

Clinical Application of a Combination Therapy of Lentinan, Multi-Electrode RFA and TACE in HCC

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ABSTRACT

Introduction: Hepatocellular carcinoma (HCC) is one of the most common cancer-related causes of death worldwide and there is a clear need for further treatment options. In this study, we assessed the efficacy of a combination of lentinan (a fungal extract), transcatheter arterial chemoembolisation (TACE) and radiofrequency ablation (RFA) in HCC patients.

Methods: Seventy-eight patients with HCC confirmed by pathology and iconographical checks were used in this study. A total of 136 tumours with a mean diameter of 6.5 cm were detected (standard deviation [SD]±0.7). Subjects were divided into four groups, receiving either TACE only, RFA

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only, RFA and TACE, or the combination group – receiving lentinan, RFA and TACE.

Results: The tumour necrosis was significantly higher in the combination group (88.6%), compared to the TACE group (37.5%), the RFA group (47.8%) and the TACE/RFA group (60.3%; $P < 0.05$). The tumour recurrence rate was significantly lower in the combination group (17.8%), compared to the TACE group (45.8%), the RFA group (34.7%) and the TACE/RFA group (29.0%; $P < 0.05$). Finally, mean survival duration was significantly higher in the combination group (28.2 months; $P < 0.05$).

Conclusion: Combination therapy involving lentinan, RFA and TACE was beneficial in terms of increasing mean survival duration, tumour necrosis and reducing the recurrence rate. Lentinan may therefore be of benefit to HCC patients.

Keywords: hepatocellular carcinoma; lentinan; radiofrequency ablation; transcatheter hepatic arterial chemoembolisation

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignant disorder and causes nearly one million deaths each year worldwide; the incidence of HCC is dramatically increasing in the USA, Europe and Asia.¹ Most sufferers are middle-aged or older, are diagnosed when the disease is quite advanced² and the tumours are large. Curative ablation or resection of the tumour can only be achieved in a minority of patients, as can liver transplantation.³ Local tumour destruction, chemoembolisation and supportive therapy are the established treatment options in HCC.⁴ Recent research combining two treatments (transcatheter hepatic arterial chemoembolisation [TACE] and multi-electrode radiofrequency ablation [RFA]) has been successful in HCC treatment.⁵ However, overall survival follow-

ing these treatments is not good and the immunological function of patients may still deteriorate – therefore further innovative treatment approaches are required.

Traditional Chinese medicine has a long history of cancer treatment by multiple pathways and multiple targets.⁶ Recently, some polysaccharides have been identified that have anticancer properties in different animal models.⁷ Furthermore, they have been demonstrated in clinical studies to benefit the immune function and reduce inflammatory factors.⁸ Lentinan, a fungal extract, has been shown to improve the treatment of cancer patients in China and Japan.³ However, the effect of a combination of lentinan with TACE and RFA to treat HCC in the clinic has not previously been studied. In this study, we assessed the efficacy of a combination of TACE, RFA and lentinan on HCC patients.

MATERIALS AND METHODS

From February 2004 to July 2006, 78 subjects were enrolled, all of which were diagnosed with HCC; 65 based on pathology research and 13 based on detection of human alpha-foetoprotein (AFP; >400 ng/ml). All subjects were recruited from the Fourth Affiliated Hospital of Harbin Medical University. The subjects consisted of 57 males and 21 females, the mean age being 60.3 years (standard deviation [SD]=9.6; range, 33–75 years). The tumour diameters ranged from 5.2 to 10.1 cm. These subjects were not suitable for operation-based therapy because of their old age, the functional disturbance of their hearts and lungs, and the position/size of the tumours. The patients were randomised into four treatment groups. Thirty-one patients received a combination therapy of lentinan, TACE and RFA (combination group); 24 patients received both RFA and TACE therapy; 11 patients received TACE therapy alone; 12 patients received RFA therapy alone. Before the treatment procedure, all of the cases were examined with respect to the AFP test, and Child-Pugh classification. The average age, the size of the tumours and Child-Pugh information of the four groups is shown in Table 1. The trial protocol was approved by the ethical committee of the Harbin Chinese Medicine University (China) and thus met the standards of the Declaration of Helsinki in its revised version of 1975 and its amendments of 1983, 1989 and 1996. In all cases the written informed consent of all the patients was obtained prior to data collection.

Clinical Procedure

In all cases, treatment complications were recorded. AFP and liver tests were completed for 1 week after the respective treatment. Both CT and AFP checks were also examined after 1 month, and periodically every 2–3 months after treatment to determine the tumour size. The treatment parameters (tumour necrosis, shrinkage and relapse) were calculated on the basis of CT scan data. If analysis suggested that the tumour was growing, TACE and RFA were used again and (in the combination group) the dosage of lentinan was increased by 100 mg per day.

RFA Group

Needles for the RFA treatment were placed using computed tomography (CT) as a guide. The equipment was the Radio Frequency Treatment Instrument WE 7568 (Peaking Welfare, China), and its export power was 100–150 W, with a frequency of 60 times per second. The ablated needle was the 14G WHK-4 multi-pole trocars with side opening (Peaking Welfare, China). On the top of the trocars, there were nine micro-electrode needles. After powering on, it could form a 5.0 cm spherical heat focus. Two methods of needle insertion were used: into-prism (with 5–8 points) or the overlap levels method (with 12 points). This was completed in accordance with a methodology previously described.⁹

TACE Group

Using the Seldinger technique,⁹

chemoembolisation was implemented via the femoral artery into the hepatic artery. The chemotherapy used was epirubicin 30–50 mg and hydroxycamptothecin 15–20 mg. The embolisation agents used were super liquefaction iodide oil 15–30 ml and gelatin sponge. The treatment frequency was 3–7 times per patient.

RFA and TACE Group

The TACE treatment method was the same as the methods described above. Patients usually underwent 1–3 TACE treatments. Patients who did not improve after this treatment (judged via CT or digital subtraction angioplasty) received RFA treatment (generally after 1 week). The export power was 100 W, with a frequency of 30 times per second. Liver function tests were completed, and included the result of a liver CT scan, and measurements of the level of aspartate aminotransferase/alanine aminotransferase. In addition, the patient's general health was carefully monitored, specifically with regards to vomiting and astriction.

Combination Group

Patients were prescribed 500 mg of lentinan per day for 18 months. It was purchased from the Fourth Affiliated Hospital of Harbin Medical University, Heilongjiang, China. The other methods and drug treatments were the same as in the RFA/TACE group.

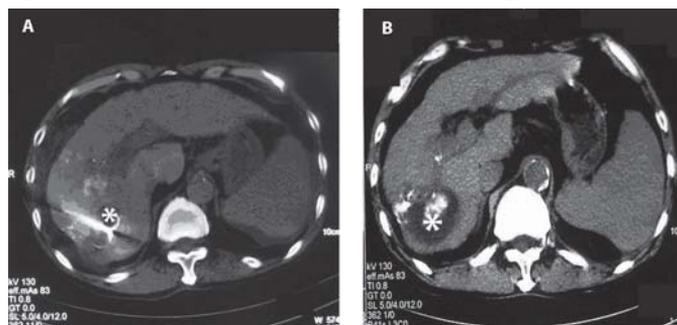
Statistical Analysis

Continuous data are denoted by the mean \pm SD. *t* tests of independent samples were used to compare the main tumour size and other continuous variables. χ^2 and Fisher's exact tests were used to determine the difference between categorical variables. $P < 0.05$ was considered statistically significant. SPSS10.0 was used as the statistical software.

RESULTS

CT scan images from a HCC patient are shown in Figure 1. Baseline and demographic data are shown in Table 1. The

Figure 1. The CT scan of a hepatocellular carcinoma patient in the combination group (male, 54-years-old, tumour diameter=6.3 cm). (A) After 1 month of treatment a large part of the tumour showed necrosis with a low homogeneous density area – the focus part still had iodide oil deposition. (B) After 2 weeks of treatment a large proportion of the tumour remained. *Indicates the position of the tumour.



clinical effect analyses are shown in Table 2, including the tumour necrosis, tumour shrinkage and the relapse rate. Survival time and the survival rate calculations are shown in Table 3.

The tumour necrosis percentage rate was significantly higher in the combination group, compared with the other groups ($P<0.05$). The tumour recurrence rate was significantly lower in the combination group, compared with the other groups ($P<0.05$). Finally, mean

survival duration was significantly higher in the combination group (28.2 months; $P<0.05$).

The mean number of treatments was 1.7 for the RFA group and 3.5 for the TACE group. For the TACE/RFA group, the mean number of treatments was 2.6 for TACE and 1.4 for RFA. The combination group received a mean of 2.6 TACE and 1.4 RFA treatments while taking an average of 500 mg of lentinan per day.

Table 1. Demographic and baseline data of the 78 hepatocellular carcinoma patients, divided into four treatment groups.

Group	Cases	Mean age, years	Gender Male/Female	Liver function (Child-Pugh)			Tumour stages (UICC)				Tumour size, cm	Number of tumours diagnosed		
				A	B	C	I	II	III	IV		1	2	≥3
RFA	12	61.0±10.4	8/4	8	6	1	0	5	10	8	5.2±0.4	8	8	10
TACE	11	57.6±11.8	8/3	10	5	0	0	5	13	6	6.4±1.0	7	1	0
Both RFA and TACE	24	59.1±11.4	18/6	11	5	1	0	7	16	8	6.6±0.6	5	19	15
Combination group	31	60.3±10.9	23/8	10	6	1	0	5	16	8	6.5±0.8	8	20	16

RFA=radiofrequency ablation; TACE=transcatheter arterial chemoembolisation; UICC=International Union Against Cancer.

Table 2. Clinical effects of the 78 cases of hepatocellular carcinoma by four treatment methods.

Group	Cases	Tumour necrosis rate, %	Tumour shrinkage rate, %	Tumour relapse rate, %
RFA	12	47.8†	56.5†	34.7†
TACE	11	37.5†	45.8†	45.8†
Both RFA and TACE	24	60.3*	83.9	29.0*
Combination group	31	88.6	91.3	17.8

Statistically different when compared with the combination group: * $P<0.05$, † $P<0.01$.

RFA=radiofrequency ablation; TACE=transcatheter arterial chemoembolisation.

Table 3. A comparison of survival times of the 78 hepatocellular carcinoma patients. Data are expressed in terms of mean percentage survival.

Group	Cases	6 months, %	12 months, %	18 months, %	Mean survival time, months
RFA	12	60.3	57.6	52.3	18.8
TACE	11	62.1	53.2	45.1	14.9
Both RFA and TACE	24	79.3	68.3	66.8	21.9
Combination group	31	94.4	81.2	77.1	28.2

RFA=radiofrequency ablation; TACE=transcatheter arterial chemoembolisation.

DISCUSSION

HCC is one of the most prevalent cancers and it kills more than 650,000 people worldwide each year.⁵ The optimum treatment of HCC is via a surgical operation.¹⁰ However, as this is not available to most patients, other treatment options are necessary.

RFA acts by rapidly increasing the temperature of the target area, to the point where tumour necrosis occurs – research has shown that it is a successful tool in HCC treatment.¹¹ TACE utilises different methods, acting by the insertion of chemotherapeutic agents and decreasing the tumour's blood flow.¹² As RFA and TACE act by different methods, they can be both be used in HCC treatment without significant complication. The findings of this study suggest that utilising both methods leads to superior efficacy, when compared with using either treatment in isolation. This finding is supported by previous research.¹³

In this study, we treated HCC using a

combination of lentinan, RFA and TACE. The results showed that the complete necrosis rate of the tumours in the combination group was significantly higher than in the other groups ($P < 0.05$). Furthermore, the tumour necrosis rate of RFA/TACE treatment was also higher than with RFA and TACE alone. The result is consistent with research by Casadei et al.¹⁴

The potent and unique properties of fungal-extracted compounds for the prevention and treatment of cancer have been increasingly demonstrated by research in Asia over the past decades.¹⁵ The research results showed that many fungal-extracted compounds could be used as immunomodulators or biological response modifiers.¹⁶ Lentinan, a high-molecular-weight polysaccharide,¹⁷ has been used in clinical trials with hundreds of cancer patients in Japan and China for a long time and has been manufactured by several pharmaceutical companies.¹⁸ The properties of antitumour activities, the prevention of metastasis, and the suppression of chemical and viral oncogenesis in animal models by lentinan were

reviewed by Wasser and Weis¹⁹ in 1999. They found that lentinan can significantly prevent metastasis in animal models. However, the clinic effect of a combination of lentinan, TACE and RFA to treat HCC has not previously been explored. Our study examined this and showed that lentinan may be a promising compensatory agent to treat HCC in the future, particularly in combination with traditional treatments such as RFA and TACE.

Although this study was limited by a small sample size and by not using a long-term follow-up, further research could rectify these issues. Additionally, further benefits may also be realised with other treatment agents, including those supplied by traditional Chinese medicine.

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