Controlling Major Portal Vein Invasion Progression during Lenvatinib Treatment by Carbon-Ion Radiotherapy in Patients with Advanced Hepatocellular Carcinoma

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Keywords
Carbon-ion radiotherapy · Hepatocellular carcinoma · Macrovascular invasion

Abstract
Macrovascular invasion (MVI), including portal vein tumor thrombosis (PVTT), is strongly associated with poor prognosis in patients with hepatocellular carcinoma (HCC). While recommended standard treatment for patients with advanced HCC is systemic therapy, various treatment approaches, including resection, transarterial chemoembolization, and radiation, have been empirically suggested to improve prognosis by eliminating or controlling MVI. Herein, we report our experience of a case with advanced HCC where MVI was controlled by carbon-ion radiotherapy (CIRT) while on systemic therapy, resulting in a prolonged survival.

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A female patient with HCC in her early 60s had multiple intrahepatic lesions (maximum 60 mm in diameter) with PVTT. The PVTT of this patient had reached the main trunk of the portal vein despite the use of lenvatinib. The other intrahepatic lesions of the patient, except PVTT, had been controlled by lenvatinib. Therefore, hoping to control PVTT, we attempted CIRT. The patient resumed lenvatinib therapy after the irradiation. During lenvatinib re-treatment, no evident progression of PVTT was observed in the patient.

Introduction

Macrovascular invasion (MVI), as represented by portal vein tumor thrombosis (PVTT), is a known poor prognostic factor for advanced hepatocellular carcinoma (HCC) [1]. Although the standard treatment of advanced HCC with MVI is systemic therapy, it has been suggested that surgical resection, transarterial chemoembolization, hepatic arterial infusion chemotherapy (HAIC), and radiation therapy are effective. In clinical practice, those treatments are often selected, with care, alongside systemic therapies [2–4]. Several previous reports have demonstrated that controlling MVI contributes to improved overall survival in patients with HCC [5–10]. Conversely, MVI progression is directly associated with the survival outcome. In particular, the invasion of PVTT into the main trunk of the portal vein (Vp4 according to Japanese classification) also leads to liver function deterioration due to decreased liver blood flow [11, 12].

Particle therapy, including carbon-ion radiotherapy (CIRT), is a radiation therapy modality realizing highly conformal dose distributions and integral dose sparing [13–15]. CIRT has been reported to have a high local control rate and safety in patients with HCC, although most of these reports addressed early to mid-stage HCC that were eligible for curative therapy [16–18]. Recently, while with limited cohort size, there have been a few reports suggesting that particle therapy is effective in patients with advanced HCC with MVI [19–22]. In this report, we present a case of a patient with advanced HCC with PVTT who underwent CIRT aimed at controlling PVTT that progressed during treatment with Lenvatinib, resulting in a prolonged survival.

Case Report/Case Presentation

A female in her early 60s presented to her primary care physician with fever and abdominal pain. Both abdominal ultrasound and contrast medium-enhanced computed tomography (CE-CT) revealed a 60-mm-diameter hepatic mass at Couinaud’s segment VI (Fig. 1a). She was referred to our hospital; we performed tumor biopsy and confirmed the pathological diagnosis of moderately differentiated HCC. The tumor had infiltrated the right branch of the portal vein (Vp3). First, we performed transarterial chemoembolization for tumor control. After tumor shrinkage was achieved, our surgical department performed a posterior hepatic segment resection and cholecystectomy. Two years later, she underwent radiofrequency ablation indicated for recurrence in segment I. In the following year, she had recurrences in segments I and V. For these recurrent intrahepatic lesions, the patient underwent radiofrequency ablation and subsegmental resection for segments I and V, respectively.

After a short time without recurrence, we diagnosed tumor recurrence in segment I and consequent tumor invasion into the Vp4 (Fig. 1b). We performed HAIC to control PVTT. Three courses of low-dose 5-fluorouracil/cisplatin (FP) therapies had reduced the size of the PVTT;
however, she developed biloma and was hospitalized for antibiotic therapy. Because of repeated biloma and cholangitis, we performed endoscopic retrograde cholangiopancreatography and placed a metallic stent (8 × 80 mm, uncovered) for a bile duct. The biloma and cholangitis were considered to be due to bile duct stenosis caused by HAIC. Therefore, she could not continue HAIC with low-dose FP.

Three months later, the PVTT had extended to the primary left and right branches. We decided to place her on a molecular target agent for lenvatinib (8 mg/day). CE-CT 3 months after the administration of lenvatinib showed that the PVTT had progressed to the Vp4 and its primary left and right branches, although there was no visible enlargement of the recurrence site in segment I. After fully informing the patient that lenvatinib, the standard treatment, was ineffective, we suggested her a strategy of performing CIRT to control PVTT. At this time, her liver function was maintained at Child-Pugh score 5A. She then consented to be treated with CIRT (total dose 60 Gy [median RBE-weighted dose] in 4 fractions) (Fig. 2). The patient had no adverse reactions to the treatment. After irradiation, prothrombin induced by vitamin K absence or antagonist-II (PIVKA-II) decreased markedly (from 5,569 to 1,609 mAU/mL), and CE-CT showed no sign of PVTT progression. Lenvatinib was resumed after CIRT since the intrahepatic lesion was controlled by lenvatinib except for the progression of PVTT. Three months later, there was no evidence of intrahepatic lesion and PVTT progression on CE-CT. Moreover, we observed partial reopening of portal blood flow (Fig. 3).
Discussion/Conclusion

Herein, we demonstrated a patient with advanced HCC in whom successful PVTT control and restoring of portal vein blood flow was achieved by CIRT, even though the PVTT progressed on lenvatinib treatment. Moreover, lenvatinib could be resumed, and the intrahepatic lesion was equally controlled.

Although standard treatment based on a high evidence level is systemic therapy, treatment options for advanced HCC with MVI are diverse in real clinical practice [23–26]. Several guidelines for HCC in Asia, including Japan, recommend treatments other than systemic therapy for advanced HCC with MVI [2–4]. In the present case, HAIC was selected as the first treatment at the time MVI was recognized. Several recent reports have demonstrated that HAIC has survival benefits compared with sorafenib, which had been a standard first-line systemic therapy, until the approval of atezolizumab plus bevacizumab, in patients with advanced disease with MVI without extrahepatic metastasis [27, 28]. After discontinuation of HAIC, the patient moved on to lenvatinib, which was the standard systemic therapy like sorafenib at that time [24–26]. Unfortunately, PVTT progressed to the main trunk during lenvatinib treatment. However, in this case, other intrahepatic lesions were controlled by lenvatinib. Therefore, we selected CIRT to control MVI aiming that a further prolongation of the prognosis would be possible if local control of PVTT could be achieved. Since the patient had a history of bile duct stenosis due to HAIC and had a metallic stent inserted, it was necessary to minimize the dose deposited to the metallic stent. Taken together with high local control ability and the ability to produce complex dose distribution, CIRT was sought to be the best treatment choice for this case.

Particle therapy, especially CIRT, is a form of radiotherapy with significant physical and biological advantages over photon irradiation [14, 15, 29]. Delivering high doses to the tumor while sparing surrounding organs at risk is possible even in larger tumors using particle therapy [22, 30].

The present case in which PVTT could be controlled by CIRT suggests the potential of this therapy combined with systemic therapy in patients with advanced HCC with MVI. MVI, including PVTT, is often a strong poor prognostic factor, even more when its control becomes difficult [11, 31, 32]. Several articles suggest particle therapy, both carbon and proton, to be effective in advanced HCC with MVI, with a possibility of cure [19–22] (Table 1). However, high subclinical presence of multiple intrahepatic lesions and/or extrahepatic metastasis associated with advanced HCC with MVI does prevent achieving long time-to-progression. Combination therapy of particle therapy to control the prognosis limiting
Recently, atezolizumab (anti-PD-L1 inhibitor) plus bevacizumab (anti-VEGF inhibitor) therapy has shown significant improvement in overall survival, progression-free survival, and objective response rate compared to sorafenib in advanced HCC, according to a global phase III trial [23]. Currently, the standard treatment for advanced HCC has been replaced by atezolizumab plus bevacizumab instead of tyrosine kinase inhibitors [33]. In the era of immunotherapy, the effect that radiation therapy has on the tumor microenvironment by being able to convert a cold tumor that has low immunogenicity and is poorly infiltrated with lesion and pharmacotherapy to control other intra-/extra-hepatic lesions could be an answer to this.
immune cells to an immune-reactive hot tumor that is well infiltrated by immune cells has been the main focus of radiation therapy [34–36]. Specifically, radiation therapy has the potential to enhance the effect of immune checkpoint inhibitors. In advanced HCC with MVI, irradiating the tumor with MVI by particle radiation therapy and combining it with an immune checkpoint inhibitor may provide synergistic treatment effects based on 2 abilities of particle radiation therapy, that is, localized tumor killing and tumor microenvironment modification. We believe this would dramatically improve the survival outcomes in patients with advanced HCC with MVI, which has the worst prognosis of HCC.

In conclusion, we experienced a patient with advanced HCC with MVI in whom PVTT that progressed while on lenvatinib treatment was controlled by CIRT. Combining CIRT with systemic therapy may be a treatment option in patients with advanced HCC with MVI.

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Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patient is deceased. The informed consent for publication was obtained from the patient’s family.

Conflict of Interest Statement

Sadahisa Ogasawara received grant support from Eisai, Bayer, and Eli Lilly, advisory fees from Eisai, Bayer, MSD, AstraZeneca, and Eli Lilly, and honoraria from Eisai, Bayer, MSD, AstraZeneca, and Eli Lilly. Yoshihiko Ooka received honoraria from Eisai. Naoya Kato received grant support from Eisai, Bayer, Takeda, and Eli Lilly, advisory fees from Eisai, Bayer, and Eli Lilly, and honoraria from Eisai, Bayer, and Eli Lilly. The other authors of this study indicated that they had nothing to declare regarding funding or conflict of interest with respect to this study.

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| Author               | n | Therapy        | RT total dose | Fx | Location | LPFS or LC rates |
|----------------------|---|----------------|---------------|----|----------|-----------------|
| Hata et al. [19]     | 12| Proton beam    | 55.0 GyE (50–72) | 10–22 Fr | Vp3, Vp4 | 67% (2-year)    |
| Sugahara et al. [20] | 35| Proton beam    | 72.6 GyE (55.0–77.0) | 22 Fr | Vp3, Vp4 | 46% (2-year)    |
| Lee et al. [21]      | 27| Proton beam    | 50–66 GyE | 20–22 Fr | Vp3, Vp4 | 64.2% (2-year)  |
| Shiba et al. [22]    | 11| Carbon ion     | 52.8–60 GyE | 4 or 12 Fr | Vv3, Vp4 | 78% (3-year)    |

HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombosis; RT, radiotherapy; Fx, fraction; LPFS, local progressive-free survival; LC, local control; MVI, macrovascular invasion; CIRT, carbon-ion radiotherapy.
Author Contributions

Conceptualization, Sadahisa Ogasawara; methodology, Sadahisa Ogasawara; investigation, Ryoi Yoshida, Keisuke Koroki, Takamasa Ishino, Keita Ogawa, Miyuki Nakagawa, Katsuki Fujiiwara, Hiemi Unoza, Terunao Iwanaga, Naoto Fujita, Takafumi Sakuma, Hiroaki Kanzaki, Kazufumi Kobayashi, Naoya Kanogawa, Soichiro Kiyono, Masato Nakamura, Takayuki Kondo, Tomoko Saio, Ryo Nakagawa, Eichihiro Suzuki, Yoshihiko Ooka, Shingo Nakamoto, Akiyo Tawada, Tetsuhiro Chiba, Makoto Araki, Takashi Kaneko; data curation, Ryoi Yoshida, Keisuke Koroki; writing – original draft preparation, Ryoi Yoshida, Keisuke Koroki, Hirokazu Makihsima; writing – review and editing, Sadahisa Ogasawara, Hirokazu Makihsima; supervision, Masaru Wakatsuki, Hiroshi Tsuji, Jun Kato, Naoya Kato; project administration, Naoya Kato.

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