p53 gene therapy for pulmonary metastasis tumor from hepatocellular carcinoma

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The objective of this study is to explore the safety, efficacy, and administration method of the recombinant adenovirus p53 gene (rAd-p53, or gendicine) in the treatment of pulmonary metastasis tumor from advanced hepatocellular carcinoma (HCC). Pulmonary metastasis tumors from HCC in 20 patients were treated by using transcatheter bronchial arterial gendicine infusion combined with transcatheter arterial embolization and intratumor injection of gendicine if the maximal diameter of a metastatic tumor is greater than or equal to 3 cm. Three patients received the combined therapy three times, seven received it twice, and ten received it once. Eighteen patients were followed for 2–12 months after treatment and two patients were lost to follow-up. Spiral computed tomography was performed during follow-up visits to monitor tumor progress. Lung metastasis tumor disappeared in four patients and the tumor size decreased in six patients, remained unchanged in five, and increased in three patients. Overall, the clinical symptoms were alleviated in 16 patients (88.9%) and were exacerbated in two patients. New metastatic lesions were found in eight patients. There were no serious adverse events except for self-limited fever (38°C–39.5°C), which was found in 16 patients. Transcatheter bronchial arterial gendicine infusion combined with transcatheter arterial embolization, with or without intratumor injection of gendicine, is a safe, effective therapy for the treatment of pulmonary metastasis tumor from HCC. ***Anti-Cancer Drugs*** **21:882–884 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors and the lungs are the most common sites of metastasis when HCC progresses to an advanced stage. After comprehensive treatment of advanced HCC, a patient's survival time is prolonged but is accompanied by the development of a late higher rate of pulmonary metastasis. Thus, the treatment of the pulmonary metastasis tumor may further prolong the survival time of the HCC patients. A few studies reported that it was effective and safe to use p53 gene therapy to treat primary lung cancer. But there is no report of using p53 gene therapy to treat pulmonary metastatic tumor from HCC. In this study, we showed that p53 gene therapy is a safe and effective method for the treatment of pulmonary metastatic tumor from HCC.

Methods

The rAd-p53, or gendicine, was from SiBiono GeneTech Co. Ltd (Shenzhen, Guangdong, People's Republic of China). From January 2008 to September 2009, we treated 20 HCC patients with pulmonary metastatic lesions. All of the 20 cases were diagnosed as advanced HCC by fine needle aspiration biopsy and by MRI or multislice computed tomography, eight of them with pulmonary metastasis at primary diagnosis, and 12 patients developed pulmonary metastasis after hepatic transcatheter arterial chemoembolization (TAE) (10 patients) and surgical resection (two patients). The patients were aged between 48 and 80 years with a median age of 52 years. Fifteen patients were male and five patients were female. Using the Liver Function Child–Pugh grade, seven patients were grade A, five patients were grade B, and eight patients were grade C. The patients' characteristics are summarized in Table 1.

Pulmonary metastatic tumors were treated using transcatheter bronchial arterial gendicine infusion combined with transcatheter arterial embolization (TAE), and by intratumor injection of gendicine if the maximal diameter of the metastasis tumor was greater than or equal to 3 cm. The volume of 2–20 ml lipiodol emulsion was injected after gendicine infusion.

Before p53 gene therapy, all patients underwent routine blood tests, liver and kidney function tests, and the chest and upper abdomen computed tomography (CT) or MRI horizontal scan and enhanced scanning. If the diameter of a single lung metastatic tumor nodule was greater than or equal to 3 cm, CT-guided multi-point and multi-direction intratumor gendicine injection was administered. The 10^{12} virus particle (vp) diluted in 2 ml physical saline was injected if the tumor diameter was between 3 and 6 cm

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Table 1 Patients' characteristics

Characteristics	Statistics
Age (years)	53 ± 24.4 (48–80)
Sex	
Male	15 (75%)
Female	5 (25%)
Number of metastatic nodules in lungs at treatment	
1	15 (75%)
2	4 (20%)
≥ 3	1 (5%)
Metastatic tumors in right or/and left lungs	
Right	12
Left	8
Both	3
Metastatic tumor size (cm)	3.1 ± 3.8 (0.8-6.4)
≤ 3	15
≥ 3	13
Primary HCC therapy	
Partial hepatic resection	5 (25%)
TAE	15 (75%)

HCC, hepatocellular carcinoma; TAE, transcatheter arterial chemoembolization.

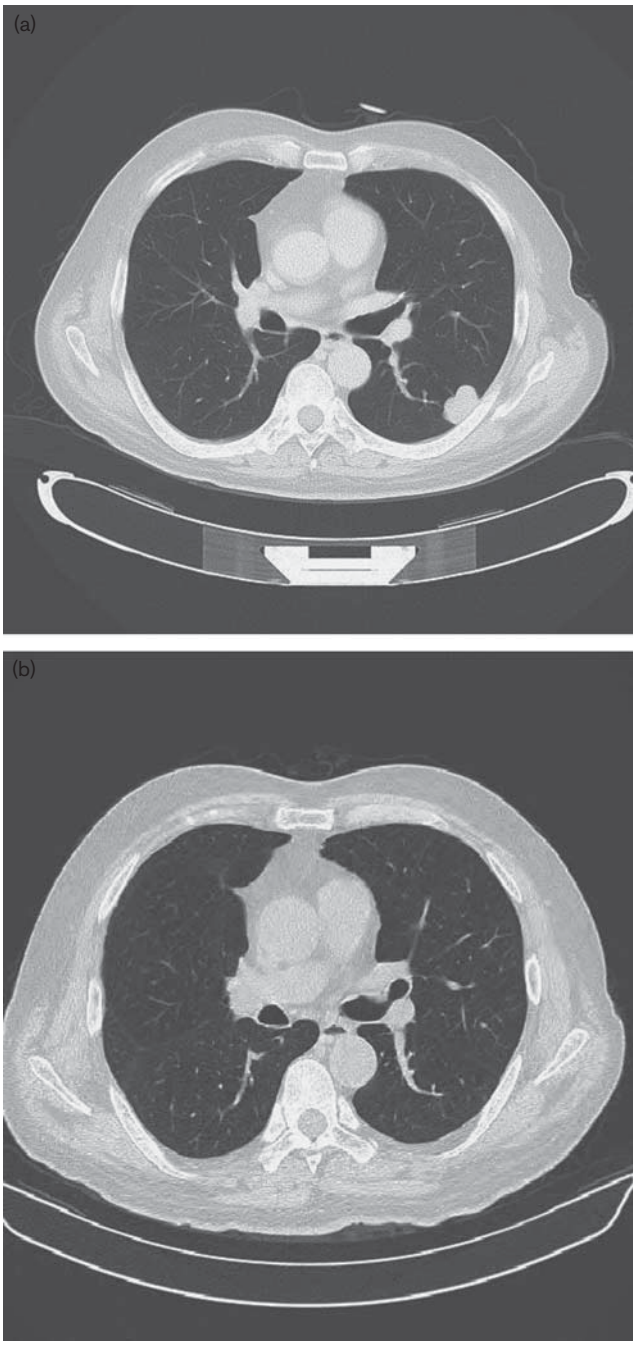
and 2×10^{12} vp was injected if the tumor diameter was greater than 6 cm. After 3–5 days of intratumor injection, 2×10^{12} vps were injected through a tumor branch of the bronchial artery and TAE was applied after the injection. The catheter was inserted to a bronchial artery through one femoral artery under CT guidance. The contrast agents were injected to find the tumor arterial branch.

We monitored the progress of the pulmonary metastatic tumors using spiral CT or MRI examination. If the metastatic tumor disappeared, the tumor size decreased, or the tumor size was kept stable without a new metastatic tumor for 4 weeks, these patients would be considered effective. Liver and kidney functions, blood routine (bilirubin, aminotransferase, blood urea nitrogen, creatinine, blood cells, and platelets) were tested at each visit. Clinical symptoms such as cough, chest pain, loss of appetite, fatigue, weight loss, etc were evaluated.

Results

Three patients received three sequences of the combined therapy, seven received the sequence two times, and ten received it only one time. Eighteen patients were followed for 2–12 months after therapy and two patients were lost to follow-up. The gendicine intratumoral injection was administered to 13 patients, and gendicine bronchial intraarterial injection combined with TAE was administered to 20 patients. Pneumothorax occurred in two patients after the intratumoral injection and was completely absorbed by closed drainage. The other patients did not have any complications. Sixteen patients had a fever of 38°C–39.5°C for 1–3 days after the treatment. Two patients with a body temperature of 39.5°C or higher were treated using intravenous 10 mg of dexamethasone diluted in 500 ml of 5% glucose and sodium chloride. Their body temperature decreased to normal in 1 day. Eighteen patients were followed for 2–12 months after treatment and two patients were lost to follow-up. Lung metastasis tumor disappeared in four patients and the tumor size decreased in six patients, remained unchanged in five and increased in three patients. Figure 1 shows a typical patient after intratumor injection was administered three times and TAE and bronchial arterial once Gendicine infusion was given once; left lung metastasis tumor had completely disappeared by the 1 year follow-up after treatment.

Fig. 1



(a) Left lung 3 × 4.5 cm nodule diagnosed by needle aspiration biopsy as pulmonary metastatic tumor from HCC; (b) pulmonary metastatic tumor completely disappeared.

Overall clinical symptoms were alleviated in 16 patients (88.9%) and were exacerbated in two patients. New metastatic lesions were found in eight patients. There were no serious adverse events except for fever.

Discussions

The human tumor suppressing p53 gene is located in the short arm of the 17 chromosome (17p13.1). The gene is 20 kb long and consists of 11 exons and 10 introns. The transcript of p53 gene is the 2.5 kb mRNA and the translation product is a protein with a molecular weight of 53 kDa. The p53 protein is involved in cell cycle control, DNA repair, apoptosis, and cell differentiation [1]. Its antitumor functions include cell cycle arrest and DNA repair [2], apoptosis [3], inhibition of angiogenesis, bystander effect, and inhibition of cell adhesion, invasion, and metastasis [4]. Studies have reported that approximately 50% of human tumors have various types of p53 gene mutation [5]. The loss or mutation of the p53 gene results in a dysfunctional protein and loss of the function in the inhibition of cancer development. Gendicine, the first antitumor gene product registered for marketing in the world, is a recombinant adenoviral p53 gene, in which a wild-type p53 gene was inserted in an adenovirus type 5 defect. Several studies reported that p53 gene therapy is effective for primary lung cancer [6,7]. Geng *et al.* [8] and other studies suggested that the p53 gene has a strong inhibition effect on hepatic tumor cells. The inhibitory effect was associated with the percentage of transfected cells. The intraarterial p53 gene injection combined with TAE was used to treat patients with HCC and showed great efficacy [9]. We treated 20 patients using transcatheter bronchial arterial gendicine infusion combined with TAE, and an intratumor injection of gendicine if the maximal diameter of the metastasis tumor is greater than or equal to 3 cm. Eighteen patients were followed for 2–12 months after the gene therapy. Lung metastasis tumor disappeared in four patients and the tumor size decreased in six patients, was unchanged in five and increased in three patients. The overall clinical symptoms were alleviated in 16 patients (88.9%) and aggravated in two patients. New metastatic lesions were found in eight patients. There were no serious adverse events except for fever, which may have been related to an immunoresponse to adenovirus.

Compared with chemotherapy or radiotherapy, p53 gene therapy has far fewer adverse events and improves the quality of the patients' life, which is more important for cancer patients with advanced stage disease. In this study, except for self-limited fever, no other significant adverse events were observed, which is consistent with other reports about using gendicine to treat malignant tumors [8–10]. We administered 13 CT-guided intratumor injections through the pleural space and only two patients developed pneumothorax. This complication was not commonly observed as mentioned before. Accurate direction and location of the injection are key to avoiding pneumothorax and injury to other important tissue structures.

Most tumors in advanced stages become resistant to standard therapies such as chemotherapy or radiotherapy, and some patients are not able to tolerate the side effects of standard therapies. Gene therapy will be an alternative method for these patients. Gene therapy has been proved as an effective method for many chemoresistant or radioresistant tumors [10,11]. One of advantages of p53 gene therapy is its synergic effect with both chemotherapy and radiotherapy. A combination of p53 gene therapy with other tumor treatments might be more effective.

The longest follow-up time for this group of patients is 12 months. Long-term results need to be confirmed by a longer follow-up and a well-designed random clinical trial.

Conclusion

Transcatheter bronchial arterial gendicine infusion combined with TACE, and intratumor injection of gendicine is a safe and effective therapy for the treatment of pulmonary metastasis tumor from HCC.

Acknowledgement

There is no conflict of interest.

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