Effect of Bushen Jianpi formula on survival of patients with moderate and advanced hepatocellular carcinoma: a retrospective study

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Abstract

OBJECTIVE: To investigate the effect of Bushen Jianpi formula (BSJP) therapy on survival of the patients with moderate and advanced hepatocellular carcinoma (HCC).

METHODS: This was a five-year retrospective study, enrolling 209 adult patients with moderate and advanced HCC patients. Log-rank test, Cox regression analysis and Kaplan-Meier analysis was applied to analyze the data.

RESULTS: The outcome of single-factor Kaplan-Meier analysis and Log-rank test showed that stage of Barcelona-clinic liver cancer (BCLC), locoregional therapy and BSJP therapy were three factors that dominantly influenced the survival of moderate and advanced HCC patients ($P < 0.05$). In Cox multi-

INTRODUCTION

Primary liver cancer (PLC) is one of those common tumors that severely impair human health. According to statistics in 2008, the number of newly diagnosed cases of PLC in the world reached 748,300 along with 695,900 cases of death, with the incidence rate of PLC ranking at the fifth and the seventh place and its mortality rate ranking at the second and the sixth place for males and females respectively in the list of malignant tumors.\(^1\) World Cancer Report 2014 revealed that both the number of newly added cases of PLC and its death toll in China topped the world list, making PLC the third greatest malignant tumor whose mortality rate ranked only after stomach cancer and lung cancer. PLC mainly includes hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC) and the mixed type of HCC and ICC, of which HCC accounts for over 90%.\(^2\) First choice of treatment for...
The aim of this study was to evaluate the effect of BSJP therapy on the survival of patients with moderate and advanced HCC patients to provide clinical evidence for the transformation and application of TCM in the domain of anti-tumor treatment.

**METHODS**

**Study design**

A total number of 209 patients with moderate and advanced HCC [stage of Barcelona-clinic liver cancer (BCLC)-B-BCLC-C] who sought treatment at Department of Hepatology in Shuguang Hospital affiliated to Shanghai University of TCM and Department of Hepatology in Longhua Hospital affiliated to Shanghai University of TCM from June 2008 to June 2013 as outpatients or inpatients were enrolled in this study. The 209 patients, including 99 cases in conventional therapies group (conventional group) and 110 cases in combined therapy with TCM BSJP (BSJP group), were collected by adopting retrospective cohort research method. Considering obviously different survival time owing to different periods of BCLC stage, the 209 HCC patients were thus further assigned into BCLC-B stage and BCLC-C stage as two subgroups for analysis.

**Diagnostic criteria**

The HCC diagnostic criteria in this study referred to that specified by American Association for the Study of Liver Diseases (AASLD). The staging of liver cancer accepted the 2010 staging criteria of BCLC, which defined moderate and advanced HCC patients as BCLC-B-BCLC-C.

**Inclusion criteria**

Patients enrolled met the diagnostic criteria of HCC and were at BCLC-B-BCLC-C stage, ranging from 18 to 80 in age, with survival time longer than three months. Patients in the BSJP group treated by TCM received TCM for no less than three months.

**Exclusion criteria**

Patients simultaneously suffered from severe diseases of other systems such as myocardial infarction, cerebral infarction, renal failure, or patients with metastatic liver cancer or multiple cancers, post-transplantation, pregnant or at lactation period were excluded from this study. Patients or inpatients were enrolled in this study. The patients or inpatients were enrolled in this study. The patients or inpatients were enrolled in this study.

**Intervention**

Conventional therapies: conventional therapies included conventional symptomatic therapy, locoregional therapy (e.g, transcatheter arterial chemoembolization, TACE; radiofrequency ablation, RFA; and percutaneous ethanol injection, PEI, etc.) and immunological therapy (e.g, interferon and thymosin), etc.

Combined therapy with TCM: combined therapy with TCM was to add one dose of BSJP every day on the basis of conventional therapy, taken at night and morning.
Drug and preparation
Each dose of BSJP consisted of 15 g Shudihuang (Radix Rehmanniae Preparata), 12 g Shanyao (Rhizoma Dioscoreae Opposita), 12 g Shanzhu (Fructus Corni), 9 g Mudanpi (Cortex Moutan Radicis), 9 g Zexie (Rhizoma Alismatis), 12 g Fuling (Poria), 12 g Danshen (Radix Codonopis), 12 g Baihu (Rhizoma Atractylodis Macrocephalae), and 6 g stir-frying with liquid adjunct Gancao (Radix Glycyrrhizae). Each dose of BSJP was soaked in 500 mL water for two hours and then boiled for 40 min before dregs were removed. Afterwards, the decoction was concentrated to 200 mL before it was finally orally administrated for 100 mL each time twice a day.

Variables
Variables needed to be inspected by Cox regression analysis in this study involved eleven factors listed as follows: gender, age, BCLC stage, viral hepatitis, cirrhosis, operation history, locoregional therapy, antiviral therapy, immunological therapy, BSJP therapy, and end points.

Statistical analysis
The study’s primary endpoint was mortality. The continuous variables are either expressed as the mean ± standard deviation ( x ± s) and compared using Student’s t test, or they are expressed as the medians and the ranges and compared with the Wilcoxon rank sum test if their distributions were not normal. The categorical variables were compared using the χ2 test or Fisher’s exact test if their expected values were below 10. Survival rate was calculated using Kaplan-Meier analysis, and comparisons between groups were made via Log-rank test. Cox regression model was employed to make multiple-factor analysis, thus to screen independent factors influencing patients’ survival time. Two-tailed P-values less than 0.05 were considered statistically significant. Data analysis was conducted using SPSS 19.0 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY, USA).

Ethical consideration
BSJP formula is widely used empirical formula in our Traditional Chinese Medicine hospitals. Patients using the formula were informed that their treatment data might be used to analyze the effect of this prescription to add evidence to the further use of this therapy. All responses were kept anonymous and confidential. The institutional review board of Longhua Hospital affiliated to Shanghai University of Traditional Chinese Medicine provided ethics approval (Approval No. 2018LC-SY441).

RESULTS
Baseline data
This retrospective study involved 209 cases, of which 93 patients at BCLC-B stage and the rest 116 patients at BCLC-C stage, with 169 males and 40 females whose mean age was 56.15, and their survival time ranged from 3 months at least to 36.1 months at most. Of the 209 patients, 175 were HBV patients and the other 34 patients were non-viral hepatitis patients. 158 suffered from hepatic cirrhosis, and 142 died. According to the statistical analysis, there existed no significant difference in baseline data between BSJP group and conventional group for survival analysis (209 cases), and neither did significant difference in baseline data exist between BSJP group and conventional group for survival analysis of BCLC-B group and BCLC-C group as two subgroups (Table 1).

Survival analysis
The outcome of single-factor Kaplan-Meier analysis and Log-rank test showed that BCLC stage, locoregional therapy and BSJP therapy were three factors that dominantly influenced the survival of moderate and advanced HCC patients (P < 0.05), whereas intervention factors such as gender, age, viral hepatitis, cirrhosis, operation history, antiviral therapy and immunological therapy made no significant statistic difference (P > 0.05). Specific statistics and survival curves of various correlative factors are described in Table 2 and Figure 1A, 1B and 1C. The results of Cox multiple-factor regression analysis revealed that BCLC stage, locoregional therapy and BSJP therapy were three independent factors affecting the survival of patients with moderate and advanced liver cancer (P < 0.05), with risk ratios (RR) of 2.016, 0.611 and 0.684 respectively; whereas gender, age, viral hepatitis, cirrhosis, operation history, antiviral therapy and immunological therapy failed to act as independent influence factors (P > 0.05) (Table 3).

Survival analysis of BCLC-B
The results of single-factor Kaplan-Meier analysis and Log-rank test showed that locoregional therapy was the principal factor influencing the survival of HCC patients at BCLC-B stage (P < 0.05). Specific statistics and survival curves of various correlative factors are displayed in Table 4 and Figure 1D. The results of Cox multiple-factor regression analysis revealed that locoregional therapy was the dominant factor affecting the survival of HCC patients at BCLC-B stage (P < 0.05), with a RR of 0.543 (Table 3).

Survival analysis of BCLC-C
The results of single-factor Kaplan-Meier analysis and Log-rank test showed that locoregional therapy and BSJP therapy were dominant factors affecting the survival of HCC patients at BCLC-C stage (P < 0.05). Specific statistics and survival curves of various correlative factors are described in Table 4 and Figure 1E and 1F. The results of Cox multiple-factor regression analysis revealed that locoregional therapy and BSJP therapy were independent factors influencing the survival of advanced HCC patients (P < 0.05), with RR of 0.602 and 0.513 respectively (Table 3).
DISCUSSION

In this study, we found that among factors including gender, age, viral hepatitis, cirrhosis, operation history, antiviral therapy, immunological therapy, BCLC stage, locoregional therapy and BSJP therapy, BCLC stage, locoregional therapy and BSJP therapy constituted principal factors affecting the survival of moderate and advanced HCC patients \((P < 0.05)\) with RR of 2.016, 0.611 and 0.684 respectively. An RR < 1 for locoregional therapy and BSJP therapy indicated that both of the two were protective factors for the survival of HCC patients which contributed to prolonged survival of patients; An RR > 1 for BCLC stage indicated its role as an adverse factor for the survival of HCC patients, and to be specific, a higher stage of BCLC represented a shorter survival. Previous studies had shown that operation and antiviral therapy were effective measures of prolonging the overall survival of HCC patients, yet this study focused on moderate and advanced patients as objects of study and investigated their survival time after they were diagnosed with moderate and advanced HCC, hence no contradiction with previous studies despite the fact that operation history and antiviral therapy failed to constitute the protective factors for the survival of HCC patients in this study.

Staging of tumor plays a decisive role in patients’ survival. Therefore, we divided recruited cases further into BCLC-B stage and BCLC-C stage as two subgroups to research separately in order to guarantee the objectivity.
of study. According to the results, locoregional therapy was the predominant factor affecting the survival of HCC patients at BCLC-B stage ($P < 0.05$) with RR as 0.543; locoregional therapy and BSJP therapy were independent factors influencing the survival of HCC patients at BCLC-C stage ($P < 0.05$), with RRs of 0.602 and 0.543 respectively. The results mentioned above demonstrated the advantage of locoregional therapy for HCC patients at lower BCLC stage and instead a more significant therapeutic effect of non-invasive treatment with BSJP for advanced HCC patients.

Tumor cells falls into the scope of toxic pathogenic factors as acknowledged in TCM, and abundant anti-pathogenic energy serves as prerequisite for the elim-
The use of modern statistical methods has further verified BSJP as an effective therapy for moderate and advanced HCC patients. The lack of anti-pathogenic energy may lead to the generation and development of tumor cells. As the combined formula of Sijunzi decoction and Liuwei Dihuang decoction as two classical "Fuzheng" formulas (formulas that can strengthen body regulation, and the body is thereby unable to inhibit over-expression of oncogenes. Therefore, TCM deems the insufficiency of anti-pathogenic energy as the very factor that leads to the generation and development of tumor cells. As the combined formula of Sijunzi decoction and Liwei Dihuang decoction as two classical "Fuzheng" formulas (formulas that can strengthen the body immunity), BSJP possesses the therapeutic effect of strengthening the vital energy in human body with an application history of a thousand years. Modern pharmacological research had indicated the anti-tumor and immunoregulatory effects of the Chinese herbal medicinal ingredients contained in BSJP previously. This study further verified BSJP as an efficacious drug for moderate and advanced HCC with certain prospects for clinical transformation and application through objective cohort studies with the application of modern statistical methods.

In conclusion, BSJP therapy and locoregional therapy both contributed to prolonged survival for moderate and advanced HCC patients.

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