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Efficacy and safety of Thai herbal recipe in advanced hepatocellular carcinoma: A pilot, randomized, controlled clinical trial

Kritiya Butthongkomvong[1], Araya Lukanawonakul[2], Sakunrat Tiewwanich[3], Pongsadhorn Pokpermdee[4], Isara Chiawiriyabunya[5] and Tanawan Kummalue[6]*

[1]Department of Medicine, Udon Thani Cancer Hospital, Amphur Muang, Udon Thani 41330, Thailand.
[2]Department of Pharmacy, Udon Thani Cancer Hospital, Amphur Muang, Udon Thani 41330, Thailand.
[3]Faculty of Nursing, Mahidol University, Bangkok 10700, Thailand.
[4]Office of the Permanent Secretary, Ministry of Public Health, Nonthaburi 11000, Thailand.
[5]Udon Thani Cancer Hospital, Amphur Muang, Udon Thani 41330, Thailand.
[6]Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

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ABSTRACT

The authors conducted a randomized, double-blind, placebo-controlled, pilot study to determine the efficacy and side effects of a well-known Thai herbal recipe in advanced hepatocellular carcinoma. Twenty advanced hepatocellular carcinoma patients were enrolled at Udon Thani Cancer Hospital, Thailand, between January 2015 and December 2017. They were divided into experimental and placebo groups, each with ten patients. The time to event was defined as the time to disease progression or death, and it was calculated using intention-to-treat analysis. Relative to the placebo group, the treatment group demonstrated a larger number of poor prognostic factors, such as larger tumor sizes, higher alpha-fetoprotein levels, worse Child–Pugh classifications, and much higher alkaline phosphatase levels. A Kaplan–Meier analysis revealed that the endpoint of the experimental group was not inferior to that of the control group, even though the experimental group had much worse prognostic factors. As to the safety of the herbal recipe, no adverse events were detected in the treatment group. The study demonstrated that the Thai herbal recipe might have some advantages for advanced hepatocellular carcinoma patients, especially in combination with supportive therapy.

Keywords: Hepatocellular carcinoma, integrative medicine, Thai herbal recipe.

*Corresponding author. E-mail: tanawan.kum@mahidol.ac.th. Tel: +66 (0) 2419 6587. Fax: +66 (0) 2418 1367.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the leading causes of malignancies and cancer-related deaths worldwide, including Thailand. The age-standardized incidence rate has recently been reported as 32.2 per 100,000 population per year in Thai men (Virani et al., 2017). The etiology of HCC is reportedly associated with hepatitis viral infections, aflatoxin, alcoholic liver disease, and non-alcoholic fatty liver disease (El-Serag, 2011). The treatment protocols for this patient group include surgical resection, radio frequency ablation, and liver transplantation, and they require a multidisciplinary approach to ensure an optimal outcome. However, those diagnosed with advanced disease usually have a poor prognosis, with a median survival of 7.9 months (Balogh et al., 2016). To date, the oral tyrosine kinase inhibitor, sorafenib, is considered as the new standard treatment for advanced HCC to improve the treatment outcomes and prolong overall survival (Llovet et al., 2008). However, many patients in Thailand cannot take this special drug due to the expensive drug cost.

There is one of the Thai herbal recipes that has been widely used to treat liver cancer at Nong Bua Lamphu Province, in the northeastern region of Thailand, for several decades. The recipe contains three roots of the herbal plants *Eurycoma longifolia*, *Dipterocarpus obtusifolius* and *Tamilnadia uliginosa*, all of which are commonly found and used as traditional medicines in Thailand, but especially in the northeast. *Eurycoma longifolia*, from the family Simaroubaceae, is used as an antimalarial, antimicrobial, and antipyretic medicine. The bioactive compounds, such as eurycolactone, eurycomaoside, eurycomalactone, eurycomanone, and 9 methoxycanthin-6-1 have been isolated from this plant. Previous reports have indicated that the root extracts have potent anticancer activities against various cancer cell lines, such as K562, Caov-3, DE-145, KB, RD, and MCF-7 (Al-salahi et al., 2013; Nurhanan et al., 2005; Rehman et al., 2016). A recent report also demonstrated that the anticancer properties of *E. longifolia* were exhibited by the induction of apoptosis via the upregulation of the expression of the p53 and Bax proteins and the downregulation of the expression of the Bcl-2 protein (Thu et al., 2017). *D. obtusifolius* is in the family Dipterocarpaceae. This plant has been used to relieve abdominal discomfort. Its stem contains sesquiterpenes, triterpenes, flavonoids, and resveratrols. It has been reported that the extracts from the stem showed antiproliferative activities against several cancer cell lines, such as HepG2, SK-OV-3, A549, and MCF-7 (Khiev et al., 2012). However, the root extracts of this plant have not yet been investigated, especially on cancer cell growth inhibition. Interestingly, the extracts of *D. obtusifolius* has also shown an anti-inflammatory effect by suppressing the production of several inflammatory cytokines, including tumor necrosis factor-alpha and interleukin 1ß (Park et al., 2017). *T. uliqinosa* is a herbal plant in the family Rubiaceae. In traditional medicine, it is prescribed for the treatment of several diseases, such as diabetes mellitus, diarrhea, and dysentery, and as an aphrodisiac. Its fruit, which can be eaten as a vegetable, also has an anti-diarrhea property, which is utilized in Thai traditional medicine (Phargarden.com). Most of the compounds isolated from its fruit are phenolic compounds and flavonoids, for example, luteolin, quercetin, vitexin, nonacosane, and caffeic acid (Deepthy et al., 2016). However, it's *in vitro* anticancer properties, especially of the root extract, have not yet been reported.

Liver cancer patients at Nong Bua Lamphu Province usually use these three roots in a herbal recipe in a traditional way, i.e., by grinding them, dissolving all of the resultant powder using 1 L of water, and drinking the water mixture in one day, everyday. To date, no scientific clinical data on the effects of this herbal recipe on liver cancer have been demonstrated. Thus, we conducted a pilot, randomized, double-blind, placebo-controlled trial to determine the efficacy and side effects of this three-root herbal recipe in the treatment of advanced hepatocellular carcinoma at Udon Thani Cancer Hospital, Ministry of Public Health.

MATERIALS AND METHODS

Herbal preparation

The roots of *E. longifolia*, *D. obtusifolius*, and *T. uliginosa* were collected from Nong Bua Lamphu Province, northeast Thailand. All of the roots were identified by comparing them with data and specimens at the Forest Herbarium (BKF nos. 141423, 143892 and 23913, respectively), Department of National Parks, Wildlife and Plant Conservation, Bangkok, Thailand.

We prepared the herbal medicine following the traditional usage method for herbal preparation, i.e., with the root of each herbal plant being cleaned with distilled water, chopped, and ground into powder. They were mixed together following the formula belonged to Department of Thai Traditional and Alternative Medicine, Ministry of Public Health, Thailand. After blending the three roots, herbal sachets containing a 1.4 g mix of the three roots were prepared. In order to eliminate any organism contamination, both the herbal sachets and the placebo were irradiated with gamma rays before being used in the clinical trial. The quality control of the herbal products, performed by the Faculty of Pharmacy, Mahidol University, included a stability test, heavy metal measurement (arsenic, lead, and cadmium), organism contamination, ash determination, and the like. High performance liquid chromatogram (HPLC) and thin layer chromatogram (TLC) were used to quantify the specific compounds of the herbs (Lueangamornnara et al., 2017).

For placebo preparation, the ingredients in 1.4 g were composed of avicel and corn starch. All components were prepared in 1 sachet.

Study design

This randomized, double-blind, placebo-controlled, pilot study for advanced HCC was conducted at Udon Thani Cancer Hospital, Udon Thani Province, Ministry of Public Health, Thailand, from January 2015 to December 2017. Patients were randomly assigned into experimental and placebo groups, each of which had ten patients. Randomization was generated using block 2 by the online block randomization software at www.randomization.com.

All patients provided written informed consent. The study was approved by the Institutional Review Board's Ethics Committee at the Department of Thai Traditional and Alternative Medicine, Ministry of Public Health, Bangkok, Thailand, in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable local laws. The study was registered at the Thai Clinical Trials Registry (no. TCTR 20180611001).

Patient eligibility

All eligible patients were diagnosed as hepatocellular carcinoma (HCC), and staging was determined using the Barcelona Clinic Liver Cancer (BCLC) classification system. The inclusion criteria were: (1) patients ≥ 20 years of age with incurable, advanced, or metastatic HCC with histological evidence on a biopsy specimen, or typical findings using phase-contrast computed tomography (CT); (2) patients that oncologist defined as no definitive therapy and receiving supportive care; (3) an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2; (4) total bilirubin ≦3 × upper limit of normal (ULN), aspartate transaminase (AST) ≦ x ULN, and alanine transaminase ≦5 × ULN; (5) hemoglobin ≧ 9 g/dl,

and a white blood cell count ≧ 3,000/ml, with an absolute neutrophil count ≧1,500/ml; and (6) patients with any Child–Pugh liver disease. The exclusion criteria were: (1) patients who had renal impairment with a calculated eGFR ≦60 ml/min; (2) the presence of other comorbid diseases, such as cerebrovascular disease, cardiovascular disease, and other malignancies; (3) a previous history of herbal drug hypersensitivity; and (4) patients with brain metastases or meningeal carcinomatosis.

Definitive cancer therapy means a design of the treatment plan to potentially cure cancer using one or more combinations of interventions, such as surgery, radiation, chemotherapy, or biological therapies. The primary purpose of definitive cancer therapy is to establish a cure, or to remove cancer cells from patients' bodies. In contrast, no definitive therapy means no specific treatment for a disease. Whereas, supportive care means symptoms management (http://www.medical-dictionary.thefree dictionary.com).

Treatment protocol and patient evaluation

Patients in the experimental group received one sachet of herbal recipe orally per day; they were required to dissolve the herbal powder in 1 L of drinking water, all of which had to be consumed during the same day. Those in the control group received one sachet of placebo per day, dissolving it in 1 L of drinking water. Every 4 weeks, the patients were followed up for a tumor assessment and evaluated for treatment adherence and adverse events. Routine laboratory and blood chemistry, such as complete blood count, fasting blood sugar, renal function, liver function, and alpha-fetoprotein, were assessed at the beginning of the trial and every 4 weeks subsequently. Hepatitis B surface antigen (HBsAg) was also investigated at the beginning to identify the common cause of HCC. Chest radiographs and electrocardiograms were performed as a baseline measurement and for the tumor assessments. Multiphase, contrast-enhanced computed tomography (CT) of the upper abdomen was done every 8 weeks. All patients were followed up and treated until they had progressive diseases, or there were unacceptable adverse events, or the patients refused treatment, or they died.

Outcome measurement

The primary efficacy outcome was the overall survival (OS) time. This was defined as the time from enrollment in the trial to either the date of death from any cause or the date of the last follow-up, and it was analyzed by intention to treat (ITT). The secondary efficacy outcome was the progression free survival (PFS) time, defined as the time from enrollment to radiological or clinical progression, analyzed by ITT. All tumor responses or stable diseases were evaluated by an investigator using the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). The quality of life was also assessed as a tertiary outcome using the Functional Assessment of Cancer Therapy–Hepatobiliary (FACT FHSI-18) questionnaires (Cella et al., 2013). The tertiary outcomes are not reported here.

Safety and adverse events monitoring

Complete blood counts and blood chemistry were assessed during each 4-week cycle. A urine pregnancy test was performed every 4 weeks for all female patients who were in their reproductive period. Each participant was asked to complete a daily care card to document their current symptoms and their illness every cycle. Safety was monitored and recorded every 4 weeks throughout the study by physical examination, including clinical and laboratory assessments. Adverse events were recorded and graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Patients who had an adverse event ≧ grade 3 related to the study treatment were discontinued from the trial.

Statistical analysis

The statistical analysis was done using PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA). The parameters referred to above were used to compare the two study groups, utilizing the independent t-test, the Mann–Whitney test, and Fisher's exact test, as appropriate. A Kaplan–Meier analysis and log-rank test were used to analyze and estimate all time-to-event endpoints. The time to event was defined as the period from enrollment in the trial to either disease progression or death. Differences were considered significant if the p-value was ≦0.05.

RESULTS

Heavy metal, organophosphate, and organism contamination

From our study, the three roots collected from Nong Bua Lamphu Province, northeast Thailand showed no contamination of any heavy metal, i.e., arsenic, lead, and cadmium. No residual organophosphate contamination nor organism was detected in our herbal materials. The GC-MS of three roots were demonstrated in supplemented data.

Patient characteristics

Twenty-three patients were assessed for eligibility in the trial during the study period. All patients had advanced hepatocellular carcinoma with no definitive therapy. Of the 23, only 3 were excluded, with the primary reasons being a poor liver function and/or an ECOG performance status over 2. The remaining 20 patients were enrolled and randomized into the placebo and experimental groups, each of which comprised 10 patients. The demographics of the two groups, such as their age and the gender differences, were well-balanced at baseline. All 20 patients were included in the intention-to-treat population. No patient withdrew during the trial. The median duration for follow-up of the patients in both groups was approximately 4 months. A diagram of the trial is shown in Figure 1.

The demographic and baseline characteristics of the patients in each group are at Table 1. Males predominated in both groups, with 90% in the treatment group and 80% in the placebo group. There was no statistical difference in the median ages of the two groups. In the case of the treatment group, ECOG performance status 1 was found in 7 patients (70%) and status 0 in 3 patients (30%). However, the placebo group demonstrated converse results, with ECOG performance status 1 being shown by 3 patients (30%) and status 0 by

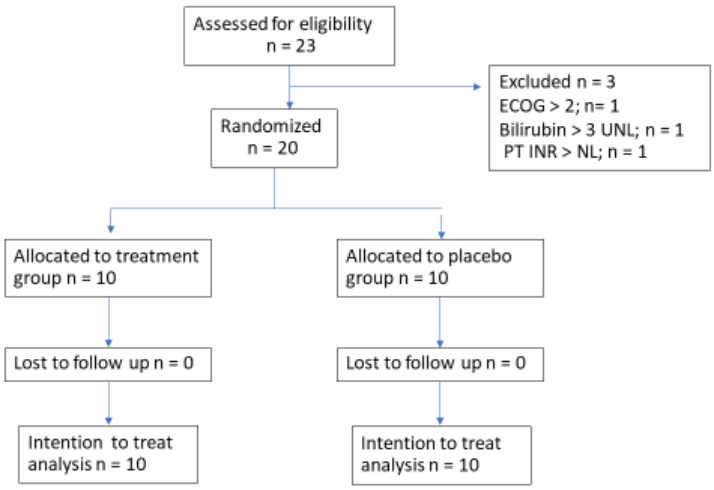

Figure 1. Trial profile. Patients were randomized into 2 groups, namely, the treatment and control groups, each comprising 10 patients. The time to event for termination of the treatment was based on either progression of the disease or death.

Table 1. Characteristics of patients in this study.

Characteristic	Treatment group (n=10)	Placebo group (n=10)	P-value
1. Sex			
Male	9 (90%)	8 (80%)	1.0
Female	1 (10%)	2 (20%)	
2. Age, years	56.6 ± 7.8	56.1 ± 5.3	0.869
3. ECOG status			
0	3 (30%)	7 (70%)	
1	7 (70%)	3 (30%)	0.073
2	0	0	
4. Child–Pugh classification			
A	2 (20%)	7 (70%)	
B	7 (70%)	3 (30%)	0.021*
C	1 (10%)	0	
5. Hepatitis B surface antigen-positive (HBsAg)	4 (40%)	2 (20%)	0.628
6. Alpha-fetoprotein (ng/ml)	1749.5 (23.4-484,000)	277.5 (6.6-94,006)	0.199
7. Alkaline phosphatase (Unit/L)	297.2 ± 183.7	161.2 ± 74.2	0.044*

The data are expressed as mean ± SD, number (%), and median (minimum-maximum).
*Data showing a significant p-value (< 0.05).

7 patients (70%). The Child–Pugh classification in the treatment group was evaluated as class B in 7 patients (70%) and class A in 2 patients (20%), whereas the placebo group had 7 patients (70%) classified as class A and 3 (30%) as class B. Compared with the placebo group, the Child–Pugh classifications in the experimental group showed a significantly severe classification, with a p-value of 0.021. Etiology related to the hepatitis B virus was found in the treatment and placebo groups, accounting for 40 and 20% of patients, respectively, with no statistically significant difference between the two groups.

Initially, the treatment group had much larger tumors than those of the placebo group, with a median size of 123.3 and 93.2 cm, respectively. The median serum alpha-fetoprotein level for the treatment group was much

higher than that for the placebo group, but there was no statistical significance between the groups. However, the mean serum alkaline phosphatase level was statistically significantly much higher for the treatment group than the placebo group, with a p-value = 0.044. Tables 2 and 3 showed the alkaline phosphatase and alpha-fetoprotein levels of patients in this study. The other liver function parameters of the two groups, such as serum bilirubin, serum alanine aminotransferase, and serum albumin, were mostly similar, with no statistical significance. The patients' laboratory parameters (for instance, complete blood count, urinalysis, fasting blood sugar, renal function, and uric acid) also showed no significant differences between the groups. No concomitant disease was found in these 20, intention-to-treat patients. The drug adverse events of the treatment protocol were also evaluated for all patients. By the end of this study, the longest time that patients received the herbal therapy was 7 months. No patients experienced intolerance nor adverse events related to the therapy during the trial.

Treatment response

All 20 patients from both groups were followed up until disease progression or death. No patient had a complete nor partial response. At the end of the study, 4 patients in the treatment group and 4 in the placebo group experienced disease progression, with tumor enlargement at the primary and metastatic sites. Thus, no statistical significance was noted in terms of disease progression. As to the remaining patients, a total of 11 deaths occurred, with the most common causes of death being sepsis and multiple organ failure. One placebo patient still remained with stable disease at the end of the trial. Based on our results, the median time to event of the experimental group was 73 days, whereas that of the placebo group was 59 days, at 75 percentile. A Kaplan–Meier curve of the patients' clinical

Table 2. The alkaline phosphatase levels of all patients enrolled in this study. Patients were followed up until the time to event, i.e., disease progression or death.

No.	Group	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
1	Placebo	158	149	161	174	189	195	192	183	166	105	174	180
2	Placebo	80	71	80	81	73	67	75	81	75	88	74	62
3	Placebo	141	146	132	148	144	146	125	137	131	152	159	
4	Placebo	176	157	131	122	130	134	112	147	198	222		
5	Placebo	101	121	131	118	128	125	119					
6	Placebo	83	88	92	91	121	148	219					
7	Placebo	238	223	474	733	821							
8	Placebo	180	164	93	116	131							
9	Placebo	134	186	441	243								
10	Placebo	321	297	246									
11	Treatment	215	211	210	184	201	202	158					
12	Treatment	188	189	171	173	239	268	222					
13	Treatment	740	493	483									
14	Treatment	349	210	469									
15	Treatment	149	152	199									
16	Treatment	218	208	232									
17	Treatment	464	500	593									
18	Treatment	195	266	278									
19	Treatment	157	169	195									
20	Treatment	297	326	349									

Table 3. The alpha-fetoprotein levels of all patients enrolled in this study. Patients were followed up until the time to event, i.e., disease progression or death.

No.	Group	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
1	Placebo	6.6	6.7	7.2	7.2	7.3	8.7	7.6	9.8	13.0	14.1	16.0	19.4
2	Placebo	15.1	16.1	23.8	38.5	60.8	58.5	56.0	69.6	93.2	76.4	90.9	132.0
3	Placebo	248.1	342.8	439.7	591.0	699.2	652.0	1,068.0	1,202.0	1,544.0	2,086.0	1,747.0	
4	Placebo	326.3	321.9	287.4	186.2	229.4	194.4	86.0	508.7	769.0	897.9		
5	Placebo	6.6	7.7	8.0	9.2	11.8	7.6	5.5					
6	Placebo	277.9	713.7	1,144.0	2,186.0	4,217.0	8,295.0	15,480.0					
7	Placebo	277.2	326.7	337.2	489.6	670.0							
8	Placebo	3,163.0	5,383.0	4,210.0	5,451.0	5,138.0							
9	Placebo	94,006.0	118,960.0	109,297.0	66,480.0								
10	Placebo	3,821.0	7,309.0	19,337.0									
11	Treatment	284.9	359.0	579.0	711.7	654.7	962.9	1,718.0					
12	Treatment	1,621.0	715.4	971.5	1,518.0	2,559.0	3,970.0	6,299.0					
13	Treatment	23.4	32.8	30.7									
14	Treatment	229.5	431.9	1,336.0									
15	Treatment	280.8	492.4	412.2									
16	Treatment	1,878.0	2,890.0	4,299.0									
17	Treatment	47,835.0	64,145.0	82,498.0									
18	Treatment	70,022.0	97,513.0	226,532.0									
19	Treatment	161,383.0	162,190.0	203,915.0									
20	Treatment	484,000.0	484,000.0	484,000.0									

responses is at Figure 2. The overall clinical outcomes of the treatment and placebo groups did not differ.

DISCUSSION

The primary objective of this study was to evaluate the efficacy and side effects of a herbal recipe which is commonly used for advanced HCC in the northeastern region of Thailand. Several reasons prompted us to conduct this trial. Firstly, treatment with targeted therapy may not be available to all patients in this category in Thailand because of financial issues. Moreover, there are many liver cancer patients in northeast Thailand who have ever used this herbal recipe and are still alive. Furthermore, this herbal recipe has never been investigated in a clinical trial for advanced HCC before. It is necessary to note that HCC is an aggressive malignancy. Most Thai HCC patients consult oncologists when they have symptoms related to severe chronic liver diseases, such as ascites and marked jaundice. Therefore, the diagnosis of HCC is often made when the patients are in advanced disease stages. Notably, a subgroup of poor prognostic factors and worse outcomes in advanced HCC has been reported, namely, high alpha-fetoprotein serum levels, Child–Pugh class B, a hepatitis B viral infection, old age, a tumor size larger than 3 centimeters, and multiple tumor nodules (Ng et al., 2017). Moreover, a high ECOG performance status (i.e., over 2) is also considered to be a poor prognostic factor for overall survival in this disease (Chan et al., 2017). It should be noted that this current study appears to have recruited patients with a more extensive disease burden in the treatment group, which is discussed below.

The present study compared data for advanced hepatocellular carcinoma. As to etiology, the treatment and placebo groups showed no statistical significance for hepatitis B viral infection. Whether the herbal recipe is beneficial for viral infection or not remains unclear.

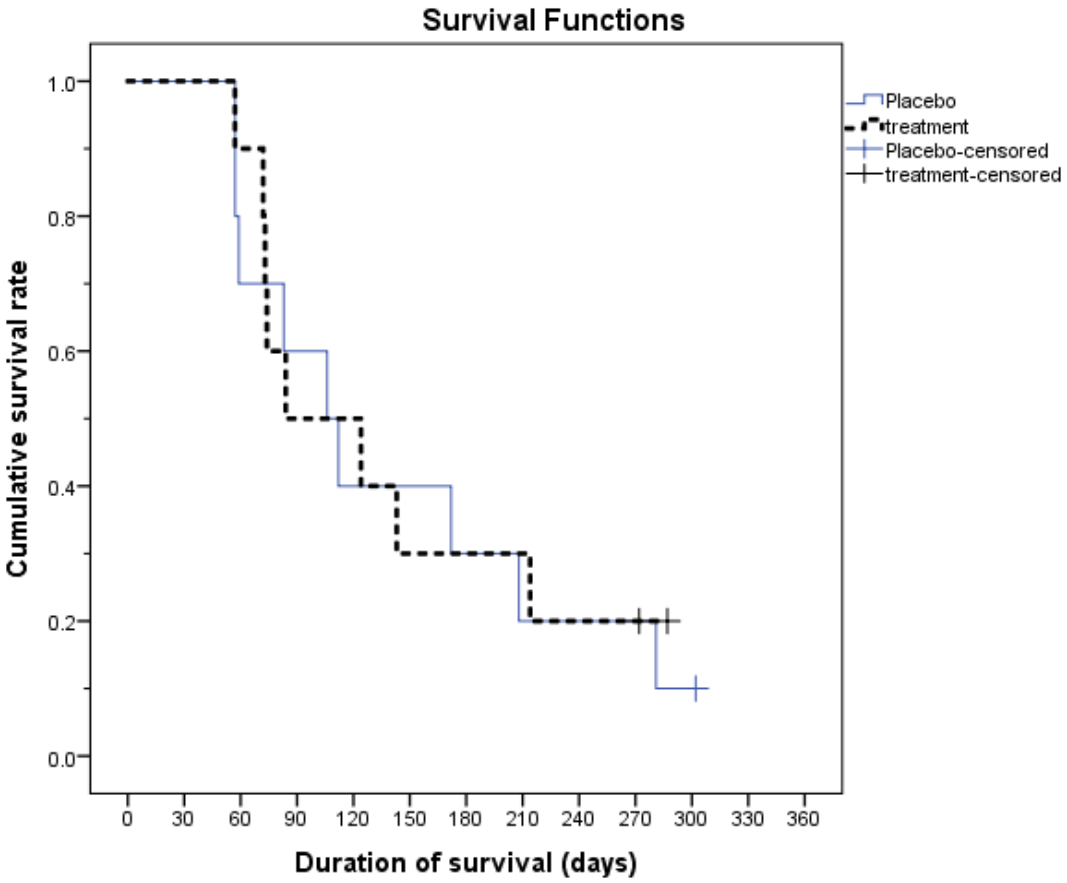

Figure 2. Kaplan–Meier curve. Patients in the treatment group shown as a dashed line, and in the control group as a solid line. The time to event was defined as the time to progression of the disease or death related to disease (censor).

Unfortunately, patients in the treatment group had much worse prognostic factors than those in the placebo group, namely, much higher alpha-fetoprotein serum levels, larger tumor sizes, and a worse ECOG performance status. A much higher alkaline phosphatase level was observed in the treatment group than the placebo group, with statistical significance. Moreover, the Child–Pugh classification of the treatment group, with class B at 70%, was significantly higher than that of the placebo group, with a p-value = 0.021. Child–Pugh class B is already recognized as one of the several poor prognostic factors. Taking all of the data into consideration, the patients in the treatment group had a much higher tumor burden and a larger number of poor prognostic factors than those in the control. This is considered as the non-selection bias. The reason for this occurrence might be due to the small number of patients in each arm of this pilot study.

In the ITT analysis of patient-focused outcomes, the median survival time of the treatment group was 84 days, whereas that of the placebo group was 106 days. Interestingly, at 75 percentile, the time to event of the treatment group was 73 days, compared with only 59 days for the placebo group. It means that patients in the treatment group had a longer time before reaching the event point than those in the placebo group. With only ten patients in each arm, there appeared to be a trend toward benefits with this herbal recipe for advanced hepatocellular carcinoma. Regarding the safety of this herbal recipe, no adverse events were detected in the treatment group.

The Thai herbal recipe consists of roots from three herbal plants, namely, *E. longifolia*, *D. obtusifolius* and *T. uliginosa*. Of the three, *E. longifolia* and *D. obtusifolius* have been investigated for their anticancer properties and found to have potent effects on cancer cell growth inhibition *in vitro*, especially *E. longifolia*. Therefore, it is highly possible that the anticancer properties of this Thai herbal recipe would be derived from the antiproliferative activities of *E. longifolia* and *D. obtusifolius*. On the other hand, increasing levels of oxidative stress and inflammation have been reported to play a key role in the progression of patients with HCC (Liu et al., 2016; Yahya et al., 2013; Akinobu and Kazuhide, 2015). Based on a previous report, *D. obtusifolius* provides an anti-inflammatory effect which can suppress the production of multiple inflammatory cytokines (Park et al., 2017). This

might have been helpful in decreasing the oxidative stress levels and producing the trend to prolong the disease progression in the treatment group, even though this group had many more poor prognostic factors.

There are two limitations to this study. Firstly, given that it was a pilot study, we recruited a small number of participants, with only 10 patients in each arm. Thus, the lack of statistical significance in the various patients' characteristics was most likely due to this. In addition, the study showed a non-selection bias in the treatment group, with an unexpected, higher level of poor prognostic factors than in the control group. This might be why the anticipated tumor responses and clinical outcomes were not obtained in the treatment group.

In conclusion, this was the first, clinical, randomized, double-blind, placebo-controlled pilot study of the Thai herbal recipe which is commonly used in northeastern Thailand. We evaluated its efficacy and side effects in the treatment of advanced HCC. The study demonstrated that the herbal recipe might have some advantages for this specific group of patients, especially in combination with supportive therapy. Moreover, a future study involving a combination of the herbal recipe with conventional chemotherapy could also be considered.

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