



Traditional Chinese Medicine to the rescue of allopathic medicine in the co-adjuvant treatment of hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related death in the world, and is the fastest rising cause of cancer-related death in the United States (1). Surgical resection of HCC is a potentially curative treatment option that can be applied to patients with no cirrhosis or compensated cirrhosis and no significant portal hypertension. However, when patients are treated even at early stage (e.g., small or few tumors) with resection, the 5-year recurrence free survival (RFS) is as low as 30% (2) due to new tumors arising in the remaining diseased liver. Treatment of concomitant hepatitis B or C infections is currently the only available established modality to reduce HCC risk post resection (3,4). Other medical therapies including sorafenib, nivolumab (5) and the recently FDA-approved lenvatinib (6) are indicated for patients with advanced disease as part of palliative treatment regimens (7). Sorafenib is not effective when given as co-adjuvant therapy after curative resection (8) and there are no large trials utilizing nivolumab or lenvatinib in this fashion. There is a great need for new therapies that can prolong RFS after surgical resection, and some attention has turned to traditional Chinese medicines (9).

Chen *et al.* (10) published the results of a multicenter, randomized, open-label blank and parallel controlled clinical trial on 1,002 patients with early and intermediate-stage HCC (Barcelona Clinic Liver Cancer stage A and B)

in 39 centers in China (82% men, 78% with hepatitis B, and cirrhosis documented in 67%). These patients underwent curative-intent surgical resection and the effect of Huaier granule on HCC recurrence during subsequent follow-up was examined. Huaier is a beige mushroom that grows on the trunks of hard wood trees and is widely distributed in the southern and eastern regions of China. It is approved by the Chinese State Food and Drug Administration to be used alone or in combination with other drugs for the treatment of leukemia, osteosarcoma, lymphoma, breast, lung, rectal, liver, gastric and pancreatic cancers (9,10).

All patients underwent curative surgical resection of HCC and the experimental arm was given Huaier granule, 20 g mixed with 100 mL of water, three times daily. Randomization was performed on day 15 after surgery, in a parallel fashion. Allocation was concealed by using scratch cards to receive Huaier or no Huaier in a 2:1 ratio. The median follow-up period during the study was 73.6 weeks. The control group was given no specific co-adjuvant therapy and was monitored serially for recurrence of HCC as per the current standard of care. Primary endpoints for the study were RFS, time from randomization to disease recurrence or death from any cause within 96 weeks after randomization. Secondary endpoints for the study were overall survival and extrahepatic HCC recurrence. 90% of randomized patients completed the trial

and most (74%) patients who dropped out of the study were lost to follow-up.

The authors reported significantly higher RFS and overall survival rate in the Huaier group compared with the control group (62.39% vs. 49.05%, $P < 0.01$ and 95.19% vs. 91.46%, $P = 0.02$, respectively) and a mortality hazards ratio of 0.55 (95% confidence interval: 0.33 to 0.92) for the Huaier treatment arm compared with controls. The rates of HCC recurrence and extrahepatic HCC recurrence were also significantly lower in the Huaier group compared with the control group (37.61% vs. 50.96%, $P < 0.01$ and 8.6% vs. 13.61%, $P = 0.01$, respectively.) Importantly, hepatitis B carriers were allowed to continue antiviral treatment during the trial, however not all patients received antivirals and the type of medications was not standardized. In a post-hoc analysis, Huaier granule resulted in a significant reduction in HCC recurrence (37.18% vs. 51.82%, $P = 0.01$) in hepatitis B carriers who never received antiviral therapy. Given these results, the authors concluded that Huaier co-adjuvant therapy is an efficacious treatment after curative HCC liver resection, and therefore should be considered in select patients.

Chen *et al.* randomized controlled design, intention to treat analysis, inclusion of multiple sites, large cohort size, and blinding of radiologists throughout the follow-up period are remarkable strengths that are somewhat atypical for trials of natural medicines. This rigorous methodological design should serve as a gold standard by which we compare other natural or non-traditional approaches in patients with chronic liver disease.

Huaier is suspected to work through multiple pathways to provide its anticancer effect (9). There is *in vitro* evidence to support activity in anti-cell proliferation pathways, cell separation/anti-metastatic pathways, and through suppression of tumor angiogenesis. Direct apoptosis of neoplastic cells by Huaier extract has been demonstrated, in addition to direct inhibition of self-renewing, cancer stem cells. Huaier has also been found to have immunomodulatory effects that may attenuate the host immune response against tumor cells.

Is Huaier, a Traditional Chinese Medicine ready to come to the rescue for all patients after surgical resection of HCC given their high recurrence rates? While promising, probably not. This is but one trial in a select group of patients. A large number ($n = 216$) of patients with intermediate-HCC stage were included in this trial, and the standard of care for these patients should instead be managed with chemoembolization according

to the latest National Comprehensive Cancer Network (NCCN) (7), American Association for the Study of Liver Diseases (AASLD) (11) and European Association for the Study of the Liver (EASL) (12) guidelines. The study was predominately composed of men older than 65 years of age with hepatitis B-related cirrhosis—a different population than in the West where patients are more likely to have hepatitis C or nonalcoholic steatohepatitis (NASH) (13). In addition, there are real concerns regarding the use of herbal and dietary supplements and risk for drug induced liver disease (14).

Chen *et al.* also address and expose a critical need for the development of effective adjuvant therapies for HCC due to high rates of recurrence. Further studies are needed utilizing Huaier granule along with standard practice for patients with intermediate-stage HCC while ensuring that additives used are safe in patients with underlying chronic liver disease not only in the East but also in the West.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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