A case of the cirrhotic patient performed living donor liver transplantation after carbon-ion radiotherapy for hepatocellular carcinoma

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Abstract

The patient was a 50-year-old female with an initial diagnosis of a single hepatocellular carcinoma in liver cirrhosis. The tumor was located in the posterior liver segment (S7) and measured 5 cm with a rapid growth rate and portal invasion. The pre-treatment Child-Pugh (C-P) was grade A (six points). The total prescribed dose of carbon-ion radiotherapy (C-ion RT) was 60 Gy (relative biological effectiveness) given in 4 fractions. Thereafter, tumor shrinkage and rapid decrease of the serum alpha-fetoprotein level were observed. At 1-year follow-up a new lesion was diagnosed in the left lobe and the underlying liver failure had worsened to C-P grade B (eight points). Thus, she was recommended to undergo living-donor liver transplantation (LDLT). The postoperative course was uneventful. At pathological examination, no viable tumor cells in the region treated with C-ion RT were detected. At the time of the last follow-up, the patient was in overall good general condition with no signs of tumor recurrence.

Keywords Carbon-ion radiotherapy · Hepatocellular carcinoma · Living-donor liver transplantation

Introduction

There are several therapeutic modalities for hepatocellular carcinoma (HCC), such as liver resection, liver transplantation (LT), ablative procedure (radio frequent ablation, microwave ablation, percutaneous ethanol injection treatment), trans-arterial treatment (chemo-embolization, radio-embolization), molecular target drugs and radiotherapy (RT) [1, 2]. In the past decade, RT has been applied for HCC as a definitive local treatment, and excellent outcomes of

stereotactic body radiotherapy (SBRT) for HCC have been reported. However, most such cases described have had tumors of relatively smaller size [3].

Carbon-ion radiotherapy (C-ion RT) is a unique external RT that achieves better dose conformity and higher biological effectiveness than conventional photon RT [4]. It is categorized as a particle RT, which has a surge of radiation dose at a certain depth from the skin surface, called the ‘Bragg peak’. Moreover, it has demonstrably stronger biological effects than X-ray, gamma ray and proton beams. Several reports on C-ion RT have indicated its efficacy for liver malignancies including large HCC [5–7].

To our knowledge, this is the first case report of living-donor liver transplantation (LDLT) after curative C-ion RT for HCC with portal vein invasion to confirm pathological complete response (pCR) of the C-ion RT.

Case report

The patient was a 50-year-old female with HCC and underlying hepatitis C virus (HCV) infection-related liver cirrhosis. She was diagnosed with chronic hepatitis C in 2002. She

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received splenectomy due to portal hypertension in 2006. Her liver function worsened in 2007, the cause was thought autoimmune disease because her liver function recovered after administrating steroidal therapy thought she did not meet the diagnostic criteria of autoimmune hepatitis. Interferon therapy was administrated several times, and she achieved a sustained virological response in 2011.

In April 2014, surveillance of a contrast-enhanced computed tomography (CECT) scan detected a liver lesion in the segment 7, but it was not definitively diagnosed as HCC even after angiography. Therefore, a close follow-up was planned. 3 months later (July 2014), CECT showed that the lesion had rapidly enlarged to about 3 cm in diameter and had invaded the segmental portal vein. No metastasis was detected. The serum alpha-fetoprotein (AFP) level had risen to 6005 ng/ml (cut-off value 10) and the serum des-gamma-carboxy prothrombin (DCP) level had risen to 213 mAU/

ml (cut-off value 40). Hence, clinical diagnosis of HCC was established though the enhancement pattern was not typical for HCC. The Child–Pugh (C-P) score was six points at that time. Including her history of splenectomy due to portal hypertension, obesity (body mass index 31.9 kg/m²) and receiving steroidal therapy, the expert surgeons of the hospital referred her thought that performing right posterior sectionectomy was risky. Trans-arterial treatments were unsuitable because of the delayed enhancement pattern of the tumor. Therefore, the patient was referred to our department and no contraindications to C-ion RT were identified.

The C-ion RT was scheduled after obtaining the informed consent. The patient was submitted to C-ion RT in September 2014. The tumor size at the time of the treatment planning was 5 cm in diameter (Fig. 1), which had been getting larger than that in July (3 cm). The total prescribed dose of the C-ion RT was 60 Gy (relative

Fig. 1 Pre-treatment images. CECT images of the HCC before the radiation. The HCC in segment 7 enlarged rapidly, up to 5 cm. **a** HCC without vascularity in the arterial phase; **b** HCC with portal invasion

suspected (arrow); **c** HCC with an unclear border in the late phase. CECT contrast enhanced computed tomography, HCC hepatocellular carcinoma

biological effectiveness (RBE)) given in four fractions (Fig. 2). The clinical target volume (CTV), identified as the expected volume of tumor microscopic infiltration, was determined to be the posterior segment of the right liver lobe, because the tumor had grown rapidly with portal invasion. The planning target volume was defined as the volume where the internal margin and set-up margin were added to the CTV. The relative liver volume irradiated more than 20 Gy was 32% and mean liver dose was 20 Gy which were acceptable even in conventional radiotherapy for the patients of Child A. A fiducial marker (Visicoil; RadioMed Corp., Bartlett, TN) was implanted prior to the C-ion RT. The tumor was irradiated from two orthogonal ports with respiratory synchronization on the prone position of the patient. Though Grade 2 general fatigue and nausea were observed during the treatment, the C-ion RT was completed without any other acute adverse events.

After completion of the C-ion RT, the tumor showed progressive shrinkage (Fig. 3a–d) and the serum AFP level decreased rapidly (Fig. 4). Her general fatigue and nausea recovered immediately. After 1 year of follow-up, a new lesion was diagnosed in the left lobe (Fig. 3e) and the underlying liver failure had worsened to C-P grade B (eight points). Performing radiofrequency ablation was thought to be inadequate because the lesion was close to the heart. After multidisciplinary discussion, the patient was determined to be a candidate for LT. Her C-P grade was B (nine points) and the Model for End-Stage Liver Disease scores was 11 points at that time. After the approval of the institutional review board she underwent LDLT in February 2016, with her son as the donor. The graft type was enlarged left lobe graft. The operation time

was 11 h and 19 min, and the blood loss was 2490 ml. During the procedure, strong diffuse adhesions were detected. In particular, the irradiated liver area was firmly attached to the diaphragm. Therefore, a partial diaphragm resection was performed. Otherwise, the LDLT was carried out without any other complications.

Macroscopically, the irradiated area showed atrophic change and had turned white in color (Fig. 5a). The pathological findings of the resected liver showed that most of irradiated area had remarkable fibrotic change and an accumulation of inflammatory cells (lymphocytes) in the right lobe, which showed a clear border between the irradiated and normal parenchyma. There were no viable tumor cells in the irradiated area (Fig. 5b, c). A lesion in the left lobe suspected on imaging of being HCC was diagnosed as a dysplastic nodule. The non-irradiated area of the left lobe presented with general liver cirrhosis (Fig. 6a). In contrast, remarkable fibrotic change was seen in the irradiated area in the right lobe. In addition, organizing obstruction and re-canalization was observed in the micro portal vein and hepatic artery, but only in the irradiated area (Fig. 6b). These findings indicated that ischemic change occurred following irradiation, leading to further fibrosis and atrophy of the liver. The finding in the micro portal vein suggested that irradiation induced both necrosis of the tumor thrombus and organizing obstruction.

At the time of last follow-up, 42 months after C-ion RT and 24 months after LDLT, the patient was alive without cancer recurrence. There was fortunately no re-activation of HCV-RNA during and after LDLT. Regarding toxicities, Grade 2 rib fractures at the irradiated area were the only C-ion RT-related adverse effects.

Fig. 2 Dose distribution. The tumor was irradiated from two orthogonal ports on the prone position of the patient. The clinical target volume was the posterior segment of the right lobe of the liver. The red line is the 95% iso-dose line of the prescribed dose of 60 Gy (RBE) given in four fractions. *RBE* relative biological effectiveness

Fig. 3 Post-treatment images. After the radiation, the tumor became smaller. **a** A CECT image of the portal phase at 3 months; **b** 6 months; **c** 9 months and **d** 12 months after irradiation. **e** The new

lesion (arrow) suspected recurrent tumor, which was finally diagnosed dysplastic nodule after the pathological examination of the resected liver. CECT contrast-enhanced computed tomography

Fig. 4 The tumor markers after carbon-ion radiotherapy. The serum AFP and DCP level decreased rapidly after the C-ion RT. The serum DCP level varied from 36 to 277 mAU/ml but the serum AFP level stayed below the cut-off value. AFP alpha fetoprotein, DCP Des-gamma-carboxy prothrombin, C-ion RT carbon-ion radiotherapy

Discussion

C-ion RT has better dose conformity and higher biological effectiveness than conventional RT [4]. Several reports

about C-ion RT for HCC have been published [5, 6]. Kato et al. [5] reported the results of a dose-escalation study of C-ion RT. Out of the 24 patients, 8 patients (33.3%) were classified as C-P grade B. The 5-year overall survival (OS) and local control rates (LCR) were 25 and 81%, respectively. Only one patient with an acute Grade 3 skin reaction was observed. Imada et al. reported a series of 64 HCC cases treated with 52.8 Gy (RBE) in 4 fractions [6]. The 5-year OS and LCR were 22.2 and 87.8% in the group whose treatments were close to (within 2 cm of) the main portal vein, and 34.8 and 95.7% in the farther group, respectively. There were 10 patients (15.6%) of all 64 patients with 2 or more points' increase in the C-P score. Non-hematologic toxicities of Grade 3 or worse were not observed. Furthermore, a recent planning study comparing dose-volume metrics between C-ion RT and SBRT for patients with HCC has clearly shown the superiority of C-ion RT to SBRT for tumors larger than 4 cm in diameter [4]. These studies suggested that C-ion RT is an effective and safe local treatment and can be indicated even for larger HCCs because C-ion RT injures normal liver tissue less than SBRT.

Fig. 5 **a** Macroscopic specimen of explanted liver. The area surrounded by the dotted line is the region treated with C-ion RT. **b** Most of the region treated with C-ion RT became necrotic with fibro-

sis. **c** The yellow dotted line is the borderline between the normal parenchyma and the region treated with C-ion RT. *C-ion RT* carbon-ion radiotherapy

Fig. 6 **a** General liver cirrhosis in non-irradiated area (left lobe). **b** In contrast, remarkable fibrotic change with an organizing obstruction, and re-canalization of micro-portal vein and hepatic artery were seen

in the irradiated area (EVG staining). *EVG* elastica van Gieson, *PV* portal vein, *A* artery

It is considered that several complexed factors such as HCV infection, autoimmune disorder and C-ion RT affected her liver function though her liver function worsened after C-ion RT despite these advantages. And then LDLT was finally performed because of both the new lesion and her severe liver dysfunction; C-P grade B with score 9 was almost grade C with 10. After LDLT pCR in the irradiated region were confirmed. To our knowledge, this is the first case report in the literature presenting a case in which LDLT was performed after curative C-ion RT for HCC. In the future, further studies with more patients and longer observations are still required.

Compliance with ethical standards

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

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