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CASE REPORT

Puncture injection of para-toluenesulfonamide combined with chemoembolization for advanced hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is difficult to eradicate due to its resilient nature. Portal vein is often involved in tumors of large size, which exclude the patient from surgical resection and local ablative therapy, such as percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) because they were considered neither effective nor safe. Currently, there is almost no effective treatment for HCC of such condition. As a unique antitumor agent in form of lipophilic fluid for local injection, para-toluenesulfonamide (PTS) produces mild side effects while necrotizing the tumor tissues quickly and efficiently. Being largely different from both PEI and RFA therapies, PTS can disseminate itself in tumors more easily than other caustic agents, such as alcohol. So PTS may offer additional benefit to HCCs with vascular involvement. We herein describe a 70-year-old HCC patient who was treated with the combination of PTS injection and transcatheter arterial chemoembolization, resulting in a significantly improved clinical prognosis.

INTRODUCTION

Transcatheter arterial chemoembolization (TACE) has become the standard treatment for unresectable hepatocellular carcinoma (HCC). Nonetheless, clinical outcomes are often unsatisfactory, especially for recurrent cases. As a novel anticancer agent, para-toluenesulfonamide (PTS) is completely different from genetic, classical chemical and molecular targeted drugs, and has shown amazing antitumor effect in animal HCC experiment[1,2]. Primary pharmacological studies suggest that PTS inhibits tumor growth by acting as a tumor necrotizing agent[1,2]. PTS may strengthen the effect of TACE in advanced HCC. We herein report a patient with refractory HCC who was treated with PTS injection after TACE, which resulted in a very good clinical prognosis.

CASE REPORT

The patient was a 70-year-old man. A mass was found in his right lobe of the liver in May 2004. He refused

to receive further diagnosis and treatment until January 2006 when he began to suffer from anorexia and dull abdominal pain. Computer tomography (CT) detected a large mass (about 9.5 cm × 8.5 cm × 8.5 cm) in the right lobe of the liver with significant enhancement (Figure 1A). Alpha-fetoprotein (AFP) level was > 1210 ng/mL. He was diagnosed with a histologically proven HCC. Due to the large tumor size and invasion to the portal vein, the patient underwent two rounds of TACE with an interval of one month. The drugs used were 5fluoro2deoxyuridine (1.0 g), epirubicin (40 mg) and lipiodol (10 mL). In May 2006, three months after the second TACE, a routine postoperative CT scan found a minimal decrease in tumor size with necrosis < 25% (Figure 1B), while the AFP level was still > 1210 ng/mL. The second angiography revealed hepatic artery-portal vein fistula and hepatic arteriovenous fistula. Although additional gelfoam pieces were used and the fistula disappeared after embolization, a poor prognosis was still predicted. Consequently, PTS (Beijing Vision Drugs Development Ltd., Beijing, China) was used to enhance the effect of TACE after informed consent was obtained from the patient.

The mass was punctured percutaneously with a fine needle under CT guidance. After the tip of the needle was manipulated into the mass, about 10 mL of PTS was injected intratumorally in a multi-point fashion. This injection was repeated four times. The interval between each procedure was between three and seven days according to the patient's clinical condition. When all five injections were completed, the AFP level dropped to 1106 ng/mL. Two months later, a routine follow-up CT showed moderate improvement, no blood being supplied to the tumor (Figure 2A), and the AFP level dropped further down to 185 ng/mL. In an attempt to investigate the increased efficacy, PTS injections were repeated three more times. Following a routine check two months later, a CT examination of the abdomen demonstrated complete deposit of oil and no signs of recurrence or tumor embolism (Figure 2B). Furthermore, the AFP was within the normal reference range (4.44 ng/mL).

The only side effect of this therapy was abdominal pain, which occurred after the first two procedures, but subsided shortly thereafter in approximately 10 min. No other discomfort was noted post-procedurally. Four years following the last PTS treatment, the patient exhibited no evidence of recurrence and no other abnormal liver function serum values, and he had a normal serum AFP level. The AFP level changes in the course of the treatment are summarized in Table 1.

Table 1 Changes of alpha-fetoprotein in the course of therapy

Time (yr-mo)	APF (ng/mL)	TACE	PTS injections
2005-4	533.8		
2006-1	> 1210	Yes	
2006-2	> 1210	Yes	
2006-5	> 1210	No	5 times
2006-6	1106	No	
2006-8	185	No	3 times
2006-10	4.44	No	
2008-6	2.69	No	
2009-3	3.84	No	
2010-4	3.86	No	

A sharp decrease in alpha-fetoprotein (AFP) levels occurred right after para-toluenesulfonamide (PTS) injections. The initial series of transcatheter arterial chemoembolization (TACE) failed to control the tumor (although the TACE's effect on fistula embolization was irreplaceable). PTS treatment appeared to be effective and well-tolerated. A 4-year follow-up showed no sign of reoccurrence.

DISCUSSION

Despite the fact that TACE has become the standard treatment for unresectable HCC, it is frequently unsuccessful. Rate of local recurrence following tumor resection is also unacceptably high[3-6]. In addition, TACE alone fails to control the tumor completely, often leading to a poor prognosis. In this report, the patient had received two sessions of TACE and embolized the fistula successfully before admission. Although little effect was got on HCC, the TACE did restrict the tumor's growth and metastasis that made it possible for PTS to eradicate the tumor later. Due to the large tumor size and involvement of the portal vein, this lesion was inoperable, and other local ablative therapies, such as percutaneous ethanol injection, microwave coagulation therapy and radiofrequency ablation (RFA) were considered neither effective nor safe. Complications caused by these modalities may result in a high mortality rate. Therefore, we attempted to treat the patient with the combined administration of PTS and TACE. Consequently, the patient's condition was significantly improved with satisfactory tumor control and without severe complications.

Para-toluenesulfonamide (P-TSA) is the active ingredient in PTS. The P-TSA is a white, odorless, crystalline substance that has a very low solubility in water. The molecular formula is $C_7H_9NO_2S$. The injection solution is a clear, colorless, oil liquid with a characteristic odor and contains 330 mg/mL P-TSA. PTS has been approved for clinical trial injection in both 3 mL ampoule and 5 mL ampoule. Recommended storage temperature is 25 ℃ (77°F), although a range of 10-35 ℃ (50-90°F) is acceptable. Long-term exposure to light should be avoided.

PTS produces mild side effects while necrotizing the tumor tissues effectively and thoroughly. However, PTS is still in the phase of clinical trial, and the mechanism of the antitumor activity of PTS is still unclear. Primary pharmacological studies suggest that PTS inhibits tumor growth by acting as a tumor necrotizing agent[1,2].

It has been shown that PTS does not cause serious side effects that have been observed frequently in conventional chemotherapy and locoregional therapy (e.g., RFA, alcohol injection, *etc.*), such as fever, bone marrow suppression, stomach discomfort, hemorrhage, needle-track seeding, lesion abscess , liver failure, biloma, biliary

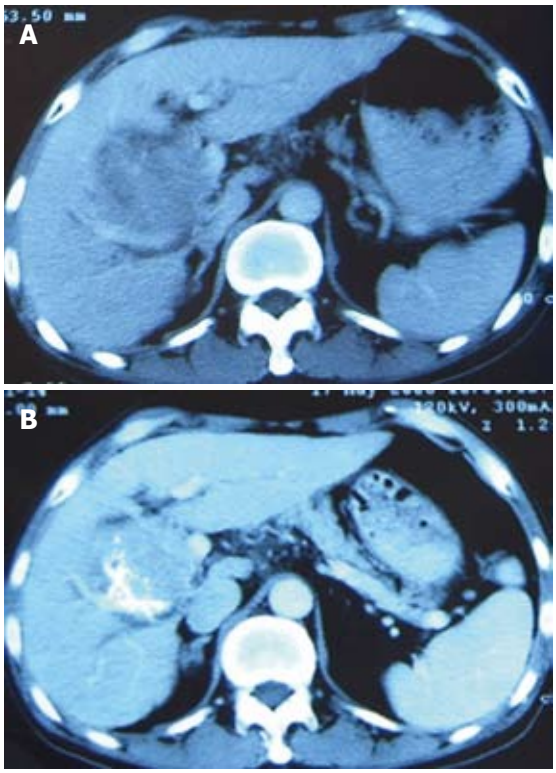

Figure 1 Transcatheter arterial chemoembolization had little effect on the hepatocellular carcinoma, but restrict the size of tumor mass. A: Contrast computer tomography (CT) before the procedure showed a huge hypodense mass with remarkable enhancement and portal vein embolus; B: Two months after the initial 2 series of transcatheter arterial chemoembolization, contrast CT still found a hypodense nodule with partial contrast enhancement and portal vein invasion.

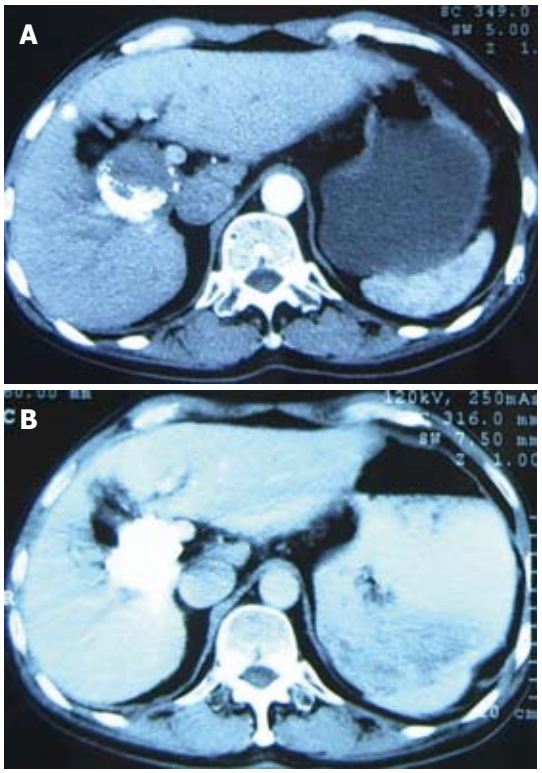

Figure 2 The following para-toluenesulfonamide injections resulted in a significantly improved clinical prognosis. A: Contrast computer tomography (CT) after the first 5 para-toluenesulfonamide (PTS) injections demonstrated a decreased nodule with partial retention of lipiodol. Remarkable necrosis and no blood supply were found in the rest part of the tumor; B: Two months after the last 3 PTS injections, contrast CT revealed homogeneous dense retention of lipiodol within the entire tumoral mass and no recurrent lesion was identified.

stricture, portal vein thrombosis, and hemothorax[7-9]. Because most anticancer drugs are corrosive and extremely toxic, they will destroy both cancer cells and normal cells when given locally at high concentrations. PTS is a local therapeutic drug that is injected directly into the tumors and has been shown to cause selectively necrosis in a variety of cancers with minimal damage to normal tissues[2,10].

Local ablative therapies share similar difficulties with surgical resection. The size, site and number of tumors, vascular and extrahepatic involvement as well as liver function of the patient pose a relatively minor effect on the usage of PTS[8,9]. PTS is a more readily available alternative to the local ablative therapies.

PTS, in form of lipophilic fluid, kills tumor cells by a rodent mode. Local and intratumoral injection is the optimal route of PTS delivery. Being largely different from both alcohol and RFA therapies, PTS can disseminate itself in tumors more easily than other caustic agents, such as alcohol. Therefore, a successful PTS administration is to approach to the anatomically dangerous or hard-to-reach areas and diffuse to the target area and induce injury to the tumor tissues. This might be the mechanism as to why PTS combined with TACE could effectively treat the HCC with vascular invasion. As a locoregional antitumor agent, PTS is safe[1,2,10]. But up to date, PTS is still only a locally-used antitumor agent. It is intended mainly for the treatment of a limited number of detectable tumors. PTS is not suitable to be used alone for the treatment of multifocal HCCs.

This case report demonstrated that PTS is effective in treating liver cancers by intratumoral injection, which was hypothesized to enhance the effect of TACE. This combined therapy may prove to be useful in the treatment of patients with refractory and recurrent HCC. Therefore, subsequent large, multi-center, randomized controlled studies are needed to facilitate the introduction of PTS as a novel modality for the treatment of cancers.

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