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Tolerability of Molecular-targeted Agents for Hepatocellular Carcinoma Treatment in Haemophiliacs

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Abstract. *Background: Hepatocellular carcinoma (HCC) is considered a leading cause of death in patients with haemophilia. Recent advances in the treatment of unresectable HCC with molecular-targeted agents (MTAs) have led to better clinical outcomes. However, the tolerability of MTAs by haemophilic patients with HCC remains unclear. Aim: This study aimed to compare the tolerability of MTAs in such patients. Patients and Methods: From January 2011 to October 2020, five haemophilic patients with HCC were treated with MTAs. Adverse events were assessed in comparison with 265 non-haemophilic patients with HCC. Results: The prevalence of hand–foot skin reaction was not higher in the haemophiliacs than in the non-haemophiliacs, whereas the rate of haemorrhagic events was higher in the haemophiliacs (6.0% versus 40.0%, p=0.037). Conclusion: Haemophiliacs tolerate long-term MTA use, without the occurrence of life-threatening complications. However, careful observation and prevention are needed for MTA-related gastrointestinal bleeding in haemophiliacs.*

Hepatocellular carcinoma (HCC) is a hypervascular tumour that occurs mostly in liver with pre-existing chronic inflammation or fibrosis. In a study carried out in 1985, all patients with haemophilia became infected with hepatitis C virus from concentrates before virus inactivation (1). Since then, HCC has been considered a leading cause of death in haemophilic patients (2). So far, tolerability of HCC treatment in patients with haemophilia has been reported for hepatectomy (3, 4), transcatheter arterial embolization/percutaneous ethanol injection (5), and radiofrequency ablation (6).

Recent advances in the treatment of HCC with molecular-targeted agents (MTAs) have led to better clinical outcomes in patients with intermediate to advanced-stage HCC (7-9). Because the viability of HCC depends on tumour vascularity, most MTAs target vascular endothelial growth factor (VEGF) to inhibit angiogenic signals in the tumour. Sorafenib was the first approved MTA for advanced HCC: HCC with extrahepatic metastases or vascular invasion (7). It exerts its antitumour effect by inhibiting serine/threonine kinases, and tyrosine kinases (10). Lenvatinib is a tyrosine kinase inhibitor which are involved in angiogenesis and malignancy of tumour (11). Lenvatinib was approved in 2018 after showing a non-inferior treatment effect when compared with sorafenib (8).

Because of their anti-angiogenic potential, VEGF-targeting MTAs are known to cause haemorrhage. Although VEGF-targeting antiangiogenic agents are used to treat several tumour types, including HCC (7,8), renal cell carcinoma (12), and thyroid cancer (13, 14), as far as we are aware, there is only one case report on the short-term administration and safety of MTA in a patient with haemophilia (15). Here we report five cases of HCC in haemophiliacs who received MTAs as long-term treatment.

Patients and Methods

From January 2011 to October 2020, 270 patients with advanced stage HCC were treated with first-line MTAs at Nagoya University Hospital, Nagoya, Aichi, Japan. To evaluate the tolerability of MTA treatment for HCC patients with haemophilia, we divided these patients into two groups: Five patients with haemophilia and 265 non-haemophilic patients. Data on the baseline patient characteristics,

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adverse events, and the antitumour effect after MTAs treatment were analysed retrospectively.

The patients were admitted for the first 2 weeks of MTA initiation. Thereafter, haematological investigations were performed during every follow-up visit for assessing adverse events. The antitumour effect was evaluated with contrast-enhanced computed tomography at 6 weeks of MTA therapy and every 2–3 months thereafter. Modified Response Evaluation Criteria in Solid Tumours were used as the standard for assessing effectiveness (16). Adverse events were assessed by the Common Terminology Criteria for Adverse Events version 5.0 (17). This retrospective study was approved by the Ethics Review Board of Nagoya University Hospital (2020-0479).

Results

The median age of the five haemophilic patients was 59 years and all the patients were male. Of these patients, four had haemophilia A, and one had haemophilia B. Three had severe haemophilia, one had moderate haemophilia and one had mild haemophilia. In one of the patients with severe haemophilia, replacement therapy was changed on demand to regular replacement therapy before starting MTA. One patient with moderate haemophilia and one with severe haemophilia received regular replacement therapy, and the other two received by on-demand replacement therapy before and after starting MTAs. The median age of the 265 non-haemophilic patients was 70 years and 214 (80.8%) were male.

The Eastern Cooperative Oncology Group Performance Status in the five haemophilic patients was 0, 1, and 2 in three, one, and one patient, respectively. Four of these patients were treated with sorafenib, and one was treated with lenvatinib. Regarding hepatic function, two of these patients had Child–Pugh score 5(A), and three patients had Child–Pugh score 6(A). The median albumin-bilirubin score was −2.34 and the median platelet count was 123,000/μl at the time of MTA initiation. According to the Barcelona Clinic Liver Cancer (BCLC) staging system (18), two patients had BCLC-B HCC, and three patients had BCLC-C HCC; as a plasma tumour marker of HCC, the median alpha-fetoprotein level was 122 ng/ml at the start of MTAs treatment in these patients with haemophilia.

On the other hand, the performance status of non-haemophilic patients with HCC was 0, 1, 2 in 176 (66.4%), 87 (32.8%), and two (0.8%) patients, respectively. Two hundred and three of these patients (76.6%) were treated with sorafenib and 62 (23.4%) were treated with lenvatinib. One hundred and forty patients (53%) had a Child–Pugh score 5(A), 92 patients (34.8%) had Child–Pugh score 6 (A) and 32 patients (12.1%) had Child–Pugh score 7-8 (B). The median albumin-bilirubin score in non-haemophilic patients was −2.30 and the median platelet count was 140,000/μl. Eighty-two patients (30.9%) had BCLC-B and 183 (69.1%) had BCLC-C, and the median alpha-fetoprotein level was 106.5 ng/ml.

Table I. *Adverse events of therapy with molecular target agents for hepatocellular carcinoma in haemophiliac and non-haemophilic patients. HFSR: Hand–foot skin reaction.*

	Haemophilia (n=5)		Non-haemophilia (n=265)	
Adverse event	Grade 1-2 n (%)	Grade 3-4 n (%)	Grade 1-2 n (%)	Grade 3-4 n (%)
Anorexia	2 (40.0)	0 (0.0)	114 (43.0)	14 (5.3)
Hypertension	1 (20.0)	0 (0.0)	99 (37.4)	14 (5.3)
HFSR	3 (60.0)	1 (20.0)	100 (37.7)	40 (15.1)
Rash	1 (20.0)	0 (0.0)	62 (23.4)	17 (6.4)
Fever	0 (0.0)	0 (0.0)	54 (20.4)	16 (6.0)
Diarrhoea	1 (20.0)	0 (0.0)	61 (23.0)	7 (2.6)
Haemorrhage	1 (20.0)	1 (20.0)	4 (1.5)	12 (4.5)

Although 59 non-haemophilic patients had no treatment history for HCC, all haemophilic patients had received multiple treatments for HCC before MTA initiation (hepatectomy in four, radiofrequency ablation in four, transcatheter arterial embolization in four).

The antitumour effect in haemophilic patients with HCC at 6 weeks of MTAs therapy was stable disease in three patients and progressive disease in one; one patient was not evaluated. The median progression-free survival was 93 days, median overall survival was 297 days, and the median duration of MTA therapy was 122 days. In non-haemophilic patients, the antitumour effect at 6 weeks of MTA therapy was partial response in 60 (22.6%), stable disease in 124 (46.8%), progressive disease in 47 (17.7%), and not evaluated 34(12.8%). Median progression-free survival was 107 days, median overall survival was 465 days, and the median duration of MTA therapy was 194 days.

Regarding tolerability in haemophilic patients, two patients had severe adverse events: One patient had a grade 3 hand–foot skin reaction (HFSR). One patient had gastric ulcer-related grade 3 upper gastrointestinal haemorrhage (Figure 1). Three of the patients had grade 1-2 HFSR, and one had grade 2 gastrointestinal haemorrhage (Table I). Compared with adverse events from the treatment of HCC in non-haemophilic patients, the prevalence of HFSR was not higher in the haemophiliacs (HFSR: 52.8% *versus* 80.0%, not significant using Fisher's exact test), whereas the rate of haemorrhagic events was higher in the haemophiliacs (6.0% *versus* 40.0%, p=0.037 using Fisher's exact test).

Discussion

This study demonstrated a significantly higher frequency of haemorrhagic complications in haemophiliacs than in non-haemophilic patients. No patient with haemophilia had episodes of gastrointestinal bleeding prior to the use of

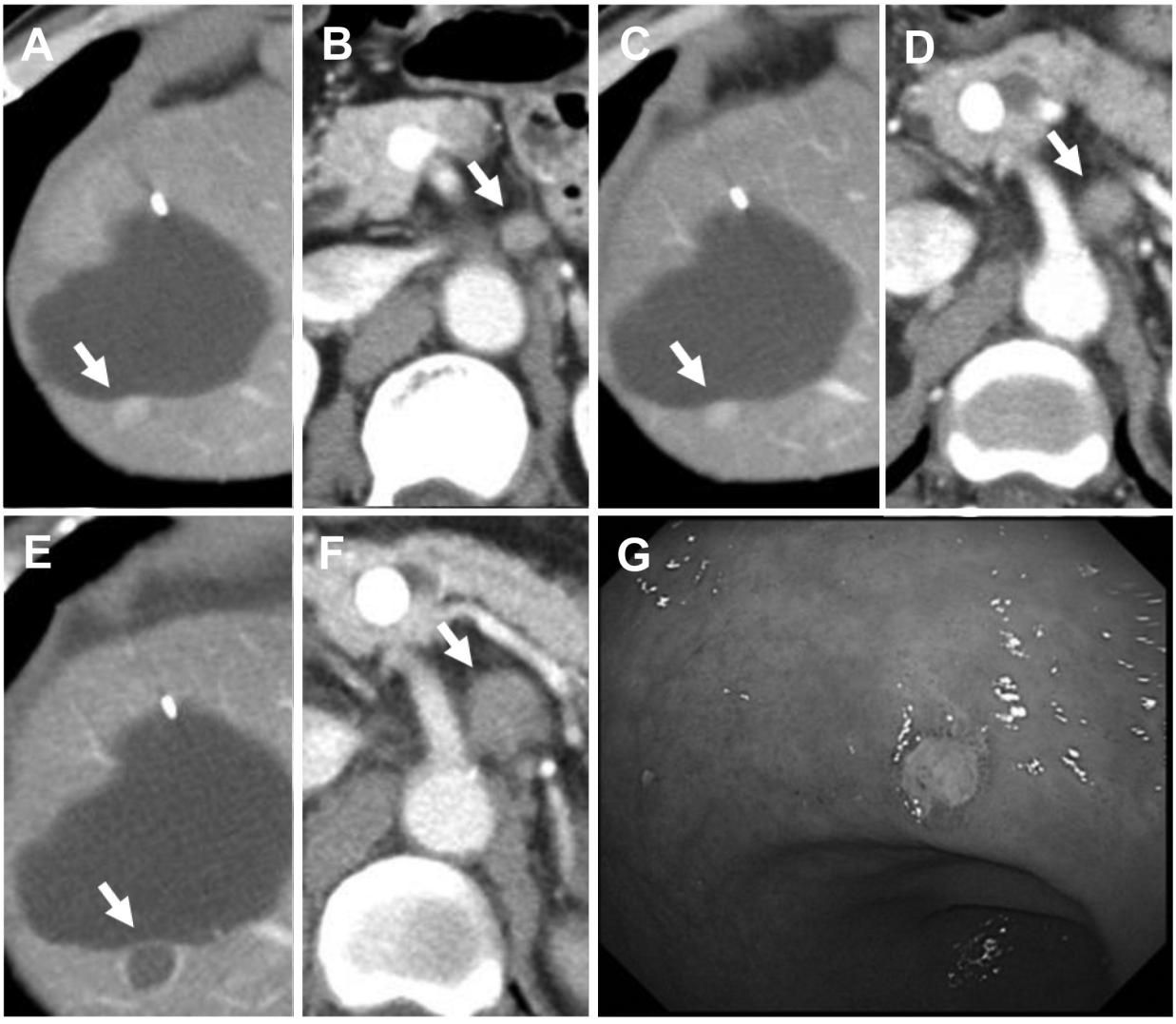

Figure 1. *A representative case of a haemophiliac patient with hepatocellular carcinoma treated using a molecular-targeted agent. A 57-year-old male with haemophilia A and hepatocellular carcinoma was administered sorafenib. Abdominal computed tomography performed before sorafenib initiation showed lymph node metastases and intrahepatic lesions (A and B). The antitumour response at 6 weeks was stable disease (C and D). Although the computed tomographic images after 20 weeks of treatment with sorafenib showed an increase in the size of the lymph node metastases, several intrahepatic lesions showed an ischemic antitumour effect (E and F). At 36 weeks of treatment with sorafenib, upper gastrointestinal bleeding was observed (G); therefore, the dose of sorafenib was adjusted, and was continued for 46 weeks after initiation of treatment.*

MTAs, therefore we speculated that the use of MTAs was associated with the bleeding episodes.

In the SHARP trial, which showed the benefit of sorafenib in patients with unresectable HCC, the incidence of sorafenib-related haemorrhage of any grade was 2.4% (7/297) and of grade 3 was 0.3% (1/297) (7). In the present study, the incidence of haemorrhage events of any grade in non-haemophilic patients was 6.0% (16/265) and of grade 3/4 was 4.5% (12/265), compared with 40.0% (2/5) and 20% (1/5) in haemophilic patients.

In individuals with haemophilia, thrombocytopenia is an important factor associated with haemorrhagic events. Thrombocytopenia associated with human immunodeficiency virus and immune thrombocytopenic purpura may result in potentially severe haemorrhage, and intervention is recommended at the time of such thrombocytopenia (19). Thrombocytopenia has also been reported as a side-effect of therapy with MTAs (20), occurring in around 10% of patients treated with sorafenib for HCC (21). However, both haemophilic patients who experienced gastric bleeding in this study had

platelet levels above 100,000/μl at the time of initiation of MTA and immediately before a bleeding event. Therefore, regardless of the platelet level, careful follow-up for haemorrhagic complications is needed in haemophiliacs receiving MTAs.

Since combination therapy with immune checkpoint inhibitors (ICIs) and MTAs has shown better clinical outcomes than sorafenib monotherapy in advanced-stage HCC (22), its use has been approved in these patients. Although ICIs have unique immune-related adverse events (23), ICIs have fewer side-effects than MTAs. Regarding bleeding events, ICI monotherapy may be safer. However, the treatment efficacy of HCC with ICI monotherapy is limited (24-26). Therefore, management of side-effects of MTAs is also important in combination therapy with ICIs and MTAs for HCC, especially in patients with a bleeding disorder.

Conclusion

To the best of our knowledge, this is the first report of complications following MTA use in haemophilic patients with HCC. Our results suggest that haemophiliacs tolerate long-term MTA use, without the occurrence of life-threatening complications; however, they are more susceptible to gastrointestinal bleeding. Careful observation and prevention are needed for MTA-related gastrointestinal bleeding in haemophiliacs.

Conflicts of Interest

None declared.

Authors' Contributions

TY, NI, KY, TI, YI, TH, SO, TK, NS, TM, MI, and MF performed the research. TY and NI designed the research study. TY analysed the data. TY and NI wrote the article.

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