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Successful Down-staging of Hepatocellular Carcinoma with Intra-arterial Therapy Prior to Liver Transplantation: A Case Report

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Abstract

Background: Down-staging strategy of Hepatocellular carcinoma (HCC) prior to Liver Transplantation (LT) is important for preventing drop-out from the waiting list for LT or further enlargement of the adaptation of LT. Hepatic arterial infusion chemotherapy with cisplatin in lipiodol and 5-fluorouracil (HAIC with lipiodol) is a novel and effective treatment for advanced HCC. Here we report a successful down-staging case of HCC by a series of therapeutic strategies using HAIC with lipiodol that provided an effective bridge to LT.

Case Report: We report a 48-year-old patient with severe liver cirrhosis, a 7.5 cm primary HCC in segment 8 and a 1.2 cm satellite lesion in segment 4, which was outside both Milan Criteria and University of California, San Francisco (UCSF) Criteria. We offered HAIC with lipiodol therapy using a temporary indwelling catheter system with intent to down-stage prior to LT. Six months after initial treatment, complete tumor remission was achieved. However, the patient developed HCC recurrence within the Milan Criteria on further six months later, and LT was performed. Examination of the explant revealed pathologic complete response of both primary and satellite lesions treated by HAIC with lipiodol showed pathologically complete necrosis. This patient is free from recurrence 5 years after LT.

Conclusion: HAIC with lipiodol using a temporary indwelling catheter system may be effective to down-stage HCC prior to LT.

Keywords: Liver transplantation; Hepatocellular carcinoma hepatic arterial infusion chemotherapy; Down-staging

Introduction

Hepatocellular Carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer-related death worldwide [1]. Most of HCCs develop in the setting of liver cirrhosis [2]. When selecting a treatment for a patient with HCC, both tumor stage and liver function are taken into consideration. There are many therapeutic modalities used for local control of tumor and improved survival for patients who have HCC with compensated liver cirrhosis, e.g. hepatic resection, ablation therapy and Transcatheter Arterial Chemoembolization (TACE) [2]. However, the only established therapy for the patients with HCC and decompensated liver cirrhosis is Liver Transplantation (LT) [3]. LT has been shown to have excellent long term survival, above 70% at 5 years, and low recurrence rates in patients with HCCs meeting the Milan criteria (single tumor ≤ 5 cm or multiple tumors; ≤ 3 nodules, ≤ 3 cm) [4]. Since a small number of patients fit the Milan criteria, other groups have proposed expanded criteria e.g. the University of California, San Francisco (UCSF) (single tumor ≤ 6.5 cm or multiple tumors; 2-3 nodules ≤ 4.5 cm and total tumor diameter ≤ 8 cm) [5], or down-staging of HCC strategy prior to LT have been proposed to decrease the drop-out from the waiting list of LT or to make the patient currently outside the Milan criteria eligible for LT [6]. TACE or various ablation therapies have been reported as effective loco-regional treatments for the down-staging of HCC prior to LT [7]. Recently, we have reported that HAIC with cisplatin in lipiodol and 5-fluorouracil was effective for the patients with advanced HCC [8]. This cisplatin-lipiodol plus 5-FU regimen comprised a combination of 50 mg cisplatin suspended in 5-10 ml lipiodol, bolus infusion of 250 mg 5-FU and continuous infusion of 5-FU (1250 mg/ 5 days). The feature of this HAIC with lipiodol treatment is a significant survival benefit with 86.3% response rate for tumors. High response rates may be used to down-stage of HCC, which may be used as a novel treatment of HCC prior to LT.

We report a case of successful down-staging of HCC that was beyond both the Milan criteria and the UCSF criteria by a series of therapeutic strategies using HAIC with lipiodol which provided an effective bridge to LT. This is the first report using HAIC with lipiodol for down-staging of HCC prior to LT.

Case Report

A 48-year-old man with Hepatitis C Virus (HCV) related cirrhosis was admitted to the hospital in August 2008. A Computed Tomography (CT) angiography showed a 7.0 cm × 7.5 cm homogeneously enhancing main tumor in segment 8 and a 1.2 cm satellite enhancing lesion in segment 4 without evidence of vascular invasion (Figure 1a and 1b). Laboratory data on admission (Table 1) were as follows: α-fetoprotein (AFP); 8.6 ng/ml, des-gamma-carboxy prothrombin (DCP); 439 mAU/ml, platelet count; 6.3 × 104 /ml, total bilirubin; 3.0 mg/dl, prothrombin time; 48.3% (INR 1.81), albumin 2.9 g/dl and NH3 125 μg/dl. His liver function was Child-Pugh class C (score 10). His tumor stage was BCLC D in the Barcelona Clinic Liver Cancer (BCLC) stage [9]. Since his tumor characteristics exceeded both the Milan criteria and the expanded UCSF criteria (Table 2), we performed the loco-regional therapy for down-staging prior to LT.

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Angiography of the left brachial artery revealed that the primary lesion was fed by the Right Hepatic Artery (RHA) from the Superior Mesenteric Artery (SMA), and the satellite lesion was supplied by the Middle Hepatic Artery (MHA) from the common hepatic artery (Figure 2a and 2b). We felt that the primary lesion would be difficult to treat using only TACE because of the large tum. or size and poor liver function, so we selected to use HAIC with lipoid [8] using a temporary indwelling catheter system [10], shown in Figure 2. The series of therapeutic strategies using a temporary indwelling catheter system are showed on Figure 4. The catheter tip was placed in the RHA and the drugs were directly only to the RHA to prevent decline of liver function (Figure 2a). The inserted portion (left brachial artery) of the temporary catheter system was fixed inside the forearm during treatment (Figure 2c and 2d). When the catheter was removed after one scheduled course, additional TACE treatment was selectively performed on the remnant main and satellite lesions (Figures 2e and 2f). A CT scan performed 6 months after the initial treatment showed complete retention of lipiodol in both the main and satellite lesions with absence of arterial enhancement, suggestive of Complete Remission (CR) (Figure 3a). DCP level at that time decreased to 29 mAU/ml. However, 6 months after accomplishment of CR, CT angiography detected 1 cm and 7 mm enhanced lesions in liver segments 8 and 4, which suggested HCC recurrence within the Milan criteria (Figure 3b and 3c). Child-Pugh at that time was class C (score 10) (Table 1). The patient was referred for LT and was listed with a MELD score of 17. LT was performed at Kyusyu University one year after initial diagnosis of HCC. The explant showed signs of cirrhosis, with complete necrosis of with the primary and satellite tumors, and 8 viable nodules which indicated pathologically well to moderately differentiated HCCs in segments 4 and 8 with no sign of vascular invasion (Figure 3d-3f). We have performed regular follow-up CT and US after LT. The patient is alive and free of from HCC recurrence at 6 years after the initial diagnosis and 5 years after LT.

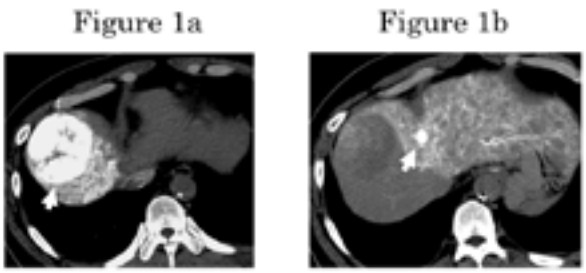


Figure 1: Computed tomography (CT) angiography showing two enhancing tumors seen at first admission. A 7.5 cm diameter primary lesion in segment 8 (1a) and a 1.2 cm diameter satellite lesion in segment 4 (1b) were detected on CT hepatic arteriography. These lesions showed low attenuation in CT arterial portography (data not shown). Arrow shows each tumor nodule

		Normal		On initial diagnosis		Before liver transplantation	
WBC	<9800		/ml	2900		2300	
Hb	>13.5		g/dl	13.		14.	
Plt	>13.1		x104 /ml	6.		4.	
PT (INR)	>70 (<	1.0)	%	48.	(2.)	40.0	(2.)
NH_3	<86		pg/dl	125		123	
AST	<40		U/1	76		82	
ALT	<40		U/1	45		42	
T.Bil	<1.0		mg/di	3.0		2.	
Alb	<4.0		g/dl	3.		3.	
AFP	<10		ng/m1	9.		13.	
L3	ND		%	ND		ND	
DCP	<40		mAU/m1	439		116	
HCV-Ab	(-)			(+)			

Table 1: laboratory findings on initial diagnosis and before liver transplantation.

	Tumor diameter	Tumor number	Total tumor diameter
Milan Criteria	50 mm (single nodule)	3 (less than 30 mm)	
UCSF Criteria	65 mm (single nodule)	2-3 (less than 45 mm)	less than 80 mm
Case patient on initial diagnosis	75 mm	2	85 mm

Table 2: The tumor status of case patient on initial diagnosis and the criterias for liver transplantation.

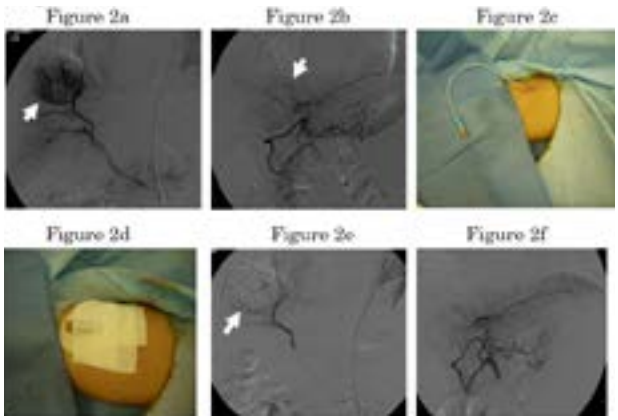


Figure 2: Angiography from left brachial artery: (a) The main lesion (Arrow) was fed by the right hepatic artery (RHA) branch of the superior mesenteric artery. The temporary indwelling catheter was placed in the RHA and treatments were performed according to the treatment schedule. (b) The satellite lesion (Arrow) was fed by the middle hepatic artery branch of the common hepatic artery. (c,d) The temporary indwelling catheter system was set up via left brachial artery. The temporary catheter system was fixed inside the forearm to prevent dislocation during the scheduled treatment. (e,f) Angiography after one treatment course, described in Table 3, showed both main and satellite lesions with no enhancement. Arrow shows the treated tumor nodules.

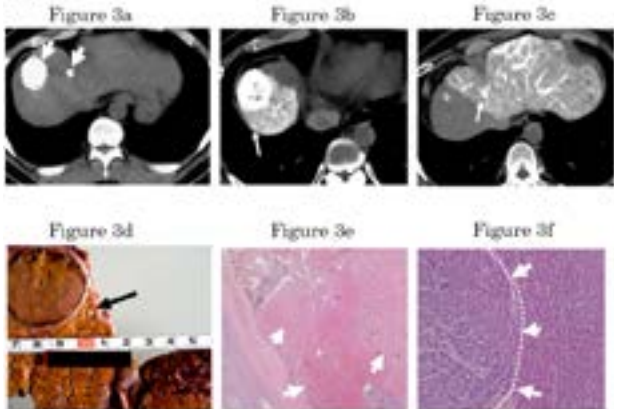


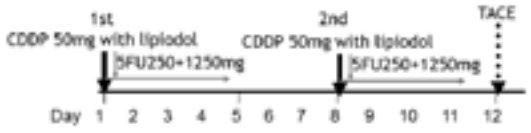
Figure 3: (a) Computed tomography (CT) 6 months after the initial treatment showed complete retention of lipiodol within the both treated lesions without any enhancement (Arrow). (b,c) CT angiography 12 months after initial treatment showed two radiologically detectable small HCCs in segment 8 and 4 of the liver (Arrow). (d) Small HCCs in a total of 8 nodules (Arrow) were detected in the explanted liver. (e) The primary tumor showed pathologic complete necrosis (Arrows). (f) The recurrent lesions showed well to moderately differentiated HCCs. (Arrows, The dot line shows the borderline between HCC and surrounding tissue.)

Discussion

Recently, down-staging strategies of HCC prior to LT have widely accepted with increasing evidence [11]. Many treatment modalities have been advocated for either down-staging or bridging patients to LT, i.e. Radiofrequency Ablation Therapy (RFA), TACE or radioembolization, radiation and hepatic resection. However, each treatment has drawbacks as loco-regional treatments prior to LT. RFA has been established as a safe and effective loco-regional treatment for small early HCC (mainly less than 2-3 cm) [12]. Several authors have reported that RFA may be an effective treatment for down-staging of HCC prior to LT [13,14]. However, the utility of RFA has been limited by tumor size in many cases [15]. The utilization of hepatic resection has been limited by tumor burden and the patient's liver function. Several authors have reported that TACE prior to LT was effective for HCC exceeding the Milan Criteria [16,17]. Down-staging HCC by TACE is possible in about one-third of LT candidates according to Graziadei's or Roayaie's reports [16,17]. However, a high drop-out rate and high HCC recurrence rate was also reported for these patients. Since TACE for HCC with portal invasion is difficult to perform because of the possibility of hepatic insufficiency or hepatic infarction, the adaptation of TACE may be limited [18]. Radioembolization and radiation have been also reported as an effective therapeutic modality prior to LT [19,20]. However, these treatments can also cause severe liver dysfunction for decompensated liver cirrhotic patients. Recently, we have reported the efficacy and safety of HAIC with cisplatin suspended in lipiodol and 5-FU for advanced HCC [8]. This treatment produced a high response rate (86.3%) and long prolonged survival (the median survival time; 33 months) for the patients with HCCs with vascular invasion. In the present case, transient complete tumor remission was achieved without depletion of liver function by only one course of HAIC with lipiodol using a temporary indwelling catheter system. In many reports of HAIC, the complications associated with indwelling catheters are raised, e.g. vascular occlusion of detained artery or problems with implanted port [21,22]. In our patient, we used a temporary indwelling catheter system for preventing the above complications. This temporary system can reduce many technical complications related with conventional indwelling catheter systems since neither putting the catheter for long term nor implanting port [10]. This temporary catheter system made possible a set of therapeutic strategies using HAIC with lipiodol, as described in Figure 4. Taken together, the series of therapeutic strategies of HAIC with lipiodol via a temporary indwelling catheter system may be useful with regard to both anti-tumor effect and patient safety.

In conclusion, we report a case of successful down-staging of HCC exceeding the UCSF criteria through a series of therapeutic strategies of HAIC with cisplatin in lipiodol and 5-FU using a temporary indwelling catheter system. This treatment strategy may be a pivotal treatment modality for down-staging prior to LT. However, prospective large studies and intention-to-treat analysis will be needed to validate this approach.

Table 3: The series of treatment schedule of HAIC with lipiodol using a temporary indwelling catheter system



A temporary indwelling catheter system is set up for the targeting artery. 50 mg cisplatin mixed with lipiodol is injected under the angiography. After 250 mg 5-fluorouracil (5-FU) bolus injection, 1250 mg 5-FU is continuously injected using balloon pump for 5 days. This treatment session is performed two times. After two treatment sessions, TACE is selectively performed to the remnant lesions. Following TACE, this catheter system is withdrawn.

Figure 4: Temporary catheter system.

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