Aggressive proton beam therapy followed by liver transplantation for a patient with large HCC with portal vein tumor thrombus

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Abstract We describe the case of a patient with large hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT) who was successfully treated with two courses of proton beam therapy (PBT) followed by liver transplantation. The patient was a 69-year-old man with hepatitis C viral infection who was diagnosed with a diffuse HCC, 8 cm in size, and a PVTT that occluded the right portal vein and reached the main trunk of the portal vein. A large tumor in the right lobe and PVTT in the main and right main portal vein were treated by PBT. PVTT in the left main portal vein developed thereafter and was treated with a second course of PBT. Although the tumor was well controlled with two courses of PBT, liver function gradually deteriorated to an irreversible status 20 months after initiation of the first course of PBT. Liver transplantation was successfully performed to maintain liver function. The patient is still alive with no evidence of disease 7 years after the first course of PBT. This case shows that aggressive PBT can be used for treating advanced HCC, with subsequent liver transplantation for hepatic failure that may be caused by PBT.

Keywords Hepatocellular carcinoma · Portal vein tumor thrombus · Proton beam therapy · Radiation · Liver transplantation

Introduction

In the treatment of hepatocellular carcinoma (HCC), it is important to maintain liver function, which may be reduced by underlying liver cirrhosis, as well as to control the tumor. Proton beam therapy (PBT) is a particle radiotherapy method with the advantage that the proton beam stops just behind the tumor so that normal tissue deeper than the tumor is not irradiated. For HCC, this makes it possible to deliver high doses to the tumor while reducing the dose to non-cancerous liver tissues. A proton beam is categorized as low linear energy transfer (LET) radiation, similar to photon radiotherapy. The anticancer effect of PBT is based on generation of DNA double-strand breaks and apoptosis, in common with high-energy X-ray radiotherapy. However, the mechanism of cell inactivation by a proton beam may differ somewhat from that of photons [11]. We recently showed that a proton beam produces slightly higher cell inactivation than photons, and we assume that the biological effectiveness of protons is 1.1 times higher than that of photons.

We have shown the effectiveness of PBT for HCC, even in patients with portal vein tumor thrombus (PVTT) or inferior vena cava tumor thrombus (IVCTT) who were unsuitable for therapies such as surgery or ablation [1–4]. We obtained a 2-year local progression-free survival rate of 91 % without severe late toxicity and final response and CR rates of 89 and 54 %, respectively [1]. Liver transplantation is a standard method for patients with HCC who meets the Milan criteria (tumor size <5 cm, tumor number

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≤ 3) or UCSF criteria [5, 6]. These patients have a 5-year survival rate of $\geq 70\%$ after transplantation. Here, we describe a patient with large HCC with PVTT who was treated with two courses of PBT followed by liver transplantation and has subsequently survived for 7 years.

Case report

The patient was a 69-year-old man with hepatitis C viral infection who was diagnosed with a diffuse HCC, 8 cm in size, in segment S7 and a PVTT that occluded the right portal vein and reached the main trunk of the portal vein. The diagnosis was made using dynamic computed tomography (Fig. 1a). We first performed arterial injection chemotherapy, which was ineffective. Three months later, PBT of 72.6 GyE was administered in 22 fractions over 31 days. Pretreatment, liver function had a Child–Pugh score of 6. The clinical target volume (CTV) was defined

as the gross tumor with a 5- to 10-mm margin in all directions. An additional 5-mm margin was included on the caudal axes to compensate for uncertainty due to respiration-induced hepatic movement. An additional margin of 5–10 mm was added to cover the entire CTV by enlarging the multileaf collimator and adjusting the range shifter (Fig. 1b).

Two months after the first course of PBT, a PVTT with a maximum dimension of 4.5 cm developed in the left main portal vein and the level of the tumor marker AFP increased (Fig. 2a). The PVTT was irradiated with PBT of 77.0 GyE in 35 fractions over 54 days (Fig. 2b).

Liver function gradually deteriorated despite the tumor being controlled, and the patient finally suffered hepatic failure at 16 months after the second course of PBT. Liver transplantation was performed for hepatic failure. Pathological findings of the resected tissue showed a residual tumor with a maximum dimension of 3 cm and occlusion by a thrombus and necrosis without residual tumor cells in the portal vein. Seven years after liver transplantation, the

Fig. 1 Contrast CT images before the first treatment with proton beam therapy. **a** The arrow indicates the PVTT in the right portal vein. **b** The dose-distribution chart, with isodose curves representing 100–10 % of the administered dose at 10 % intervals

Fig. 2 Contrast CT images before the second treatment with proton beam therapy. **a** The arrow indicates the PVTT in the left portal vein. **b** The dose-distribution chart, with isodose curves representing 100–10 % of the administered dose at 10 % intervals

patient is still alive with no evidence of disease, a liver function Child-Pugh score of 5, and a performance status of 0.

Discussion

We have shown that PBT is effective for treatment of HCC regardless of tumor size and underlying liver function [7–9]. In this case, the patient had a very large HCC with PVTT in the main and right main portal vein, and PBT appeared to be the only treatment method. The patient underwent PBT for the large tumor with PVTT through posterior and right lateral ports to spare the non-cancerous liver tissue from radiation. The second course of PBT to the left main portal vein PVTT was given through the anterior port with the same goal of sparing non-cancerous liver tissue, but the final volume of non-irradiated non-cancerous liver tissue was very limited. Therefore, the non-cancerous liver tissue gradually lost its function, and regeneration of the remaining non-irradiated non-cancerous tissue was insufficient, with a consequent gradual deterioration in liver function.

In this case, PVTT recurred soon after PBT, probably because an undetectable tumor was already present when the first PBT was performed. We previously reported that 3 of 35 patients with PVTT treated by PBT developed progressive disease only 1–3 months after PBT and that 22 of the 35 patients had an initial recurrence outside the irradiated area after PBT [1]. In several cases of recurrence after PBT, the recurrent tumor was well controlled by further treatment. In this case, the recurrence of PVTT was so rapid that treatment such as RFA or surgery was considered difficult. Therefore, we selected PBT as treatment for the recurrent PVTT.

Liver function after PBT is maintained in many cases, but in our experience this is significantly dependent on the percentage volume of normal liver that is not irradiated [10]. Therefore, in cases with a limited normal liver volume, care must be taken to maintain liver function when performing PBT.

The Milan criteria are widely used to determine eligibility for liver transplantation [5]. In these criteria, patients who satisfy the following conditions are eligible for transplantation: a solitary tumor ≤ 5 cm in size, two or three oligonodular tumors of ≤ 3 cm, no distant metastases, and no major vascular invasion. In our case, the patient did not meet these criteria before the first course of PBT. However, after administration of two series of PBT the tumors were well controlled, the residual tumor had shrunk, and PVTT had disappeared, making the patient eligible for liver transplantation. A pathological examination showed that PVTT had disappeared and been replaced by a thrombus and that the main tumor had shrunk by up to

3 cm. This examination was performed soon after administration of radiotherapy, and it is likely that the tumor would have disappeared if long-term observation had been performed.

Our case is the first use of liver transplantation after PBT. Currently, PBT is not indicated for treatment of patients with liver dysfunction (Child-Pugh class C). Therefore, performance of liver transplantation for liver dysfunction after PBT is rare. In general, patients with large and/or vascular invasive HCC are not eligible for liver transplantation. However, these patients might be appropriate for this procedure if it could be performed after PBT. The efficacy and safety of PBT in HCC patients with liver dysfunction requires further examination, but it may be possible to perform PBT in patients with liver dysfunction (Child-Pugh Class C) who may not be indicated for liver transplantation because of the size of tumors and/or vascular invasion. If the tumor size can be decreased by PBT and the condition for liver transplantation is satisfied, it may be possible to establish a liver transplantation strategy for these patients.

This case shows that aggressive PBT can be used for treating advanced HCC, with subsequent liver transplantation for hepatic failure that may be caused by PBT. The successful outcome in this case suggests that planned liver transplantation after PBT has the possibility to be curative for patients with a poor condition. For example, initial PBT may be performed for a patient with poor liver function due to large HCC or PVTT. Patients in which the tumor is well controlled by PBT and with no other tumor outside the irradiated area after PBT could then be selected for liver transplantation. This proposed new treatment strategy of planned liver transplantation after PBT requires further investigation.

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Conflict of interest The authors declare that they have no conflict of interest.

References

1. Sugahara S, Nakayama H, Fukuda K et al (2009) Proton-beam therapy for hepatocellular carcinoma associated with portal vein tumor thrombosis. *Strahlenther Onkol* 185:782–788
2. Mizumoto M, Tokuuye K, Sugahara S et al (2008) Proton beam therapy for hepatocellular carcinoma adjacent to the porta hepatis. *Int J Radiat Oncol Biol Phys* 71:462–467
3. Mizumoto M, Tokuuye K, Sugahara S et al (2007) Proton beam therapy for hepatocellular carcinoma with inferior vena cava tumor thrombus: report of three cases. *Jpn J Clin Oncol* 37:459–462

4. Hata M, Tokuuye K, Sugahara S et al (2005) Proton beam therapy for hepatocellular carcinoma with portal vein tumor thrombus. *Cancer* 104:794–801
5. Mazzaferro V, Regalia E, Doci R et al (1996) Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 334:693–699
6. Yao FY, Ferrell L, Bass NM et al (2002) Liver transplantation for hepatocellular carcinoma: comparison of the proposed UCSF criteria with the Milan criteria and the Pittsburgh modified TNM criteria. *Liver Transplant* 8:765–774
7. Mizumoto M, Okumura T, Hashimoto T et al (2011) Proton beam therapy for hepatocellular carcinoma: a comparison of three treatment protocols. *Int J Radiat Oncol Biol Phys* 81:1039–1045
8. Chiba T, Tokuuye K, Matsuzaki Y et al (2005) Proton beam therapy for hepatocellular carcinoma: a retrospective review of 162 patients. *Clin Cancer Res* 11:3799–3805
9. Hata M, Tokuuye K, Sugahara S et al (2007) Proton irradiation in a single fraction for hepatocellular carcinoma patients uncontrollable ascites technical considerations and results. *Strahlenther Onkol* 183:411–416
10. Mizumoto M, Okumura T, Hashimoto T et al (2012) Evaluation of liver function after proton beam therapy for hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 82:e529–e535
11. Gerelchuluun A, Hong Z, Sun L et al (2011) Induction of in situ DNA double-strand breaks and apoptosis by 200 MeV protons and 10 MV X-rays in human tumor cell lines. *Int J Radiat Biol* 87:57–70