

HCC Patients Treated with TACE Combined with Thymalfasin – One Year Follow up–

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Hepatocellular carcinoma (HCC), a fatal malignancy endemic in Southeast Asia, has become the second most common cause of cancer death in China. Treatment of HCC remains a critical issue, particularly in China, as it is estimated that Chinese patients represent 40% of HCC cases worldwide. Surgical resection or liver transplantation are the optimal treatments for early HCC, but most patients are diagnosed too late, already presenting with advanced disease. Transcatheter arterial chemotherapy and embolization (TACE) is a reliable palliative alternative with moderate adverse effects. According to previous studies, the 1-year and 5-year survival rates for TACE-treated patients were 50-60% and 20%, respectively. Other alternative treatments, such as percutaneous ethanol injection, radio frequency or microwave ablation, are also widely used.

Thymalfasin is a chemically synthesized peptide with immune modulating properties centered primarily around augmentation of T-cell function. Thymalfasin acts as an immune stimulant, increasing the Th1 subset of T and NK cells; blocks apoptosis of T cells, and has direct anti-cancer effects as well. Taken together, these data suggest that thymalfasin would be an interesting choice for combination therapy of HCC.

The aim of our open-label study was to evaluate the efficacy of TACE combined with thymalfasin in 32 patients. Results were compared to a historical control group (n=26) matched for gender, age, Okuda staging, Child's score, serum α -fetoprotein and viral hepatitis infection, who were treated with TACE alone. Up to 80% of patients in both groups were positive for hepatitis B viral markers. Three types of HCC tumor variants were included: massive, nodular and diffuse types.

The TACE procedure was performed as follows: 1) puncture of the femoral artery; 2) angiography of abdominal arteries to choose the vessel to be embolized; and 3) injection of 5-15 ml iodinated oil combined with 40-60mg adriamycin, 100-200mg carboplatin and 1g 5-FU. Thymalfasin was given subcutaneously for 10 consecutive days, starting on the day of each TACE treatment, at a dose of 1.6 mg per injection.

Changes in AFP, ALT, WBC, renal function and symptoms were recorded before treatment, at the end of treatment, and two weeks after cessation of treatment. Changes in CD3+, CD4+, CD8+ and NK cells count were also recorded. Survival rates were followed at months 3, 6, 9, 12 and beyond (until the date of death).

Symptoms that improved in both the TACE + thymalfasin and TACE alone groups, respectively, included relief of liver-area pain (63% vs. 58%, $p = ns$), increase in appetite (66% vs. 35%, $p = ns$), and decrease in fatigue (66% vs. 50%, $p = ns$). In the thymalfasin treated group, average AFP level gradually decreased from 512 ng/ml to 354 ng/ml after treatment and to 215 ng/ml two weeks after cessation of therapy. This decrease

compared to baseline was marked and statistically significant. However, the change in AFP level was not significantly different from the group treated with TACE alone.

In the thymalfasin treated group, CD3+ cell count and NK cell activity increased significantly two weeks after cessation of treatment ($p < 0.05$). The CD4+/CD8+ ratio was also significantly increased, from 1.07 before to 1.55 two weeks after therapy. There were no significant differences in the TACE alone group for any immune parameters except NK cell activity, which increased from 42% before treatment to 52% two weeks after therapy.

Patients treated with the combination of thymalfasin plus TACE showed a better survival rate compared to the historical control group treated with TACE alone (Figure 1). Survival at three months was 96% for both groups. In the thymalfasin treated group, survival rates at months 6, 9 and 12 were 91%, 88% and 78% respectively, while in the TACE alone group, they were 77%, 58% and 46% respectively. The survival rates at 6, 9 and 12 months between groups were significantly different ($p < 0.05$).

In summary, the addition of thymalfasin to TACE in the treatment of HCC improved symptoms and immune parameters. No thymalfasin related complications were reported. Importantly, treatment with thymalfasin resulted in a statistically significant increase in survival. These results suggest that thymalfasin is a safe and effective adjuvant for chemotherapy in the treatment of advanced hepatocellular carcinoma.

FIGURE 1

