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Original Article

The efficacy and safety of LDF, a Chinese herbal formula, compared with sorafenib for the treatment of advanced hepatocellular carcinoma in Chinese patients: a retrospective cohort study

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Abstract: Background: Sorafenib constitutes the only first-line drug approved for the treatment of advanced hepatocellular carcinoma (HCC). However, due to its low response rate, limited survival benefits, serious, poisonous side effects, and high price, its application is greatly narrowed. In China, traditional Chinese medicine (TCM) has thousands of years of history in the prevention and treatment of cancer and has been demonstrated to be effective and safe by a large number of studies on the modernization of TCM. Methods: In accordance with the criteria of inclusion and exclusion, 80 enrolled patients were randomly divided into a treatment or a control group, so each group included 40 patients. The patients in the treatment group were given LDF, and the patients in the control group were given sorafenib. The medium overall survival (mOS), medium time to progression (mTTP), disease control rate (DCR), and adverse reactions were compared between the two groups at week 12. Alpha fetoprotein (AFP), alanine aminotransferase (ALT), total bilirubin (TBIL), and albumin (ALB) were tested at weeks 4, 8, and 12. Results: The study showed that the mOS was 7.6 months in the treatment group and 6.1 months in the control group (7.6 vs 6.1 months, $P<0.05$); the mTTP in the treatment group was 4.3 months, but in the control group it was only 3.6 months (4.3 vs 3.6 months, $P<0.05$). The DCR of the treatment group and the control group were 45.0% and 32.5% ($P>0.05$). After treatment, the levels of AFP, ALT, and TBIL were remarkably decreased at weeks 4, 8, and 12 ($P<0.05$), and the ALB remained stable throughout the treatment ($P>0.05$). No serious drug-related adverse reactions were found during the whole follow-up period in the two groups. Conclusion: The mOS, mTTP, and biochemical indicators of the hepatic functions showed some benefits when compared with the control group. Therefore, TCM may be a safe and clinically effective treatment for advanced HCC.

Keywords: Advanced hepatocellular carcinoma (HCC), sorafenib, a Chinese herbal formula (LDF), a retrospective cohort study

Introduction

Primary liver cancer is the second leading cause of cancer-related deaths worldwide [1, 2]. Advanced HCC is the most common type of primary liver cancer, comprising 75%-85% of cases. It is now believed that HCC is associated with chronic infection with hepatotropic viruses, heavy alcohol intake, and the consumption of aflatoxin-contaminated food-stuffs [3, 4]. Statistics on the number of new liver cancer cases in China account for approximately 50% around the world every year [5]. HCC is characterized by an aggressive invasion, an insidious onset, and a rapid progression. Most HCC cases are found in the intermediate and advanced stages and are therefore unsuitable for surgical excision, transcatheter arterial chemoembolization (TACE), local ablation, or liver transplantation [6]. Studies have shown that untreated patients with HCC have a median survival time of less than 4 months [7].

Sorafenib, a multi-target tyrosine-kinase inhibitor (TKI), is the first Food and Drug Administration (FDA) approved for advanced HCC with preserved liver function [8], since it has shown statistical differences compared with a placebo

Table 1. The formula of ASF (one dose)

Herb	Medicinal parts	Origin	Amount in preparation (g)
Astragalus membranaceus	Radix	Gansu Province	160
Panax ginseng	Radix	Jilin Province	40
Poria cocos	sclerotium	Yunan Province	60
Atractylodes macrocephala Koidz	Radix	Zhejiang Province	60
Rhizoma sparganii	Tuber	Jilin Province	100
Curcuma zedoaria	Rhizome	Guangxi Province	100
Semen Persicae	Seed	Sichuan Province	100
Carthamus tinctorius L.	flower	Sichuan Province	100
Radix Glycyrrhizae Preparata	Radix	Xinjiang Province	30

in mOS (6.5 vs 4.2 months in an Oriental trial) [9-11]. However, it provides only moderate benefits in mOS, but it comes with notable adverse reactions [12], such as diarrhea, fatigue, alopecia, rash, hypertension, and a hand-foot skin reaction, etc. [13-17]. And its price is expensive. Therefore, it is urgent to explore an effective and safe strategy for advanced HCC.

Previous studies have shown the efficacy of traditional Chinese medicine (TCM) on liver cancer [18]. TCM is one of the recommended therapies for tumor treatment in China [19]. Therefore, we can continue to study the efficacy of TCM in the treatment of advanced HCC. LDF, a Chinese herbal formula, has been widely used in our department and has achieved a good clinical efficacy in liver cancer. In order to confirm the efficacy of the formulae on liver cancer and provide supportive clinical data for the fatal disease, we designed this clinical trial.

Material and methods

Study design

The study cohort included patients who were diagnosed with advanced HCC on the basis of the previously issued *Guidelines for the Diagnosis and Treatment of Primary Liver Cancer in China* (2017 edition) [20] and treated at the Hospital of Chengdu University of Traditional Chinese Medicine between January 2012 and December 2015. Patients with advanced HCC formed a treatment group or a control group according to whether they took LDF or sorafenib therapy in a 1:1 ratio. The patients in the treatment group were given LDF, and the patients in the control group were given sorafenib. Both groups received standard comprehensive internal medicine [20]. The provisions for written informed consent were abandoned on account of the retrospective nature of the study.

Inclusion criteria

(1) Meet the clinical diagnostic criteria of primary liver cancer; (2) Child-Pugh class A or B and Eastern Cooperative Oncology Group performance status (ECOG-PS) scores between 0 and 2; (3) Barcelona Clinic Liver Cancer (BCLC) criteria: stage B or C [21]; (4) Treatment with sorafenib was initiated; (5) Ranging in age from 18 to 80 and of either sex; (6) Good patient compliance.

Exclusion criteria

(1) Patients with secondary liver cancers; (2) Patients with other serious cardiovascular or cerebrovascular diseases, kidney diseases, hematopoietic diseases, and psychiatric patients; (3) Patients with other better treatment indications such as surgery, liver transplantation, TACE, radiotherapy and so on; (4) Patients who were pregnant or breastfeeding; (5) Patients with poor compliance.

Treatments

80 eligible patients were given standard comprehensive medical treatment [20]. On this foundation, the treatment group was treated with LDF (tid, 100 ml/time, specific prescriptions shown in **Table 1**), and the control group received sorafenib (Bayer Pharma AG, 0.4 g bid).

Clinical and laboratory data

(1) The primary outcome was the OS, which was defined as the time of starting treatment in our

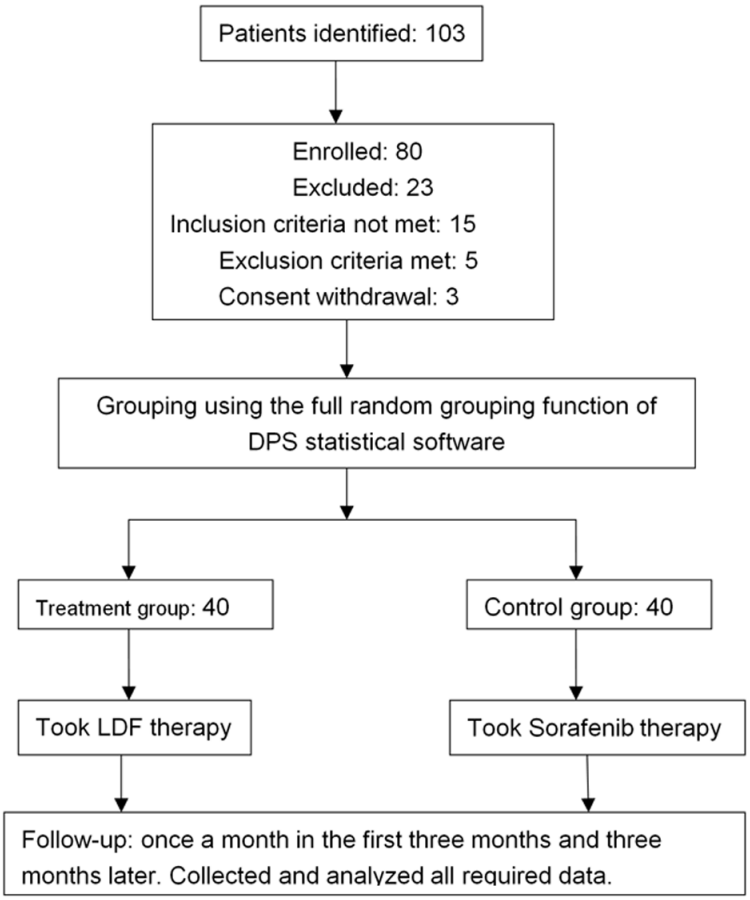

Figure 1. Process of the whole experiment.

hospital as an advanced HCC patient until the occurrence of death for any cause or until the last follow-up time on September 10, 2019; (2) The secondary outcomes consisted of TTP and DCR. TTP was defined as the time treatment started in our hospital for advanced HCC until the radiological diagnosis of the progression of the tumor conforming to the modified response evaluation criteria in solid tumors (mRECIST) [22]; (3) DCR was defined as the sum of patients who achieved any complete response (CR) or a partial response (PR) or progression-free stable disease (SD) after treatment; (4) Serum AFP, ALT, TBIL, and ALB were determined at weeks 4, 8, and 12 respectively; All assays were tested using an Automatic Analyzer (7170A, Hitachi, Japan); (5) Adverse reactions.

Safety assessment

Adverse events, including any clinical symptoms or signs were well documented. For each adverse event, the start date, end date, and degree were documented and considered for causality with the drugs. Patients with any drug adverse reaction would accept proper treatment.

Statistical analysis

Statistical testing was performed using SPSS software for Windows, version 17.0 (SPSS Inc., USA). Quantitative data were expressed as the means ± standard deviation. The differences among the quantitative data were compared using an independent-samples t-test. The qualitative data were described using percentages. The differences among the qualitative data were analyzed using an χ^2 test or Fisher's exact test. The survival data were assessed using the Kaplan-Meier method and compared using a log-rank test. All P values were two-sided, and $P<0.05$ was considered to be statistically significant.

Results

Study flow chart

Altogether, 103 patients were identified for possible inclusion in this study. Strictly following the inclusion and exclusion criteria, 80 patients were enrolled. A random number table was generated using DPS statistical software. The patients were randomly distributed to a treatment group or a control group (**Figure 1**). No significant differences were found in baseline characteristics between the two groups (**Table 2**).

Evaluation of imaging studies

At the end of week 12, the DCRs of the treatment and control groups were 45.0% and 32.5%, and no significant difference was found between these two groups ($P>0.05$). The results are shown in **Table 3**.

The mOS and mTTP

As shown in **Figures 2** and **3**, the results showed that the mOS of in treatment group was 7.6

Table 2. Baseline characteristics

n (%)	Treatment Group (n=40)	Control Group (n=40)	t/χ^2	*P*
Males (%)	29 (72.5%)	26 (65.0%)	0.524	0.469
Age (years)	50±9.92	51±8.22	0.461	0.646
ECOG PS			0.340	0.891
0	3 (7.5%)	4 (10.0%)		
1	25 (62.5%)	23 (57.5%)		
2	12 (30.0%)	13 (32.5%)		
BCLC Stage			0.202	0.653
B	19 (47.5%)	17 (42.5%)		
C	21 (52.2%)	23 (57.5%)		
Child-Pugh class			1.250	0.264
A	30 (75.0%)	34 (85.0%)		
B	10 (25.0%)	6 (15.0%)		
AFP	537.09±213.15	564.71±160.04	0.655	0.514
ALT	87.07±53.60	79.25±49.16	0.680	0.498
TBIL	32.76±16.32	36.26±16.93	0.942	0.349
ALB	34.90±8.16	34.36±6.93	0.315	0.754
MVI			0.238	0.626
Yes	11 (32.5%)	13 (35%)		
No	29 (67.5%)	27 (65%)		
EHS			0.808	0.369
Yes	24 (60.0%)	20 (50.0%)		
No	16 (40.0%)	20 (50.0%)		

NO statistical significant difference between groups (all *P*>0.05).

Table 3. Evaluation of the imaging studies

n (%)	Treatment group (n=40)	Control group (n=40)	χ^2	*P*
CR	0 (0%)	0 (0%)		
PR	4 (10.0%)	3 (7.5%)		
SD	14 (35.0%)	10 (25.0%)		
PD	22 (55.0%)	27 (67.5%)		
DCR (DCR=CR+PR+SD)	18 (45.0%)	13 (32.5%)	3.215	0.730

NO statistical significant difference in DCR (*P*>0.05).

months, but the mOS was 6.1 months in control group. The mTTP in the treatment group was 4.3 months, but in the control group it was only 3.6 months. There were significant statistical differences in the mOS and mTTP between the two groups (*P*<0.05), suggesting that LDF can better prolong the survival time and delay the disease progression of patients with advanced HCC compared with sorafenib.

Biochemical indicators

As shown in **Table 4**, the levels of AFP, ALT, TBIL and ALB were compared between the two groups. As the treatment progressed, the AFP, ALT, and TBIL decreased in both groups at weeks 4, 8, and 12 (all *P*<0.05), but the albumin remained stable (all *P*>0.05).

Safety

As shown in **Table 5**, the common adverse reactions include conditions such as diarrhea, fatigue, dizziness, rash, and so on. There was no significant difference in adverse reactions between the two groups (all *P*>0.05). All adverse reactions can be spontaneously alleviated.

Discussion

Hepatocellular carcinoma is one of the primary causes of cancer deaths in China. The incidence and mortality of HCC are still increasing year by year [23]. Accordingly, preventing the occurrence and development of hepatocellular carcinoma and prolonging patients' survival time and improving their quality of life have become hot spots and focuses in current medical research. Sorafenib is widely used in therapy for unresectable or metastatic HCC. It has dual anti-tumor activity [24], inhibiting tumor proliferation and angiogenesis by targeting the Raf/MEK/ERK signaling pathway and blocking the vascular endothelial growth factor receptor (VEGFR)-1/2/3 and platelet-derived growth factor receptor-β [25, 26]. A growing number of studies have found that sorafenib confers only a moderate survival benefit in OS, comes with many adverse reactions, and is hampered by drug resistance. And it is generally known that sorafenib is not an economical choice for patients. In this retrospective cohort study, sorafenib served as a positive control drug. It must be noted, however, that the curative effect of sorafenib is moderate, with mOS prolonged only by two or three months compared with a placebo [10].

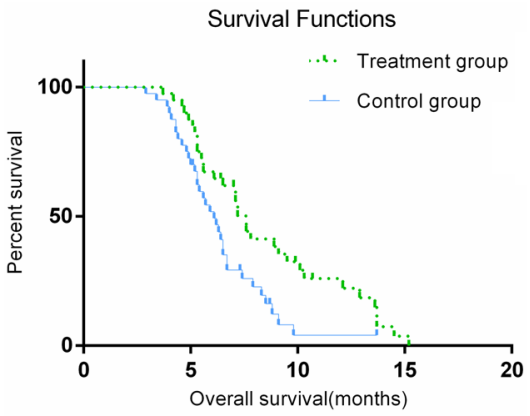

Figure 2. Overall survival in the two groups.

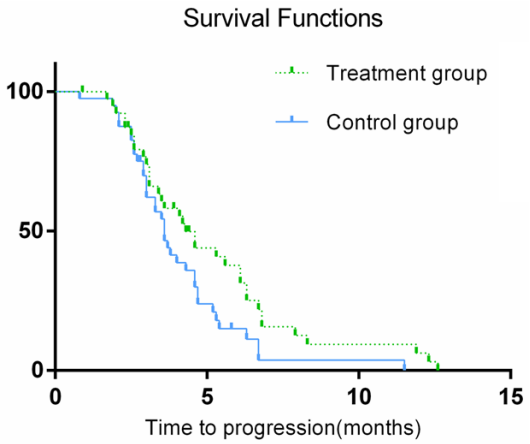

Figure 3. Time to progress in the two groups.

In China, TCM has been used to treat HCC effectively for more than 1,000 years [27-31]. The LDF applied in this study had been practiced for many years in our hospital and we have found that patients' symptoms and serologic indicators were improved after taking it. So it might be a clinically effective means to rescue these critical patients. We were not satisfied with the initial clinical success, hence clinical data collection and statistical analysis were carried out for the sake of scientifically explaining the efficacy and safety of LDF with statistical methods. And in this retrospective cohort study, our results demonstrated that LDF, compared with sorafenib, could better improve liver function, prolong the mOS, and delay the mTTP. Our results indicated that LDF seemed to have a better clinical efficacy than sorafenib. The results showed that the mOS was 7.6 months in the treatment group and 6.1 months in the control group (P<0.05). As the primary outcome, the mOS could be extended by a further 1.5 months compared with sorafenib. Although it was not very good, it really was of terrific significance for such a serious disease. Similarly, the mTTP was delayed compared with sorafenib. The mTTP in the treatment group was 4.3 months, but in the control group it was only 3.6 months (P<0.05). But there were no significant differences in DCR between these two groups (P>0.05). In the meantime, LDF could better improve the biochemical indicators of patients with advanced HCC compared with sorafenib. The results were mainly reflected by decreases in AFP, ALT and TBIL at weeks 4, 8, and 12 (P<0.05). But the ALB remained stable at weeks 4, 8, and 12 (P>0.05). A possible reason might be that traditional Chinese medicine improved the liver function and then prolonged the survival time of advanced HCC. As for albumin, it might be due to the symptomatic treatment of intermittent albumin infusion throughout the treatment, so there was no statistical difference between the two groups.

In our study, the Chinese herbal formula consists of *Astragalus membranaceus*, *Panax ginseng*, *Poria cocos*, *Rhizoma sparganii*, *Curcuma zedoaria*, etc. This formula has the effect of tonifying Qi and invigorating the circulation of blood in the deficiency of vital energy and blood stasis. In contemporary pharmacotherapy, *Astragalus* polysaccharides could reduce or even counteract the side-effects of chemotherapeutic drugs [32]. *Panax ginseng* has been indicated to lower the cancer risk of liver, lung, stomach, pancreas, and various other cancers [33]. Ginsenosides and polyacetylenes have been shown to reduce the malignant potential of HCC [34]. *Poria cocos* possesses anticancer, anti-inflammation, and immune-stimulation activities [35]. Atractylodes rhizoma atractylodis can improve cachexia by reducing the serum IL-1 and TNF-alpha levels and the urine PIF level, thus achieving the effect of cancer treatment [36]. Rhizoma sparganii can inhibit the proliferation of tumors. Curcuma zedoary can inhibit the growth and metastasis of liver cancer by reducing endogenous H2S levels [37]. *Carthamus tinctorius* enhances the antitumor activity by promoting the recognition of antigens and polarization toward Th1 cytokines [38]. *Carthamus tinctorius* L. also inhibits the angiogenesis of HCC by blocking the ERK/

Table 4. The serum levels of AFP, ALT, TBIL, and ALB

Characteristics	Treatment group	Control group	t	*P*
Week 4				
AFP	394.05±100.04	464±104.96	3.067	0.003
ALT	60.356Intis	71.506Intis	2.208	0.030
TBIL	24.876Inti	31.276Inti	3.413	0.001
ALB	35.82610.53	34.30610.5	0.725	0.471
Week 8				
AFP	316.7010.53ti	368.7510.53t	2.347	0.021
ALT	48.47510.53	65.90510.53	3.952	0.000
TBIL	20.77510.5	27.12510.5	3.638	0.000
ALB	35.42510.53	35.12510.5	0.135	0.893
Week 12				
AFP	201.2220.53ti	264.9220.53t	2.945	0.004
ALT	37.62220.53	54.80220.53	4.077	0.000
TBIL	16.05220.5	20.55220.5	2.634	0.010
ALB	36.85220.5	35.05220.5	0.896	0.373

All values are expressed as the mean ± SD (%).

Table 5. All adverse reactions during treatment

Diarrhea	Treatment (n=40)	Control (n=40)	χ^2	*P*
Fatigue	1	3	0.263	0.608
Dizziness	0	2	0.513	0.474
Rash	2	4	0.180	0.671
Nausea	0	1	0.000	1.000
Headache	2	1	0.000	1.000

MAPK and NF-κB transduction pathways in H22 tumor-bearing mice [39].

Of course, this study had some limitations. A retrospective cohort study is based on a review of clinical cases that have occurred. We all know that a randomized controlled trial (RCT) has the highest level of evidence. However, retrospective cohort studies have difficulties in following the randomization principle, and selection bias is their main disadvantage. Our group collected the data of all the patients who met the inclusion criteria from January 2012 to December 2015, and we carried out a retrospective study to show the efficacy and safety of traditional Chinese medicine with objective data, rather than just basing our study on the subjective feelings of patients. All in all, our study showed that patients treated with LDF were better than those treated with sorafenib in the OS, TTP and clinical parameters. Henceforth, well-designed prospective cohort studies need to be carried out to appraise the long-term efficacy and safety of patients treated by TCM.

Conclusion

In conclusion, LDF, compared with sorafenib, demonstrates some superiority in patients with advanced HCC. LDF can better improve patients' liver function and prolong their survival times. The current study results might provide a new option for treating advanced HCC metastasis, which will prove valuable to further in-depth studies.

Acknowledgements

This study is a retrospective cohort study, mainly involving the case collection and statistical analysis of medical records. All the patients' data were from our hospital's computerized information system. The purpose of this study was to retrospectively review the patient's clinical records. Thus we don't need an institutional review board statement.

Disclosure of conflict of interest

None.

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