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A Case of Advanced Multiple Hepatocellular Carcinomas with Portal Vein Tumor Thrombosis Successfully Treated by Oral Tegafur/Uracil

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ABSTRACT

A case of advanced multiple hepatocellular carcinomas (*HCC*) *with portal vein tumor thrombosis successfully treated by oral tegafur/uracil is reported. A* 69*-year-old Japanese woman with advanced HCC with tumor thrombosis underwent transcatheter arterial infusion chemotherapy in April* 2001. *However,* 1 *year later, the patient experieced a recurrence with advanced multiple HCC with portal vein tumor thrombosis and ascites. Treatment with oral tegafur/uracil was started in May* 2002 *and resulted in the partial response of liver tumors and the complete improvement of ascites. She remained in good health for about* 6 *years. This case strongly suggests that oral tegafur/uracil is an effective treatment for some cases of advanced HCC with portal vein tumor thrombosis.*

Keywords: *Advanced Hepatocellular Carcinoma, Portal Vein Thrombosis, Oral Tegafur/Uracil, Chemotherapy*

1. Introduction

Various treatment modalities, such as transcatheter arterial chemoembolization (TACE), percutaneous ethanol injection therapy (PEIT), and radiofrequency ablation (RFA) have been recently developed and are used worldwide to treat patients with hepatocellular carcinoma (HCC) [1-4]. However, the use of these modalities for advanced HCC is limited.

On the other hand, it has been reported that patients with multiple HCCs with tumor thrombosis in the major portal branches were successfully treated with intra-arterial 5-fluorouracil perfusion chemotherapy combined with subcutaneous interferon-alpha administration [5,6]. Such combination therapy may be a promising treatment modality for advanced HCC with tumor thrombosis. However, the prognosis of advanced HCC with tumor thrombosis (VP4) is still unsatisfactory. A rare case of advanced multiple HCCs with portal vein thrombosis (VP4) that was successfully treated by oral tegafur/uracil (UFT®, Taiho Pharmaceutical Co. Ltd. Tokyo, Japan) and had a good prognosis, with survival for more than 5 years, is reported.

2. Case Presentation

A 69-year-old woman with advanced HCC with tumor thrombosis underwent transcatheter arterial infusion chemotherapy in April 2001. However, 1 year later, the patient experienced advanced multiple HCCs with portal vein thrombosis (VP4) and ascites (**Figure 1**). As shown in **Table 1**, the patient had decompensated liver cirrhosis due to hepatitis C virus. On admission, the alpha-fetoprotein (AFP) level was 317.2 ng/ml, and the level of tumor marker known as protein-induced vitamin K antagonist II (PIVKA-II) was 162,210 mAU/ml. Treatment, such as TACE, PEIT, or RFA, was not administered. She was treated with oral UFT® in May 2002. This treatment resulted in the partial response of liver tumors and the complete improvement of ascites (**Figure 2**). At the same time, the AFP level was 303.9 ng/ml and the PIVKA-II level was 468 mAU/ml.

In January 2005, the AFP level was 93.7 ng/ml and the PIVKA-II level was 38 mAU/ml. The patient then experienced recurrent tumors in liver segment five, for which TACE was performed each time.

The patient remained in good health for about 6 years.

In July 2008, acute peritonitis developed due to tumor invasion into the duodenum and the patient died.

3. Discussion

Several treatments, such as TACE, PEIT, RFA, and hepatic resection, have been established as effective and safe therapeutic modalities for HCC [7,8]. However, frequent HCC recurrence, even after curative treatment, and advanced stages of HCC, such as in cases with portal invasion, remain major clinical problems.

The product UFT® combines tegafur, a prodrug of 5-fluorouracil, with uracil, a biomedical modulator, in a molar ratio of 4:1. UFT® has been reported to be effective against colorectal and lung adenocarcinomas as well as HCC. Therefore, the patient in this case report, with advanced multiple HCCs with portal vein tumor thrombi, was treated with UFT®. As a result, this patient showed marked tumor regression without side effects and had a good prognosis.

Recently, UFT® has received considerable attention as

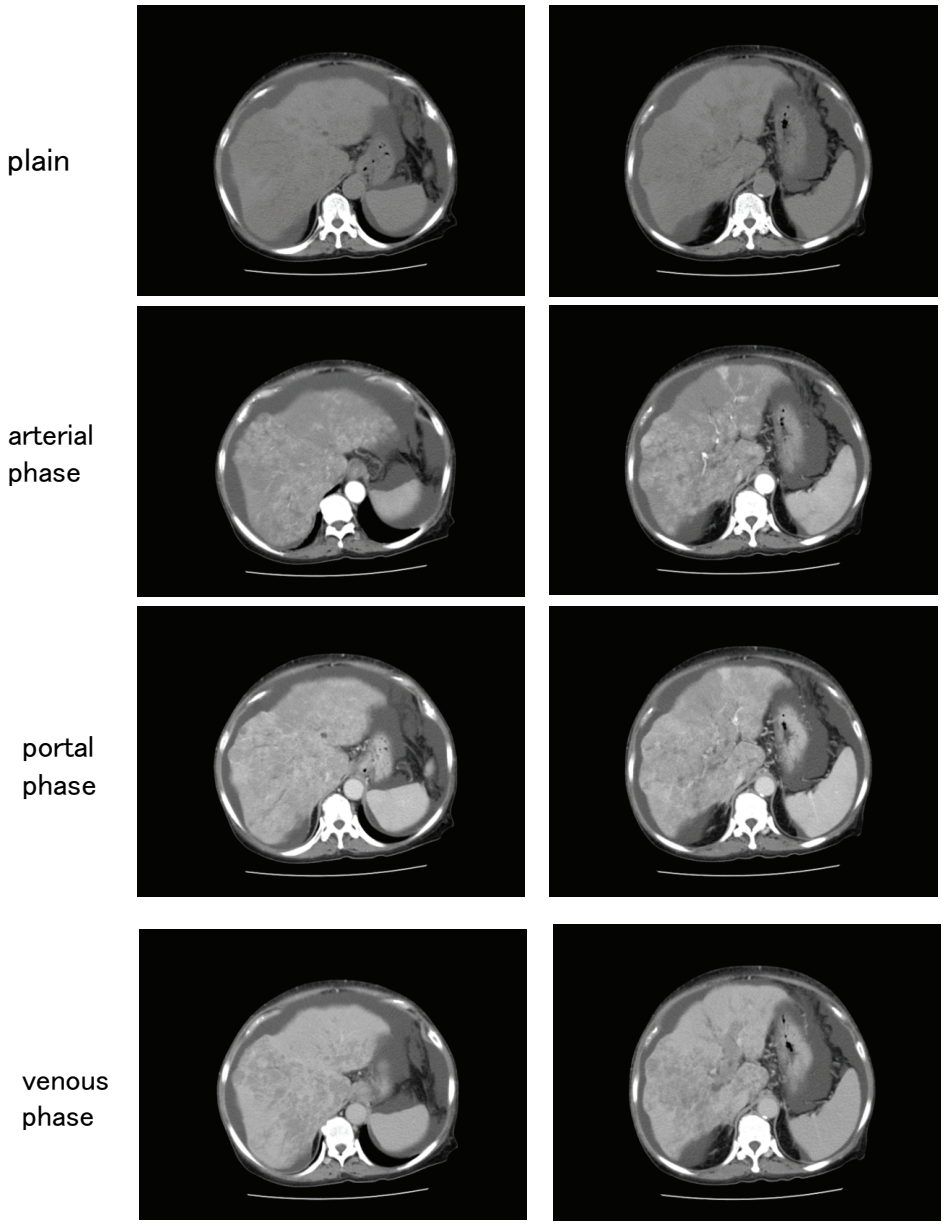

Figure 1. A large mass occupies the entire liver and tumor thrombi are apparent in main portal vein. Moderate ascited is detected.

Table 1. Laboratory data on admission.

WBC	8800/ul	BS	14l mg/dl
Neutro	60.9%	CRP	2.52 mg/dl
Eosin	3.6%	Na	139 mEq/L
Baso	0.5%	k	3.6 mEq/L
Mono	9.1%	CI	99 mEq/L
Lympho	25.9%		
RBC	508×10^4/ul		
Hb	16.1 g/dl	AFP	317.2 ng/ml
Ht	48.0%	PIVKA-II	162210 Mau/ml
PIt	15.6×10^4/ul		
TP	7.1 g/dl		
Alb	3.2 g/dl		
BUN	18 mg/dl		
Cr	0.7 mg/dl		
T-Bil	1.5 mg/dl		
D-Bil	0.6 mg/dl		
AST	122 IU/L		
ALT	39 IU/L		
PT %	53.3%		
PT INR			
LDH	357 U/L		
γ -GTP	330 U/L		

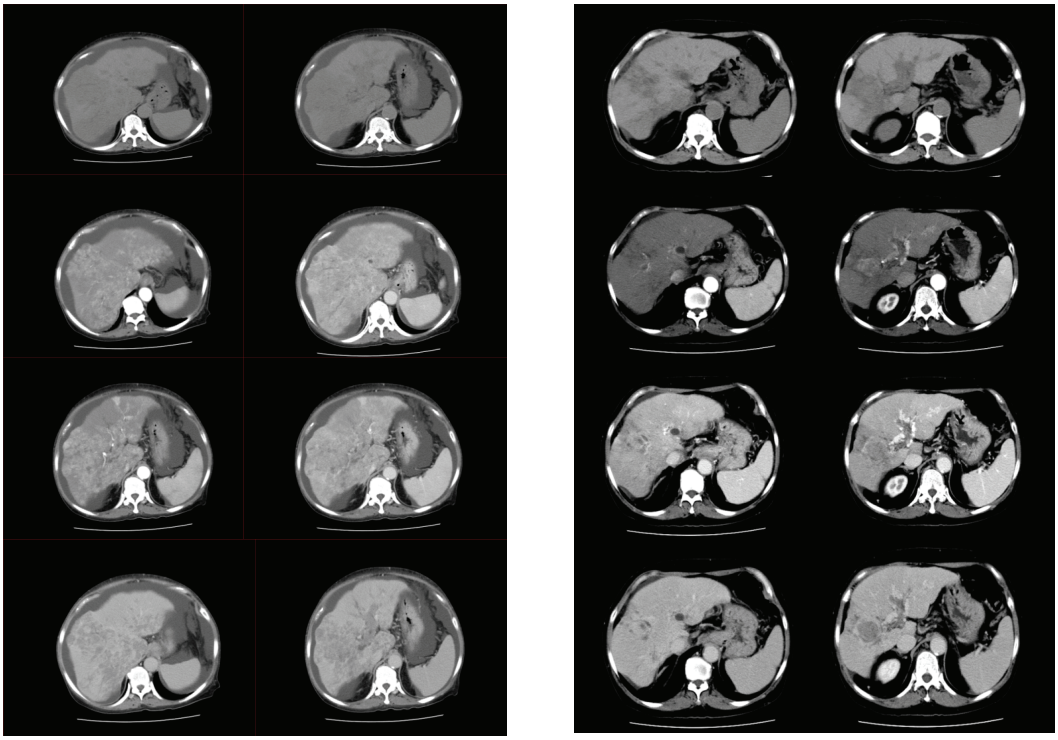

Figure 2. A large mass occupied the entire liver become smaller 8 months after treatment. Though tumor thrombi in main portal vein do not disappear, cavernous transformation by portal vein is formed. Ascites is disappeared.

an effective anticancer therapy [9-12]. However, the effectiveness of UFT® has been controversial, as some studies have suggested that the efficacy of UFT® may have been overestimated [13].

Tegafur is slowly metabolized by mitochondrial cytochrome 450 to 5-fluorouracil (5-FU) and the additional uracil potentiates the efficacy of tegafur by inhibiting its catabolism [14,15]. The mechanism of this inhibition by uracil is the blockage of dihydropyrimidine dehydrogenase (DPD) activity [16]. Therefore, rapid degradation of 5-FU by high levels of DPD activity in hepatoma cells has been implicated in 5-FU insensitivity. On the other hand, patients with low DPD activity in HCC tissues have a high concentration of 5-FU, which may have a potent anticancer effect against HCC. In this regard, Baba H *et al.* showed that some HCC tissues have low DPD activity and such HCC tissues may be 5-FU sensitive [17].

Recently, we showed that UFT® administration after TACE in cases of advanced HCC was advantageous and that it contributed to the inhibition of tumor angiogenesis through vascular endothelial growth factor (VEGF) [18]. In addition, some studies have shown that UFT® inhibits tumor angiogenesis in several cancer types. Our findings suggest that the HCC derived from the patient in this case report had low DPD activity and that tumor angiogenesis was effectively inhibited by UFT® treatment.

In conclusion, the present report demonstrates marked tumor regression and a good prognosis following oral UFT® treatment in a patient with advanced multiple HCCs with portal vein tumor thrombosis. This case strongly indicates that oral UFT® can be an effective treatment for some cases of advanced HCC with tumor thrombosis (VP4).

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