Partial Splenic Embolization for Lenvatinib Therapy-associated Thrombocytopenia Among Patients With Hepatocellular Carcinoma

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Abstract. *Background:* Lenvatinib, a newly developed oral multi-tyrosine kinase inhibitor, has amazing potential in the multidisciplinary treatment of advanced or metastatic hepatocellular carcinoma. Thrombocytopenia is a serious adverse event that causes drug dose reduction or withdrawal. Partial splenic embolization is currently being used as a non-surgical treatment for thrombocytopenia caused by various pharmacotherapies. *Case Report:* Partial splenic embolization was performed for three patients with hepatocellular carcinoma receiving lenvatinib therapy with/without transarterial chemoembolization. Partial splenic embolization was advantageous for various situations, including the induction of lenvatinib for patients with thrombocytopenia, application of lenvatinib after multiple transarterial chemoembolization using cisplatin and radiotherapy, and re-administration of lenvatinib after lenvatinib therapy-induced thrombocytopenia. In all cases, lenvatinib therapy was completed without need for cessation due to thrombocytopenia. *Conclusion:* We strongly recommend the new concept of combining partial splenic embolization and lenvatinib therapy for hepatocellular carcinoma.

Multidisciplinary treatment, including molecular targeted therapy, is recommended for advanced or metastatic hepatocellular carcinoma (HCC) (1-4). Lenvatinib is a newly

developed oral multi-tyrosine kinase inhibitor that can provide greater tumor regression and tumor necrosis compared to sorafenib (5-7). Since March 2018, lenvatinib has become available for use in the treatment of HCC in Japan and its use has been spreading globally (8-10).

Lenvatinib is generally indicated for patients with good liver functional reserve, *i.e.* those with Child-Pugh score of 5 or 6 points (5, 6). Nonetheless, even for patients with advanced HCC who have chronic liver disease, lenvatinib was reported to have an acceptable safety profile (4, 9, 10). The phase III REFLECT trial comparing lenvatinib and sorafenib demonstrated different adverse events profiles. Accordingly, more than 5% patients in the lenvatinib group developed several grade three or more adverse events, including hypertension (23%), reduced appetite (5%), reduced weight (8%), protein urine (6%), reduced platelet count (5%), elevated aspartate aminotransferase (5%), and increased blood bilirubin (7%). (6) The lenvatinib group had fewer instances of palmar-plantar erythrodysesthesia (27%) than the sorafenib group (52%). Moreover, a systematic review and meta-analysis for lenvatinib cancer therapy demonstrated that thrombocytopenia (25.4%), hypertension (17.7%), and peripheral edema (15.5%) were the most frequent adverse events (grade ≥ 3) (11).

Partial splenic embolization (PSE) has been developed as a non-surgical treatment for alterations in blood cell count, especially platelet count (12-14). However, hypersplenism due to liver cirrhosis has remained the main reason for application of PSE. Recently, indications for PSE have expanded to include coexisting hypersplenism in chemotherapy patients, pretreatment for antiviral therapy of hepatitis virus infection, and thrombocytopenia caused by oxaliplatin- or cisplatin-containing chemotherapy (15-19).

We believe that PSE can play a key role in the continuation of lenvatinib therapy for HCC. Therefore, we retrospectively

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Key Words: Partial splenic embolization, hepatocellular carcinoma, lenvatinib therapy.

Table I. Patient characteristics.

	Patient		
Characteristic	1	2	3
Age, years	65	66	60
Gender	Female	Male	Male
Etiology	HCV (SVR)	Alcoholic cirrhosis	HCV cirrhosis
Child-Pugh classification (score)	A (6)	A (6)	A (6)
Interval from initial treatment for HCC to LEN, days	658	1693	2902
Platelet count, $\times 10^4/\mu\text{l}$			
Before PSE	5.0	5.2	7.7
Before LEN	7.0	12.7	14.3
Prior treatment for HCC	HR 2, TACE 3,	TACE 5, RT 1, PSE 2	HR+ RFA 1, sorafenib,
RT 2, PSE 2			TACE 2, RT 1
Pre-PSE splenic volume, ml	335	341	640
Splenic embolized volume, ml	137	286	516
Splenic embolized rate, %	40.8	83.8	80.6
Cause of LEN introduction	Liver, bone	Liver, bone	Liver, lymph node
Starting dose of LEN, mg	8	12	8
Period of taking LEN until the end of October 2019, days	114	224	198
Adverse event grade ≥ 3 after LEN therapy*	Hepatic injury, herpes zoster	Hand-foot syndrome	Hypothyroidism, fatigue

HCV: Hepatitis C virus; SVR: sustained virologic response; HCC: hepatocellular carcinoma; LEN: lenvatinib; PSE: partial splenic embolization; HR: hepatic resection; TACE: transarterial chemoembolization; RT: radiotherapy; RFA: radiofrequency ablation. *By Common Terminology Criteria for Adverse Events version 4.0 (28).

Figure 1. Treatment course and changes in alpha fetoprotein (AFP) level. PLT, Platelets; PSE: partial splenic embolization; LEN: lenvatinib; Gr.: grade by Common Terminology Criteria for Adverse Events version 4.0 (28).

Figure 2. Treatment course and changes in protein induced by vitamin K absence or antagonist-II (PIVKA-II) level. PLT: Platelets; PSE: partial splenic embolization; LEN: lenvatinib; Gr.: grade by Common Terminology Criteria for Adverse Events version 4.0 (28).

analyzed data for patients with HCC treated with PSE across various situations: before or during lenvatinib therapy with/without transarterial chemoembolization (TACE).

Case Report

Clinical characteristics and details of PSE and lenvatinib therapy in three patients are summarized in Table I.

Case 1. A 65-year-old woman with HCC and sustained virologic response of hepatitis C virus was referred to our hospital 3 years and 9 months ago and underwent two laparoscopic liver resections. After 15 months, she was diagnosed with unresectable multiple HCC and TACE was performed twice alone and in combination with first PSE. Prior to lenvatinib therapy, second PSE was conducted. Treatment course and changes in alpha fetoprotein (AFP) level were demonstrated (Figure 1). One year and a half

later, she received radiotherapy twice for cancer pain related to multiple bone metastases, and TACE was performed a third time between the two radiotherapies. After the second PSE, lenvatinib was started and continued for 114 days. Lenvatinib was discontinued because of tumor progression and herpes zoster infection. Unfortunately, the patient died 3 months after discontinuing lenvatinib.

Case 2. First TACE for a 66-year-old man with HCC in alcoholic cirrhosis had been performed at another hospital 5 years and 3 months earlier. Two years later, TACE was performed three times to treat newly developed HCC. The first PSE was performed with the fourth TACE to minimize platelet decrease induced by TACE using cisplatin (18). Treatment course and changes in protein induced by vitamin K absence or antagonist-II (PIVKA-II) level were recorded (Figure 2). During the two additional TACE treatments, the platelet count remained $\geq 5.0 \times 10^4/\mu\text{l}$, but tumor response was

Figure 3. Treatment course and change in protein induced by vitamin K absence or antagonist-II (PIVKA-II) level. PLT: Platelets; PSE: partial splenic embolization; TACE, transarterial chemoembolization; LEN: lenvatinib; Gr.: grade by Common Terminology Criteria for Adverse Events version 4.0 (28).

insufficient. Sacral bone metastasis was treated using radiotherapy. The second PSE was performed before introducing lenvatinib. Lenvatinib administration was continued for 7 months and was ongoing at the time of writing, however, the dose administered was reduced from 12 to 4 mg due to reasons other than thrombocytopenia. Nonetheless, platelet count was maintained at $\geq 8.0 \times 10^4/\mu\text{l}$.

Case 3. A 66-year-old man with HCC and hepatitis C was referred to our hospital. He had been diagnosed with HCC 8 years earlier and had undergone liver resection at another hospital. Immediately after surgery, sorafenib was started and continued for about 6.5 years to treat the diagnosed intrahepatic and pulmonary metastases. Sorafenib administration was performed irregularly. Unfortunately, details remain unknown. The patient was then referred to our hospital because of uncontrolled primary HCC and multiple intra-abdominal lymph node metastases. Treatment course and changes in PIVKA-II level were recorded (Figure 3). Although lenvatinib therapy was started, grade 3 thrombocytopenia was observed 2 weeks later. After performing PSE, lenvatinib administration was continued providing that the platelet count was maintained at $>8.0 \times 10^4/\mu\text{l}$. The PIVKA-II level

dramatically decreased due to tumor necrosis of bulky para-aortic lymph node metastases (Figure 4). Lenvatinib was continued for more than 6 months, during which the patient was doing well with no symptoms.

Discussion

The application of PSE for patients with HCC receiving lenvatinib treatment is a new concept. We did not find any article in PubMed using the key words “partial splenic embolization” and “lenvatinib” until November 1, 2019. The current study showed that PSE was quite beneficial for improving thrombocytopenia in various situations, including in the induction of lenvatinib for patients with insufficient platelet count (Case 1), application of lenvatinib after multiple TACE using cisplatin and radiotherapy (Case 2), and re-administration of lenvatinib after thrombocytopenia caused by prior lenvatinib therapy (Case 3). In all cases, lenvatinib therapy was completed without cessation caused by thrombocytopenia. Thrombocytopenia can be caused by coexisting liver cirrhosis and lenvatinib therapy. Approximately a quarter of the patients met lenvatinib administration criteria (platelet count $\geq 7.5 \times 10^4/\mu\text{l}$) (5,6), and

Figure 4. Changes in computed tomography findings for case 3. Axial contrast-enhanced computed tomography scans showing a primary liver tumor upon referral to our hospital (A), before lenvatinib therapy (B), and 5 months after treatment (C). Coronal contrast-enhanced computed tomographic scans showing multiple intra-abdominal lymph node metastases upon referral to our hospital (D), before lenvatinib therapy (E), and 5 months after treatment (F). Liver tumor (arrow head) had decreased in size (40% reduction in diameter) but this was accompanied by obvious enhancement (B, C). Para-aortic lymph node metastases (arrow) showed complete necrosis in the tumor area after lenvatinib therapy (E, F).

adverse events (grade $\geq$ D3) of thrombocytopenia had been demonstrated (11). Because platelet-derived growth factor is known to promote platelet recovery and the development of bone marrow colony-forming unit-megakaryocytes (20), its inhibition by lenvatinib might induce thrombocytopenia.

Currently, PSE has been widely used for patients with thrombocytopenia as a result of various pharmacotherapies, including antiviral, platinum, or targeted drugs (15-19). PSE is not beneficial for patients with hypersplenism with poor bone marrow function. To avoid meaningless PSE, determining the presence of splenomegaly using diagnostic images and assessing immature platelet fraction in the peripheral blood are imperative (21, 22). Moreover, a bone marrow aspiration test is needed for certain cases. From the point of view of safety, excessive embolization (infarcted splenic volume $\geq$ 540 ml) and application of PSE for patients with Child-Pugh class C should be avoided (13). However, in patients with a large spleen (>700 ml), repeated PSE is recommended to avoid serious complications (23). In the present study, only mild fever and abdominal pain were

observed as complications of PSE during some preoperative days. No serious complications, including overwhelming sepsis, were observed.

Considering that long-term lenvatinib administration is required to achieve excellent antitumor effect, a prolonged increase in platelet count after PSE is essential. We have already reported positive correlation between infarcted splenic volume and increase in platelet count (12). Accordingly, a cut-off for infarcted splenic volume of 388 ml was needed to increase platelet count by $5.0\text{--}8.0 \times 10^4/\mu\text{l}$ over 1 year. Because an infarcted splenic volume of 516 ml was achieved in case 3, lenvatinib therapy was continued for more than 6 months. In case 2, the infarcted splenic volume was only 286 ml because of a relatively small spleen, however, the platelet count was maintained at $>5.0 \times 10^4/\mu\text{l}$ for 7 months. In case 3, multiple HCC and lymph node metastases were initially treated with TACE using cisplatin lipiodol and radiotherapy, respectively. Due to insufficient antitumor effect, lenvatinib was started followed by re-introduction of lenvatinib after PSE. Interestingly the

antitumor effect was different for the primary liver tumor and para-aortic lymph node metastases. Because the obvious tumor necrosis effect observed was limited to lymph node metastases, additional TACE will be planned for this case.

It has been reported that simultaneous hepatectomy and splenectomy in patients with HCC was associated with better tumor-free or disease-free survival compared to hepatectomy alone (24, 25). Another study has shown that spleen size affected postoperative HCC recurrence and overall survival after liver resection (26). It is suspected that the spleen may inhibit immunological function in patients with HCC because higher levels of T-helper cytokine interleukin-2 and interferon- γ and lower levels of interleukin-10 were observed in hepatectomy and splenectomy groups (24). Furthermore, studies have shown that splenectomy increased the number of natural killer cells (27). Similarly, better antitumor immunological function can be obtained after PSE, which will have a synergistic effect with lenvatinib.

In conclusion, PSE is a safe and quite beneficial tool for patients with HCC receiving lenvatinib. Further investigations will be required to determine patient selection, as well as optimal timing for performing PSE and the optimal infarcted volume of PSE.

Conflicts of Interest

The Authors have no conflicts of interest.

Authors' Contributions

NS and TB identified the concept and wrote the draft of the article; all Authors actually performed interventional or medical treatments; NS, TB, KK, KS, SY, TM, SC, and SA provided critical revisions.

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