Changes in immature Platelet Fraction is a Predictive Factor of the Efficacy of Lusutrombopag Administration

Toru Ishikawa*, Marina Okoshi, Kei Tomiyoshi, Yuichi Kojima, Ryoko Horigome, Michitaka Imai, Yujiro Nozawa, Akito Iwanaga, Tomoe Sano, Terasu Honma and Toshiaki Yoshida

Department of Gastroenterology and Hepatology, Saiseikai Niigata Daini Hospital, Japan

Abstract

Aim: Lusutrombopag is a low-molecular-weight thrombopoietin receptor agonist used in clinical settings to temporarily increase platelet levels; however, predictive factors indicating its efficacy for this purpose have not yet been established. Immature platelet fractions (IPFs) reflect the productive capacity of platelets in the bone marrow and are associated with megakaryocyte levels. We determined whether an IPF change is a predictive factor for thrombocytosis during lusutrombopag administration in patients with chronic liver disease before undergoing radiofrequency ablation (RFA) for hepatocellular carcinoma and determined the efficacy and safety of lusutrombopag.

Methods: Participants included 41 patients with platelet counts <50,000/μL who were administered lusutrombopag for cirrhosis and scheduled for RFA for hepatocellular carcinoma between March 2016 and December 2018. After administering lusutrombopag tablets (3 mg/day) for 7 days, we investigated platelet count and IPF changes, platelet transfusion avoidance rate, and presence/absence of onset of complications.

Results: The mean platelet count before lusutrombopag administration was 44,600 ± 4,600/μL, and the mean IPF was 4.65 ± 1.65. Platelet count peaked at 137,200 ± 41,800/μL at 13.2 days after the start of administration; IPF peaked at 7.10 days. No clinical symptoms were observed. There was no portal vein thrombosis or hemorrhage or other serious adverse events, indicating that RFA could be performed without any problem in these patients.

Conclusions: Lusutrombopag increased platelet count, and platelet transfusion could be avoided without major adverse events. IPF values peaked before platelet levels, indicating that IPF could aid to avoid risks, such as exceeding thrombocytosis and accompanying thrombosis, in patients.

Keywords: Lusutrombopag; Thrombocytopenia; Radiofrequency ablation; Hepatocellular carcinoma; Thrombopoietin receptor agonist; Chronic liver disease

Introduction

Measurement of reticulated platelets is reported to be an indirect index of platelet hematopoiesis in the bone marrow. It was recently shown that the immature platelet fraction (IPF) could be measured using an automated hematology analyzer [1].

IPF reflects the platelet production capacity and is associated with megakaryocyte levels. The measurement of IPF could be effective, even in chronic liver diseases [2,3].

Thrombocytopenia may become a major complication with progression of fibrosis in chronic liver diseases, and counter measures are required.

Thrombopoietin (TPO) is a humoral factor that promotes hematogenesis and the production of megakaryocytes and platelets. Recently, TPO was demonstrated to be an important cytokine in platelet hematogenesis [4-7]. Historically, the use of TPO receptor agonists against thrombocytopenia in chronic liver diseases has been covered by insurance. However, predictive factors for the effects of treatment are not clear. In this study, we investigated whether a change in IPF may act as a predictive factor for thrombocytosis during TPO agonist administration in patients with chronic liver disease prior to undergoing radiofrequency ablation (RFA) against hepatocellular carcinoma and investigated the efficacy and safety of the TPO receptor agonist lusutrombopag.

Methods

The study included 41 patients with hepatocellular carcinoma with a platelet count <50,000/μL who were scheduled to undergo RFA in our department between March 2016 and December 2018. Patients...
were administered lusutrombopag tablets (3 mg/day) for 7 days, and changes in platelet count and IPF were investigated. We also analyzed the platelet transfusion avoidance rate and the presence/absence of onset of complications, along with background factors.

Data are expressed as the mean and standard deviation (SD). A P value <0.05 was considered statistically significant. All statistical analyses were performed using Easy R (EZR) version 1.29 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [8].

Results

The mean age of the patients was 68.95 ± 10.28 years, and there were 21 males and 20 females. Background liver diseases included hepatitis B positive (n = 3), hepatitis C positive (n = 19), non alcoholic steatohepatitis (n = 9), autoimmune hepatitis (n = 1), and alcoholic hepatitis (n = 9). The mean platelet count prior to drug administration was 44,600 ± 4,600/μL, and the mean IPF was 4.65 ± 1.65 (Table 1). The platelet count reached a peak of 137,200 ± 41,800/μL, at an average of 13.2 days after the start of lusutrombopag administration (Figure 1), and the IPF peaked at an average of 7.10 days after administration (Figure 2). After the peak platelet elevation, IPF tended to decrease to the values obtained prior to lusutrombopag administration. Further, 1 patient showed no changes in IPF; thus, the platelet transfusion avoidance rate was 97.5%. No clinical symptoms, such as thrombosis, fever, or rash were observed. There was no portal vein thrombosis or hemorrhage or other serious adverse events in any of the patients, indicating that RFA could be performed without problems in these patients with thrombocytosis.

Discussion

Reticulated platelets are young or immature platelets that are released from the bone marrow and are rich in RNA. The life span of platelets is 3 to 10 days (mean, 8 days); they are considered to be reticulated platelets for the first 24 to 36 h. Reticulated platelets reflect platelet hematopoiesis in the bone marrow [9].

IPF can be routinely measured using an automated hematology analyzer XE2100 or XE-5000 [XE IPF master (Sysmex Corporation)]. IPF reportedly reflects platelet production in the bone marrow, in a similar manner as reticulated platelets [10,11].

In idiopathic thrombocytopenic purpura (ITP), which is an autoimmune disorder with the pathophysiology of thrombocytopenia, IPF is increased compared with that found in healthy individuals and is a useful factor for diagnosis [12].

During treatment accompanied with bone marrow suppression, IPF reaches a peak before the platelet count recovers in the peripheral blood; therefore, it is considered a useful predictor for platelet count recovery. The confirmation of increased IPF enables the prediction of thrombocytosis and indicates the requirement to reduce platelet infusion.

IPF reflects the capacity of platelet production and is correlated with megakaryocyte levels in the bone marrow. During normal bone marrow function, the platelet count increases with decreased megakaryocyte levels, and megakaryocyte levels increases with decreased platelet count. Thus, IPF and platelet count are inversely correlated.

TPO is a humoral factor that promotes megakaryocyte and platelet hematogenesis, and has been successfully cloned in 1994 [4-6]. TPO is primarily produced in hepatocytes. In chronic liver diseases, failure to produce TPO leads to thrombocytopenia [13].

Following the successful cloning of TPO, its molecular structure, effects against the hematogenesis system, the mechanism of production control, and the mechanisms of signaling transduction were determined. Accordingly, the pharmaceutical development of TPO as a treatment drug is underway.

Eltrombopag was approved by the US Food and Drug Administration for the treatment of refractory chronic ITP. Numerous reports have shown the efficacy of eltrombopag against ITP, leading to decreased steroid use in many cases, indicating that patients with low IPF prior to administration respond well to eltrombopag [14,15].

Response to ITP treatment (e.g., steroid use) decreases the IPF. Because IPF increases before the platelet count recovers, it is a useful predictor of platelet count recovery following chemotherapy or hematopoietic cell transplantation, and can be useful in determining the requirement for platelet transfusion. In fact, the immature
Presently, the efficacy of TPO agonists against thrombocytopenia accompanying chronic liver diseases is expected. In a clinical trial wherein eltrombopag was administered to patients with thrombocytopenia due to chronic liver diseases, the side effects of portal vein thrombosis were significantly greater in 6 out of 143 patients (4%) who received eltrombopag compared with the placebo group. In all six patients, thrombosis occurred in the portal vein, and in five patients, the platelet count at onset was elevated to \( \geq 20.0 \times 10^{11} \) \( \mu \text{L} \), which is considered a risk factor for the onset of thrombosis [16].

In Japan, the use of the human TPO receptor agonist, lusutrombopag, was launched in September 2015 for the “improvement of thrombocytopenia in patients with chronic liver diseases scheduled to elective invasive procedure [17,18].”

During lusutrombopag treatment, the platelet count should be measured approximately 5 days after the start of administration to prevent an excess increase in platelet count. Administration should be stopped when the platelet count reaches \( \geq 2.0 \times 10^{11} / \mu \text{L} \) or if it is elevated to \( \geq 5.0 \times 10^{11} / \mu \text{L} \). Portal vein thrombosis presents a variety of clinical symptoms depending on the site and range, and it may even be asymptomatic; however, in case of massive thrombosis that causes a circulatory disturbance in the mesenteric vein, symptoms such as fever, abdominal pain, and increase in ascites may appear [19,20]. Even during lusutrombopag administration, rapid thrombocytosis may increase the risk of portal vein thrombosis. However, treatment predictive factors and the prediction of rapid thrombocytosis during lusutrombopag treatment remain unclear. Thus, in chronic liver diseases, excess thrombocytosis caused by TPO agonist administration is considered as a risk, and a marker of thrombocytosis is necessary. In the present study, we investigated whether changes in IPF could be a predictive factor of platelet production effects.

Lusutrombopag administration showed that IPF increased before the platelet levels also increased in most cases. However, in some patients, IPF did not change, and these patients did not develop thrombocytosis.

Following lusutrombopag administration, the IPF peaked at 7.10 days and the platelet count peaked at 13.2 days, which demonstrated a time lag. This indicates that IPF can be an index of recovery of platelet production function following hematopoietic stem cell transplantation, similar to the phenomenon observed after hematopoietic stem cell transplantation, known as the IPF surge (IPF/surge) during normal bone marrow function, an increase in platelet levels leads to a decrease in IPF, and vice versa, reflecting whole-body homeostasis [9,22].

The increase in IPF seemed poor in the patient with splenomegaly. During lusutrombopag administration, excessive thrombocytosis could be avoided in the temporal observation and was useful in determining treatment effects.

In conclusion, we demonstrated that change in IPF could be used as a predictive factor for treatment effects of lusutrombopag against thrombocytopenia in chronic liver diseases.

**Acknowledgment**

Sources of support: There are no conflicts of interest in the manuscript.

**Declaration of personal and funding interests:** None.

**Financial Disclosure**

The authors declare that they do not have any current financial arrangements or affiliations with any organization that may have a direct interest in their work.

**References**


