure.[19,20] In contrast, lusutrombopag can be given orally, which is not invasive, and therefore, might be a more convenient and safer therapeutic approach for thrombocytopenia than splenectomy or splenic artery embolization.

To date, there have been no reports examining repeated use of lusutrombopag in clinical settings. Thus, many factors remain unclear, such as the effect on the platelet count after repeated use, the safety of repeated use, and the required duration of a washout period between the first and repeated treatment.

Repeated use of lusutrombopag prior to RFA in patients with recurrent hepatocellular carcinoma and thrombocytopenia was safe and effective, although further studies should be undertaken to examine the efficacy of lusutrombopag in larger sample sizes and in patients who are on other treatments.

In conclusion, repeated use of lusutrombopag led to appropriate increases in platelet counts in patients with thrombocytopenia associated with chronic liver disease

and cirrhosis. It also led to the avoidance of platelet transfusion prior to an invasive procedure and was safe to use in this patient population.

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