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Novel concept of "sequential particle radiotherapy" with atezolizumab plus bevacizumab for HCC with portal vein tumor thrombus

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Short title: Sequential particle radiotherapy

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Abstract

Owing to the high objective response rate of atezolizumab plus bevacizumab (Atez/Bev) for hepatocellular carcinoma (HCC), the concept of sequential conversion to local treatment after Atez/Bev has recently become mainstream. The conversion concept is mainly applied for Barcelona Clinic for Liver Cancer (BCLC) stage B cases, and radiotherapy is rarely considered as the conversion local treatment. We report three

patients who were treated with the novel concept of “sequential particle radiotherapy” consisting of Atez/Bev therapy followed by particle radiotherapy (PRT) for HCC with advanced portal vein tumor thrombus (Vp3/4 PVTT). All patients achieved partial response radiologically and were switched to PRT. All patients were recurrence-free 1 year after introduction of Atez/Bev therapy without any additional treatment. This upcoming combination strategy includes the advocacy of sequential concepts for BCLC stage C cases and the introduction of PRT as a local treatment after Atez/Bev.

Introduction

The advent of atezolizumab plus bevacizumab (Atez/Bev), the combination of a programmed death-ligand 1 inhibitor and an anti-vascular endothelial growth factor antibody, has dramatically changed the composition of systemic chemotherapy for hepatocellular carcinoma (HCC) [1]. Based on the effectiveness and feasibility of Atez/Bev as demonstrated by several clinical data, its position as first-line treatment has been established. Recent concerns have shifted to how to treat or manage HCC after Atez/Bev therapy. Kudo et al. advocates the novel concept named “ABC conversion” which consists of Atez/Bev therapy followed by curative conversion therapy [2]. This is a groundbreaking concept and has the potential to revolutionize treatment strategies for advanced HCC. However, this concept has mainly been investigated in HCC cases classified as Barcelona Clinic Liver Cancer (BCLC) stage B, with the sequential conversion concept regarding those with BCLC stage C rarely being examined. In addition, the options for curative local treatments under consideration for sequential conversion therapy are hepatectomy, radiofrequency ablation, and transarterial chemoembolization; radiotherapy is generally not included.

Particle radiotherapy (PRT) has recently gained attention as an innovative form of radiation therapy. Unlike conventional radiation therapy, PRT is highly curative and is characterized by a high dose concentration. To this end, it has already been positioned as an effective local treatment for HCC following the review of various clinical data [3]. HCC with portal vein tumor thrombus (PVTT), especially extending to the first-order portal branch (Vp3) or the main portal trunk (Vp4), is considered to have an advanced tumor status, and available treatment options are strongly limited. Based on the BCLC classification, systemic chemotherapy, mainly with Atez/Bev, is expected to be the mainstay of treatment, although the clinical course of HCC with Vp3 and Vp4 (Vp3/4) PVTT initially treated with Atez/Bev remains unknown. The present study reports on three cases of HCC with Vp3/4 PVTT treated with a novel concept of "sequential particle radiotherapy" consisting of Atez/Bev therapy followed by PRT.

Patients and methods

Patient characteristics

Between October 2020 and December 2022, 82 patients with unresectable HCC received Atez/Bev therapy at the Kobe University Hospital. Thirty-six (43.9%) and 46 (56.1%) patients had BCLC stage B and C disease, respectively. Of 82 patients, 29 patients (35.3%) had extrahepatic metastases before Atez/Bev therapy. Twenty-one patients (25.6%) had macroscopic vascular invasion, including portal vein tumor thrombus, hepatic vein tumor thrombus, and bile duct thrombus. Among these, three consecutive cases of unresectable HCC with Vp3/4 PVTT treated with Atez/Bev followed by PRT were enrolled in the study. Our treatment policy for HCC with Vp3/4 PVTT is up-front hepatectomy if resectable both oncologically and with retained

hepatic functionality. However, for unresectable cases, Atez/Bev is the first-line treatment. Our follow-up policy after introduction of Atez/Bev is to determine the feasibility of applying sequential local therapeutic intervention for cases including HCC with Vp3/4 PVTT, in which the local control of intrahepatic tumors may contribute to a prolonged prognosis. Hepatectomy is the first choice of sequential local treatment in resectable cases, while other local treatments, including PRT, are significant alternatives for unresectable cases.

All patients received Atez/Bev therapy according to the recommended dosage (1200 mg atezolizumab and 15 mg/kg of bevacizumab intravenously every 3 weeks) and subsequent PRT after Atez/Bev therapy. Radiological evaluation was assessed using computed tomography (CT) or magnetic resonance imaging (MRI), and the therapeutic response was determined based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and modified RECIST. Adverse events were assessed using the National Cancer Institute Common Toxicity Criteria version 5.0. Statistical analysis was performed using JMP 14 statistical package (SAS Institute, Cary, NC, USA), and statistical significance was set at $p < 0.05$. This study was conducted in accordance with the ethical standards of the Declaration of Helsinki, and written informed consent was obtained from all patients.

RESULTS

Patient profiles

Th patients' baseline characteristics are shown in Table 1. Regarding the invasion of PVTT, two patients had Vp4, and the remaining one patient had Vp3. The maximum tumor sizes were 114, 85, and 63 mm. Distant metastases were not detected in all cases,

and the intrahepatic tumor number was solitary in two patients and two in one. None of the patients had a history of systemic chemotherapy, and the initiated Atez/Bev therapy was the first systemic chemotherapy. AFP levels in the patients before treatment were 212, 7783, and 212537 ng/ml, and the PIVKAII levels before treatment were 172, 6976, and 207276 mAU/ml.

A representative case of HCC with Vp4 PVTT treated with Atez/Bev therapy and sequential PRT is shown in Fig. 1. Abdominal CT (Fig. 1A) before Atez/Bev therapy showed a huge HCC with Vp4 PVTT (white arrow). After six kurs of Atez/Bev, the tumor shrank in size with regression of the PVTT from the main portal trunk to the bifurcation of the anterior and posterior branches (white arrow) (Fig. 1B). Sequential carbon-ion radiotherapy (76 gray equivalent/20 fraction) was performed on the main tumor and PVTT (Fig. 1C). Abdominal CT 4 months after carbon-ion radiotherapy demonstrated no apparent signs of recurrence in the liver (Fig. 1D).

Atezolizumab plus bevacizumab therapy

The regimen of Atez/Bev therapy for the three patients was seven kurs in two and six kurs in one. Radiological responses were all classified as partial responses according to both RECIST and modified RECIST criteria. In all cases, tumor marker levels decreased immediately after the introduction of Atez/Bev. The ratio of AFP levels relative to pretreatment levels for each month after Atez/Bev therapy is shown in Supplementary Fig. 1. All cases showed decreased AFP levels until 9 weeks after Atez/Bev introduction, although 2 of 3 began to increase thereafter (both cases from 15 weeks).

The maximum tumor sizes decreased from 114 to 78 mm (case 1), 63 to 33 mm

(case 2), and 85 to 23 mm (case 3). All patients eventually underwent PRT and maintained tumor shrinkage on imaging.

Particle radiotherapy

Among the three patients receiving PRT, proton radiotherapy was delivered to one patient, and carbon-ion radiotherapy was delivered to two. The protocols used were 76 gray equivalent/20 fractions for all patients (both proton and carbon-ion radiotherapy). For cases with large tumors or those in close proximity to the gastrointestinal tract, protocols of reducing the one-time dose of each fraction and increasing the total fractions were used to prevent gastrointestinal tract adverse events and damage to normal liver. The interval between the final administration of Atez/Bev and introduction of PRT was 19, 76, and 107 days, (Case 1, 2, and 3) respectively. The reasons for the delay of PRT introduction in Cases 2 and 3 were prolonged general fatigue after Atez/Bev therapy and fracture of the femoral neck requiring surgery, respectively. The ratio of AFP levels relative to pre-PRT levels for each month after PRT is shown in Supplementary Fig. 2. Two of the three patients showed drastically decreased AFP levels soon after the completion of PRT. One patient (case 3) had already achieved normalization of AFP level before the start of PRT. The AFP level increased 8 weeks after PRT completion and gradually decreased to near-normal levels. All patients were alive and recurrence-free 1 year after the start of Atez/Bev therapy, without any additional treatment after PRT.

DISCUSSION

The present study indicates the significant potential of the novel concept of “sequential

particle radiotherapy" consisting of Atez/Bev therapy followed by PRT for HCC with Vp3/4 PVTT. The novel findings of this study include the following two insights: advocacy of sequential local treatment for BCLC stage C cases and the introduction of PRT as a local treatment after Atez/Bev.

HCC with Vp3/4 PVTT is a highly advanced disease with poor prognosis. The favorable outcomes of hepatectomy for HCC with PVTT extending until Vp2 (PVTT invading a second-order portal branch) have been proven with the Japanese national data [4]. In contrast, surgical indications are quite controversial for HCC with Vp3/4 PVTT because the surgical outcomes are less than ideal. The prognosis of HCC with Vp3/4 PVTT remains poor, owing to the lack of effective treatment. Although systemic chemotherapy is the only recommended treatment based on BCLC classification, the median survival time with Atez/Bev for HCC with Vp4 PVTT was only 7.6 months in the subgroup analysis of the IMb 150 trial [5]. Since complete control of HCC with Vp3/4 PVTT with Atez/Bev alone is considered difficult, the introduction of sequential local treatment at the time of nadir would be beneficial.

PRT, such as proton and carbon-ion radiotherapy, has several radiotherapeutic advantages owing to its physical property of dose deposition, known as the Bragg peak [6]. Due to the lack of clinical evidence from randomized control trials, the position of PRT in the guidelines has not yet been established. However, several reports with large cohorts have demonstrated the clinical effectiveness of PRT for HCC, considering it a curative local treatment. The tumor factor of vascular invasion is proven to not be the risk factor for local recurrence after PRT [7], and the excellent treatment outcomes of PRT for HCC with PVTT have been demonstrated clinically [8]. Accordingly, the newly developed concept of "sequential particle radiotherapy" after Atez/Bev has

emerged, and the present study demonstrated the impressive clinical progression of HCC patients with Vp3/4 PVTT on this combination treatment. The optimal duration with respect to the interval between the final administration of Atez/Bev and introduction of PRT is unknown. Although the timing of PRT introduction may vary depending on the adverse events of Atez/Bev therapy and the patient's general condition, our policy is to introduce PRT within 1 month from the final administration of Atez/Bev. As a sequential local therapeutic intervention after Atez/Bev therapy, we consider that the role of PRT is adequate as alternative to hepatectomy, thus considering hepatectomy unnecessary for post-PRT tumors. In addition, hepatectomy after post-PRT site is in principle contraindicated due to the reported high risk of hepatectomy-related complications.

Radiotherapy has direct cytotoxicity against cancer cells and also exerts a strong antitumor immune response in the tumor microenvironment through various mechanisms, such as tumor antigen presentation and enhanced MHC class I expression. These immune responses have antitumor effects not only on the irradiated local tumor but also on distant metastases, which is called the abscopal effect [9]. Tumor cells are known to acquire resistance to radiotherapy through an immune escape mechanism by enhancing PD-L1. The combined use of immune checkpoint inhibitors is expected to attenuate this radiotherapy resistance and enhance the local therapeutic effect [10]. Radiotherapy also results in immunogenic tumor cell death, thereby priming tumor-specific T cells and enhancing MHC class I expression in tumor cells. This may also restore the antitumor effects of tumor cells that are resistant to immune checkpoint inhibitors [11]. Although it remains a matter of speculation, it is possible that these factors may contribute to the overall enhancement of the therapeutic effect.

The limitations of the present study include the small sample size, short-term observations, and patient selection bias. Although long-term follow-up with careful attention is required, considering that all cases were advanced HCC with Vp3/4 PVTT, favorable clinical progression with survival for more than 12 months without any recurrence and having a drug-free status in all cases might be considered clinically significant. The newly suggested concept of “sequential particle radiotherapy” after Ate/Bev for HCC with Vp3/4 PVTT may be a promising treatment strategy.

Declarations

Disclosure The authors have no conflicts of interest or funding to declare.

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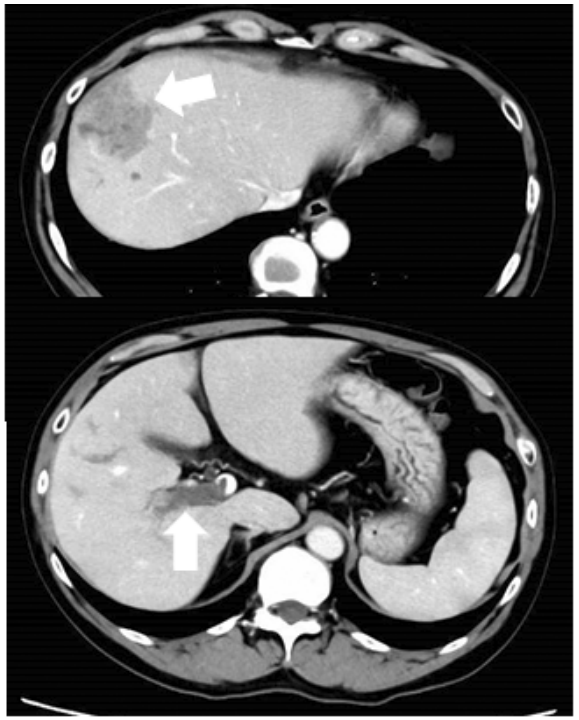
Figure legends

Fig. 1 (A) Abdominal CT before Atez/Bev therapy showed a huge HCC with Vp4 PVTT (white arrow). (B) The tumor shrank in size with regression of the PVTT from the main portal trunk to the bifurcation of the anterior and posterior branches (white arrow) after 6 kurs of Atez/Bev. (C) Sequential carbon-ion radiotherapy (76 gray equivalent/20 fraction) was performed on the main tumor and PVTT. (D) Abdominal CT 4 months after carbon-ion radiotherapy demonstrated no apparent signs of recurrence in the liver. CT, computed tomography; Atez/Bev, atezolizumab plus bevacizumab; HCC, hepatocellular carcinoma; Vp4, portal vein tumor thrombus extending to the main portal trunk; PVTT, portal vein tumor thrombus.

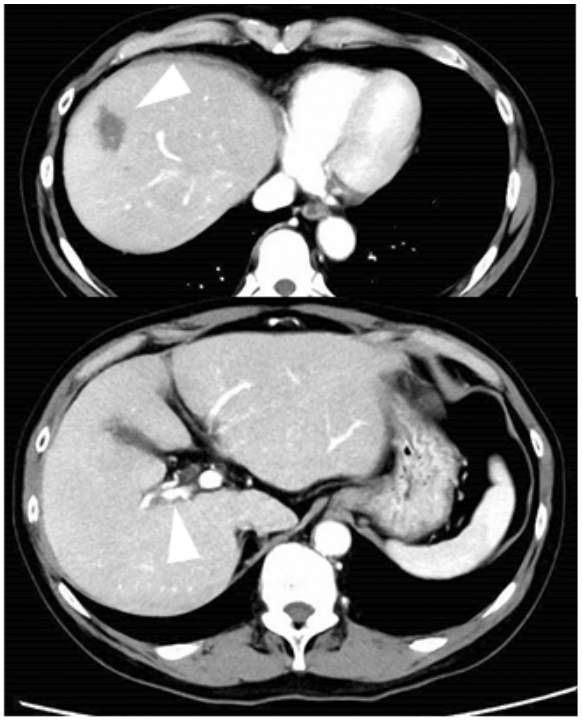
Supplementary Fig. 1 Ratio of alpha-fetoprotein levels relative to pre-treatment levels for each month after atezolizumab plus bevacizumab therapy

Supplementary Fig. 2 Ratio of alpha-fetoprotein levels relative to pre-particle radiotherapy levels for each month after particle radiotherapy

(A)



(B)



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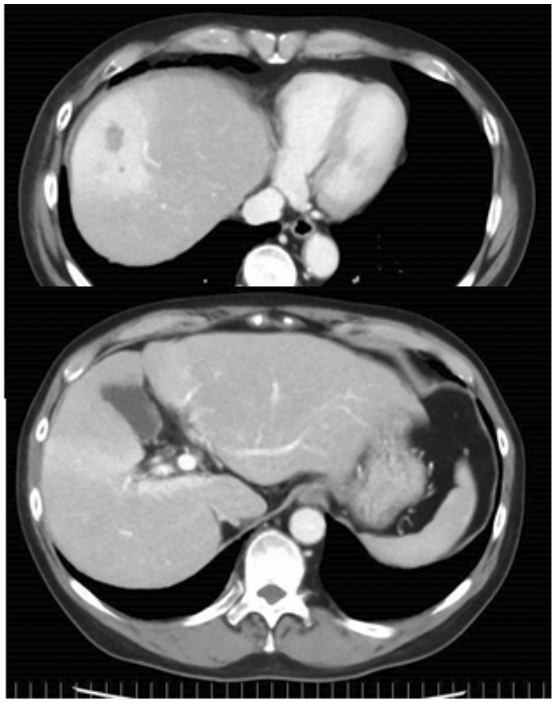

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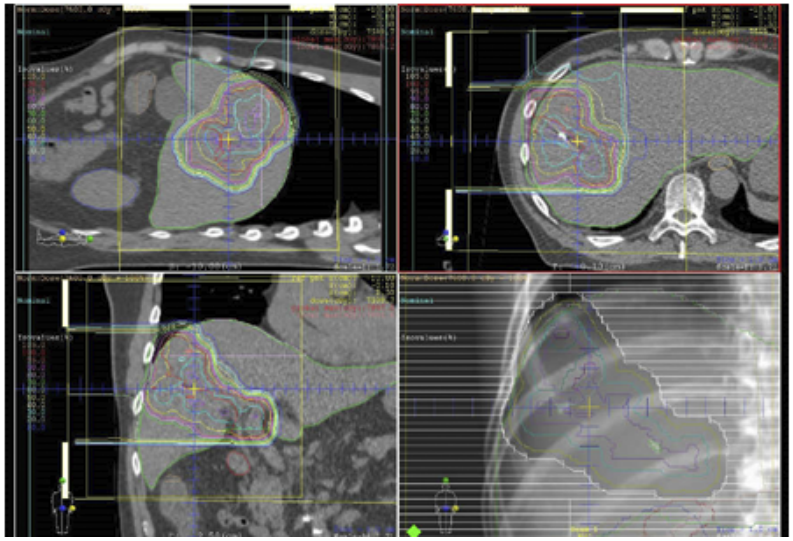

Table 1 Clinical details of 3 patients treated with Atez/Bev and sequential particle radiotherapy

Case	Age Sex	Child-Pugh grade	ALBI grade	Intrahepatic tumor numbers	PVTT Status	Maximum tumor size	AFP (ng/ml)	Duration of Atez/Bev	AFP 1month/before	Response by Atez/Bev	Particle radiotherapy	Status survival
1	74, M	5A	2	1	Vp3	114 mm	7783	7 kurs	0.811	PR*, SD**	Proton 76GyE/20Fr	Alive, 14 months
2	67, M	5A	1	1	Vp4	63 mm	212	6 kurs	0.203	PR*, PR**	Caron ion 76GyE/20Fr	Alive, 12 months
3	82, F	5A	1	2	Vp4	85 mm	212537	7 kurs	0.153	PR*, PR**	Caron ion 76GyE/20Fr	Alive, 22 months

Atez/Bev atezolizumab plus bevacizumab, *ALBI* albumin-bilirubin, *PVTT* portal vein tumor thrombus, *AFP* alpha-fetoprotein, *PR* partial response, *SD* stable disease, *GyE* gray equivalent, *Fr* fraction

*evaluated by modified Response Evaluation Criteria in Solid Tumors

**evaluated by Response Evaluation Criteria in Solid Tumors