Transarterial Chemoembolization with and without Microballoon Occlusion for Hypovascular Hepatocellular Carcinoma

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Abstract

An 85-year-old woman developed locally recurrent hepatocellular carcinoma (HCC) after previous radiofrequency ablation combined with transarterial chemoembolization (TACE). Dynamic computed tomography (CT) and magnetic resonance imaging revealed a hypovascular tumor, which was suspected as poorly differentiated HCC. TACE was performed using a microballoon catheter. First, a suspension of miriplatin mixed with iodized oil (miriplatin-lipiodol suspension [MLS]) was injected without balloon occlusion. When the tumor-feeding artery was near stasis, the balloon was inflated and MLS was forcefully injected. CT after TACE showed accumulation of iodized oil throughout the tumor. The tumor had been controlled without recurrence for 22 months, at the time of writing this manuscript. The therapeutic efficacy of conventional TACE (C-TACE) for poorly differentiated hypovascular HCC is generally limited. In the present case, a good therapeutic result was achieved when balloon-occluded TACE was used in addition to C-TACE.

Key words: Hepatocellular carcinoma, Hypovascular, Microballoon-occluded transcatheter arterial chemoembolization

Introduction

Transarterial chemoembolization (TACE) is a well-established and effective treatment for unresectable hepatocellular carcinoma (HCC) \cite{1, 2}. It is known that the vascular system of HCC changes with the degree of tumor differentiation \cite{3, 4}, and that the therapeutic effects of TACE may depend on tumor vascularity \cite{5}. Hypovascular HCC has a poor arterial blood supply, so it is difficult to control with conventional TACE (C-TACE) \cite{4, 6}. Balloon-occluded TACE (B-TACE), which induces the dense accumulation of iodized oil in HCC to prevent proximal migration and leakage of iodized oil by occlusion of the hepatic artery, is a promising method for improving the efficacy of C-TACE \cite{7, 8}. Here, we report a case in which good therapeutic control of a hypovascular tumor suspected as poorly differentiated HCC (pHCC) was achieved using B-TACE in addition to C-TACE.

Case Report

Our institutional review board approved this study. The patient was an 85-year-old woman with Child-Pugh class A liver cirrhosis related to hepatitis C. Follow-up dynamic computed tomography (CT) performed 10 months after first combined C-TACE and B-TACE with radiofrequency ablation (RFA) for a 20-mm tumor suspected as moderately dif-
fermented HCC (mHCC) in segment 8 of the liver revealed accumulation of remnant iodized oil in the margin of a hypovascular tumor of size 15 mm (Fig. 1). The serum alpha-fetoprotein (AFP) level increased from 93 ng/mL to 607 ng/mL (normal, <10 ng/mL), and the level of serum protein induced by vitamin K absence or antagonists II (PIVKA-II) increased from 20 mAU/mL to 136 mAU/mL (normal, <40 m AU/mL), compared with the levels observed 3 months earlier. On magnetic resonance imaging (MRI), the lesion showed increased signal intensity on diffusion-weighted imaging. The apparent diffusion coefficient (ADC) value for the lesion was $1.04 \times 10^{-3}$ mm$^2$/s. Gadoteric acid-enhanced MRI showed that the lesion had the same enhancement behavior as that observed on dynamic CT. Hepatobiliary phase MRI showed hypointensity compared with the surrounding liver parenchyma. These findings suggested that pHCC locally recurred after first combined C-TACE and B-TACE with RFA. The patient was recommended partial hepatectomy, but she refused it and wished to undergo TACE first. Therefore, written informed consent was obtained from her, and second combined C-TACE and B-TACE was performed using a 1.8-Fr tip microballoon catheter (LOGOS; Piolax Medical Devices, Inc., Kanagawa, Japan). A8 angiography without balloon occlusion showed a vaguely demarcated stain of liver parenchyma (Fig. 2a). CT angiography (CTA) was performed using XperCT (Philips Healthcare, Best, The Netherlands), a kind of cone-beam CT, to evaluate the vascular supply to the tumor. The XperCT acquisition time was 5 s. CT images were acquired 5 s after the start of injection, and 10 mL of diluted contrast material with 5 mL of saline were injected at a rate of 1 mL/s into A8. CTA without balloon occlusion revealed no obvious tumor enhancement (Fig. 2b). In contrast, CTA with balloon occlusion showed slight enhancement in a small part of the tumor, and liver parenchyma around the tumor was enhanced much more strongly and broadly than that on CTA without balloon occlusion (Fig. 2c). A mixture of 30 mg of miriplatin (Miripla; Dainippon Sumitomo, Osaka, Japan) and 1.5 mL of iodized oil suspension (Lipiodol; Guerbet, Aulnay-sous-Bois, France) (MLS) was prepared and injected slowly, without balloon occlusion. When the tumor-feeding artery was near stasis, the balloon was inflated, and injection of MLS was continued. MLS was forcefully injected, and accumulation of iodized oil was observed throughout the tumor (Fig. 2d). Subsequently, 1-mm gelatin sponge fragments (Gelpart; Nippon Kayaku, Tokyo, Japan) were injected. XperCT performed immediately after the procedure showed dense accumulation of iodized oil in the tumor (Fig. 2e). The patient was suggested additional RFA, but her informed consent for the procedure could not be obtained. Three months later, her tumor markers decreased to normal levels (AFP 5.9 ng/mL, PIVKA-II 18 mAU/mL). Follow-up CT performed 22 months after the second combined C-TACE and B-TACE showed dense accumulation of the remaining iodized oil throughout the tumor, and no locally recurrent HCC (Fig. 3).

Fig. 1. Arterial phase of computed tomography performed 10 months after the first combined conventional transarterial chemoembolization and balloon-occluded transarterial chemoembolization with radiofrequency ablation shows that the accumulated iodized oil has been further washed out and is observed only at the margin of the lesion; the 15-mm lesion shows low attenuation.

**Discussion**

In C-TACE, iodized oil can be injected forcefully into a tiny feeding artery, and, therefore, it may be more widely distributed through arterioarterial and arterioportal communications via the peribiliary vascular plexus and/or the drainage route from the hypervascular tumor portion [6]. Compared with C-TACE, balloon occlusion of the hepatic artery enables more forceful injection of iodized oil, leading to its effective distribution into tumor sinusoids through smaller feeding vessels. Irie et al. reported that flow of iodized oil into normal liver parenchyma was limited by the balloon, and inflow of iodized oil into HCC nodules could continue, thus achieving more accumulation of iodized oil. They also reported that B-TACE induced dense accumulation of iodized oil in 91% of HCC nodules that were hypervascular on arterial phase CT [7]. In addition, more embolic agents can be injected to prevent their proximal migration.

Further, Ishikawa et al. reported that occlusion of the hepatic artery caused hemodynamic changes, and injection under these changes induced more effective accumulation of iodized oil [8]. In the present case, compared with CTA without balloon occlusion, arteriogram and CTA with balloon occlusion showed slight arterial enhancement, and much stronger and broader enhancement of the surrounding area of the tumor. These findings might reflect hemodynamic changes. However, from our experience, the difference depends on HCC vascularity, liver condition, position of the catheter tip, or other unknown factors in each case; hence, clarification of the exact mechanism might be difficult.

In C-TACE, iodized oil can be injected forcefully into a
tiny feeding artery; however, at the end of the injection process, it is difficult to maintain enough pressure owing to proximal migration of the iodized oil. We speculated that if B-TACE was performed when the tumor-feeding artery was near stasis in C-TACE, injection of even more iodized oil more forcefully into tumor sinusoids through smaller feeding vessels would be possible. Therefore, we performed combined C-TACE and B-TACE.

In the present case, recurrent tumor after first combined C-TACE and B-TACE with RFA had a rich hypovascular component, and it showed a high ADC value with a high AFP level. Some studies reported that the proportion of hypovascular tumors on CT was higher in well-differentiated HCC (wHCC) and pHCC than in mHCC [3], and Oishi et al. reported that a serum AFP level more than 400 ng/mL might be a useful criterion for predicting pHCC [9]. Additionally, Guo et al. reported that the ADC value for pHCC was $(1.16 \pm 0.16) \times 10^{-3} \text{mm}^2/\text{s}$, and that it was significantly lower than that for wHCC and mHCC [10]. Therefore, we thought that the lesion might be pHCC, although the diagnosis was not proven by histopathological analysis.

Yoshimitsu reported that compared with wHCC or mHCC, pHCC had larger tumor sinusoids and, thus, a smaller chance of being exposed to chemotherapeutic agents, and that it had anaerobic metabolism. Further, both chemotherapeutic and sufficient ischemic effects are neces-

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Fig. 2. A8 angiography without balloon occlusion shows vaguely demarcated stain of liver parenchyma (a). Computed tomography angiography (CTA) without balloon occlusion (coronal view) shows no obvious tumor enhancement (b). CTA with balloon occlusion (coronal view) shows weak enhancement in a small portion of the tumor, and liver parenchyma around the tumor is enhanced much more strongly and broadly than on CTA without balloon occlusion (c). As forceful injection of the mixture continues, accumulation of iodized oil in the tumor increases (d). XperCT performed immediately after the second combined conventional transarterial chemoembolization and balloon-occluded transarterial chemoembolization (coronal view) shows dense accumulation of iodized oil throughout the tumor (e).
Fig. 3. Arterial phase of computed tomography performed 22 months after the second combined conventional transarterial chemoembolization and balloon-occluded transarterial chemoembolization shows persistent dense accumulation of iodized oil throughout the tumor, and no locally recurrent HCC.

ecessary for the control of pHCC [4]. In the present case, B-TACE induced effective distribution of iodized oil into the tumor sinusoids through the decreased feeding arteries, and could block the feeding arteries with enough embolic agents under balloon occlusion. Finally, 22 months after second combined C-TACE and B-TACE, good local control of the lesion could be achieved. To the best of our knowledge, this is the first case of pHCC being sufficiently controlled using combined C-TACE and B-TACE.

The present case had some limitations. First, pathological confirmation of the target tumor could not be obtained. Second, portal perfusion of the tumor and liver segment was not examined on CT during arterial portography with and without balloon occlusion. Third, HCC locally recurred after first combined C-TACE and B-TACE with RFA; hence, the utility of combined C-TACE and B-TACE remains controversial.

In conclusion, the therapeutic efficacy of C-TACE for hypovascular pHCC is generally limited. In the present case, however, a good therapeutic outcome was achieved using B-TACE in addition to C-TACE.

Conflict of interest: The authors declare that they have no conflicts of interest to report.

References