

**Research Article**

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Report the Effective of Integrated Palliative Care using for Advanced Cancer as Second-Line or Later Treatment by Herbal Extractive Medicine

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Background: The on-going treatments of unresectable pancreatic, hepatocellular and late-stage lung cancer (PC\HCC\LC) are less effectiveness as second-line or later treatment. However, the palliative care is alternative option. Here, we reported the patients who received palliative care by herbal extractive medicines (CHM).

Methods: 13 pancreatic, 31 hepatocellular and 168 lung cancer patients were enrolled. CHM (Senghuang, SH; Xianhe Baijiang, XB), which approved by the China Food and Drug Administration (CFDA), hyperthermia and arginine were initiated. Survival time, quality of life (QOL) and toxicity were evaluated.

Result: The average ECOG score improved and no severe hematology and digestion side-effects were observed. In PC group, the median and the average survival time were 5.1 and 6.5 months; The 3-, 6-, and 10-month survival rates were 92.3%, 46.2%, and 30.8%, respectively. The longest survival time was 16.7 months and patient still alive. In HCC group, the average and median survival time were 12.48 and 5.03 months; The 3-, 6-, and 12-month survival time rates were 77.42%, 38.71%, and 29.03%, respectively. The longest survival time was 84.2 months. In LC group, the 6 months, 1-, 2- and 5-year survival time rates were 33.93%, 19.05%, 14.29% and 4.17%, respectively. Meanwhile, in lung cancer group, once the survival time was over 6 months, the average and median survival time were 29.98 and 14.80 months; and the 1-, 2- and 5-year survival time rates were up to 56.14%, 42.11% and 12.28%, respectively.

Conclusion: CHM can be considered as complementary and alternative medicine that provide moderate effective and low toxicity for advanced cancer.

Keywords: Palliative care; Herbal extracted medicine; Advanced cancer

Introduction

Lung cancer (LC), hepatocellular carcinoma (HCC) and pancreatic cancer (PC) are severe malignant cancer. According to GLOBOCAN 2012 report, accounting for 19.45% of all newly diagnosed pancreatic cancer cases in China and 19.27% of all deaths from pancreatic cancer worldwide [1]. Usually, surgery, chemotherapy, radiation therapy and target therapy are used as the first line treatment. Surgery should have been a potentially curative therapy for early stage lung cancer, hepatocellular carcinoma and pancreatic cancer [2], however, many patients are not eligible for surgery [3]. For instant, surgical resection may offer a 5-year survival up to 70% in liver cancer patients, but for patients with advanced disease, surgical resection is an option for less than

20% [4]. Recently, PD-1 and PD-L1 anti-body therapy had been approved in lung and liver cancer, but no standard treatments for such stage patients after 1st/2nd line failure are recommended. Nowadays, the median overall survival (OS) for late-stage liver, lung and pancreatic cancer were 7.9 months, 8.2 and 5.3 months, respectively [1, 5-8]. Integrated palliative care is focused and seems as rational anti-cancer way for advanced cancer patients with low toxicity and moderate effectiveness. Herbal extractive medicines represent relatively low-toxicity and anti-cancer ability of multi-targets by regulating tumor microenvironment and immune system [9-11]. According to clinical studies, while the late-stage patients who had been failure with second-line or later treatment, integrated palliative care that includes herbal extractive medicine

was considered priority as a salvage treatment. Meanwhile, our previous laboratory studies have indicated that TGF- β , EGF, VEGF, IL-10 cytokines expression and micro-vessel density could be downgraded by Senghuang capsule (SH) and Xianhe Baijiang capsule (XB) that extracted from Ginseng, Herba Agrimonia, Hairyvein and Arginine etc in 4T1 and CT26 cell lines model.

In this study, herbal extractive medicines were given to advanced lung cancer, hepatocellular cancer and unresectable pancreatic cancer patients, and quality of life (QOL), toxicity and survival time were observed.

Methods

Patients

In total, 212 late-stage cancer patients including 13 unresectable pancreatic cancer patients, 31 hepatocellular cancer patients and

168 lung cancer patients, who were failure with first line treatment or could not tolerate toxicity treatments, were enrolled. All patients had radiographic and pathological diagnosis. The retrospective study had been approved by Ethics Committee of Chengdu Fuxing Hospital.

Drugs and treatment

Herbal extractive medicines, which approved by the Chinese Food and Drug Administration (CFDA), hyperthermia and arginine were used. Survival time, quality of life (ECOG score) and toxicity were observed. The prescription was shown in Figure 1: Arginine 15ml, Senghuang capsule (SH) 1.80g and Xianhe Baijiang capsule (XB) 0.8g Qid and hyperthermia 41-41.5°C Biw for four weeks as one cycle. Previous test by HPLC shows that the main ingredients of SH and XB consist of flavonoid, saponins and glucosides etc (Figure 1).

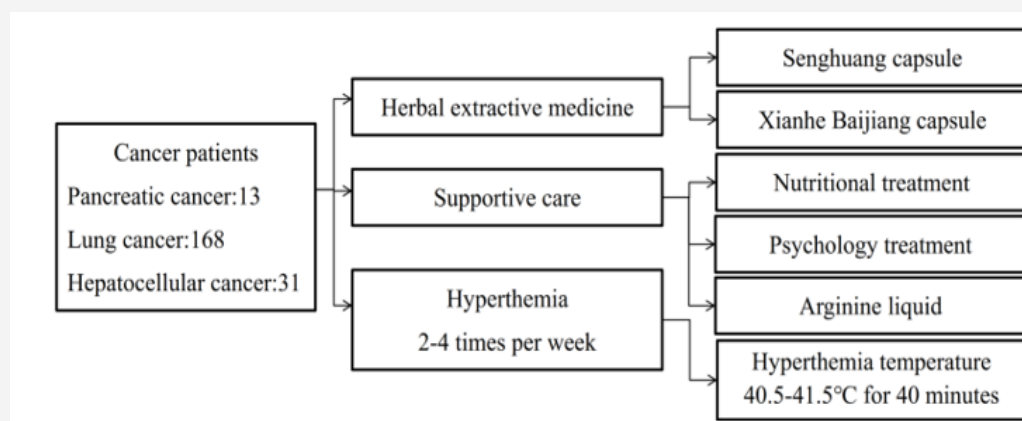


Figure 1: Herbal medicines, hyperthermia and supportive care were combined and used as complementary and alternative medicine. Herbal extractive medicine and hyperthermia acted on regulating tumor growth. Supportive care provided moderate nutrition such as arginine, glutamine and electrolyte, and psychology therapeutic intervention was given at the beginning.

Data collection and safety & efficacy assessment

Prior therapies, patient's condition and drugs' dose, treatment information (i.e. current dose, dose adjustments), adverse events of LC, PC and HCC were recorded. ECOG score were documented at baseline and/or follow-up. Efficacy criteria included overall survival (OS) and quality of life (QOL). Adverse events were recorded and graded by National Cancer Institute Common Terminology Criteria version 3.0 (CTCAE 3.0).

Result

Patient characteristics and treatment

A total of 212 patients were enrolled including liver cancer (HCC), pancreatic cancer (PC) and lung cancer (LC) in late stage. Patients demographic and baseline characteristics was shown in Table 1. The median age was 58.0(PC), 62.7(LC) and 55.0(HCC) year-old, respectively, and the majority of patients were male (53.8% PC, 64.9% LC and 77.4% HCC). 4.7% (10/212) patients were tumor-node-metastasis (TNM) stage at III, and 95.3% (202/212) patients were stage IV. According to the Eastern Cooperative Oncology Group (ECOG) score evaluation criteria, 92.3%(PC), 34.8%(HCC)

and 36.3%(LC) were up to 2 score, and 7.7%(PC), 65.5%(HCC) and 63.7%(LC) were at 3-4 score, respectively. Treatment plan was shown in Table 2 (Table 1,2).

Table 1: Description of patients' distribution. Patients who were suffered from III-IV stage cancer or the first/second line treatment failure were enrolled. (HCC: hepatocellular carcinoma; PC: pancreatic cancer; LC: Lung cancer).

	Unresectable PC (n=13)	Stage III-IV LC (n=168)	Stage IV HCC (n=31)
Median age	58	62.7	55
Male	7	109	24
Female	6	59	7
ECOG Performance Status			
2	12	61	8
4-Mar	1	107	23
Prior-Treatment			
0	8	27	5
2-Jan	4	141	26
TNM Stage			
III	0	10	0
IV	13	158	31

Table 2: Treatment plan was shown. Arginine liquid, Senghuang capsule (SH) and Xianhe Baijiang capsule (XB) were given four times per day by oral use.

	Treatment	Times
Arginine Liquid	15.0ml	Qid
Senghuang Capsule (SH)	0.8g	Qid
Xianhe Baijiang Capsule (XB)	1.2g	Qid
Hyperthermia	Biw	
Supportive Care	If needed	

Safety assessment

Safety data were reported in Table 3. Dyspepsia and skin injure were the most common adverse events. Dyspepsia was drug-related adverse events that was experienced 15.1 % (n=32) patients under grade 2; and no patients suffered over grade 3 on hematology as drug-related adverse events. Meanwhile, 10.9% patients (n=23) experienced skin injure events duo to hyperthermia treatment. No patients were excluded caused by severe side-effect (Table 3).

Table 3: Drug-related side-effects were shown (all grades), Data were presented as count (percentage).

	Grade 1-2	Grade 3-4
Dyspepsia	15.1(32)	0
Skin Injury	10.9(23)	0
Hematology		0
RBC	34.9(74)	0
WBC	63.7(135)	0
PLT	12.7(27)	0
Treatment Emergent Death	0	0

Efficacy

First, for 168 lung cancer patients. The 6 months, 1-, 2- and 5-year survival time rates were 33.93%, 19.05%, 14.29% and 4.17% (Table 4), respectively. However, once the survival time was extended over 6 months (57/168), the average and median survival time were up to 29.98 and 14.80 months (Table 5); and the 1-, 2- and 5-year survival time rate were up to 56.14%, 42.11% and 12.28% (Table 4), respectively. The longest survival time reached to 134 months (Table 5). According to ECOG criteria, QOL in 59.6 % (34/57) patients were improved (Figure 2). Meanwhile, according to the data, such sub-group patients, who respond to herbal extractive medicine at least one month, could get better benefit from herbal extractive medicine based palliative care, and the drug-related effectiveness would maintain. Second, for unresectable pancreatic cancer patients. The 3-, 6-, and 10-month survival rates were up to 92.3%, 46.2% and 30.8%, respectively (Table 4). The median and the average survival time were up to 5.1 and 6.5 months. The longest survival time was 16.7 months and patient still alive (Table 5). According to ECOG, QOL in 53.8 % (7/12) patients were improved (Figure 2). Third, for liver cancer patients. The 6-, 12-, 24 months and 5-year survival time rates were up to 45.16%, 29.03%, 12.90% and 3.23%, respectively (Table 4). The average and median survival time were 12.48 and 5.03 months, respectively, and the longest survival time was 84.17 months (Table 5). According to ECOG, QOL in 28.5 % (4/14) patients were improved and QOL in another 28.5 % (4/14) patients were stable (Tables 4,5) (Figure 2).

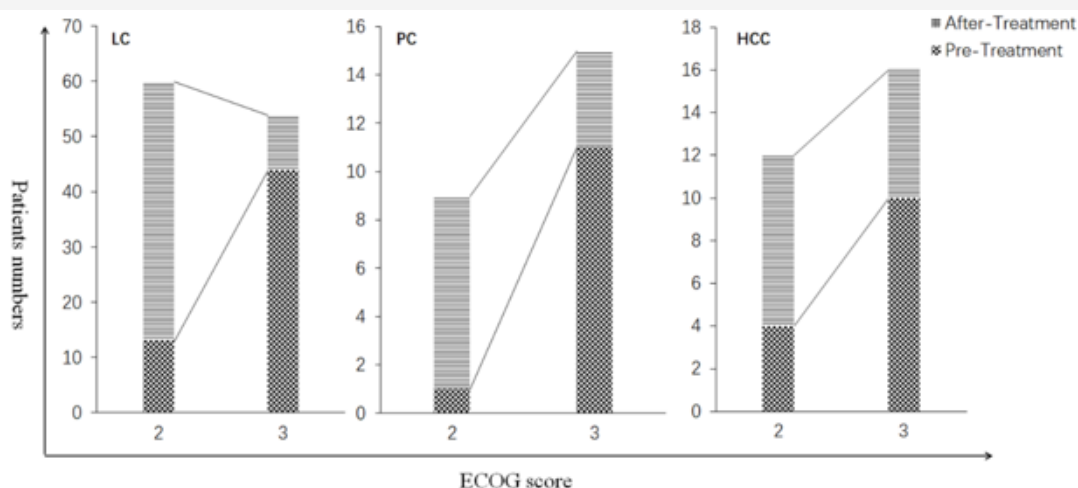


Figure 2: Comparison of ECOG score between pre-treatment and 6 months later for LC and HCC, or 3 months later for PC. According to the data, life quality of the patients has improved after treatment.

Table 4: Distribution of survival time of the LC, PC and HCC patients. The result shown that such terminal stage patients would reach acceptable survival time by using herbal extractive medicine as alternative treatment.

		3 Months	6 Months	9 Months	12 Months	24 Months	60 Months
LC	All patients (%)		33.93 (57/168)		19.05 (32/168)	14.29 (27/168)	4.17 (7/168)
	Once alive over 6 months (%)				56.14 (32/57)	42.11 (27/57)	12.28 (7/57)
PC (%)		92.3 (12/13)	46.2 (6/13)	30.8 (4/13)			
HCC (%)			45.16 (14/31)		29.03 (9/31)	12.9 (4/31)	3.23 (1/31)

Table 5: The median, average and longest survival time of Lung cancer patients, pancreatic cancer and HCC were shown. According to the data, for the LC, 57 patients who alive over 6 month were observed and the average survival time was up to 29.98 months; for 13 PC and HCC patients, the median survival time was up to 6.5 months and 12.48 months, which reached the preview studies.

	LC(Month)	PC(Month)	HCC(Month)
Median Survival Time	14.8	5.1	5.03
Average Survival Time	29.98	6.5	12.48
Longest Survival Time	134	16.7	84.17

Discussion

This paper reported the patients who fail to on-going anti-cancer treatments. Approximately 30% of cancer patients who received first-line therapy need further subsequent treatment [12]. Tyrosine kinase inhibitor (TKI) such as Gefitinib, Solafinib or Laptinib have been shown to improve survival and symptoms in NSCLC and HCC. However, despite advances in pancreatic cancer therapy, the average survival rate at 5 years remains only 6% [13], especially for unresectable pancreatic cancer. Within these few treatment choices, adverse effects of recent drugs have further restricted patient clinical use [14], and their effectiveness for HCC and pancreatic cancer is not satisfactory. Nevertheless, herbal extractive medicines represent relatively low-toxicity and anti-cancer ability of multi-targets by regulating tumor microenvironment and immune system, which is preferred as second or later treatment and manage symptoms [15]. In clinical trials, it was proved by multidisciplinary teams, but the intensity of interventions varied considerably. Based on some clinical trials, integrated palliative care decreased overall mortality (HR 0.77; 95% CI 0.61 to 0.98), and short-term (1-3 months) effects of integrated palliative care on QOL was improved, but longer-term (6-12 months) effects on QOL was not improved [16-20].

Recently, once the definition of palliative care intervention characteristics was interpreted clearly, the more precise understanding of the impact of integrated palliative and oncology care on outcomes would approach [21]. Study by Temel et al, 151 NSCLC patients were delivered to early palliative care integrated with ongoing oncology care or to standard oncology care alone group in order to prove the importance of supportive care. Not only the patients who received early palliative care had better quality of life and less depression, but also were less likely to receive useless chemotherapy (33% vs. 54% in the standard chemo-treatment, $p = 0.05$). The patients, who received early palliative care, lived longer compared with standard treatment group (11.6 months vs. 8.9 months, $P=0.02$) [12,17]. Meanwhile, palliative care for pancreatic cancer were recommended in the course of illness and concurrently with active treatment [22, 23]. The use of Chinese herbal medicines (CHM) in symptom management for cancer palliative care is common in Chinese populations and clinical evidence on their effectiveness is already to be confirmed, and quality of life among cancer patients are affected. More than that, herbal medicines acted on the tumor and micro-environment though multi-targets [11]. Depend on our laboratory research, active ingredients, which were extracted from Ginseng, Herba Agrimonia, White Flower Patrinia

Herb etc., consist of glycoside, saponin and flavone and could inhibit proliferation on HepG2, A549, 4T1 and CT26 cell lines, and decrease p-AKT and mTOR protein expression.

In this report, the late-stage patients received acceptable treatment result by using herbal extractive medicines as second or later treatment, which provide moderate effective and low-toxicity, and it could be considered as an as complementary and alternative medicine. In PC group, the median and the average survival time were 5.1 and 6.5 months; The 3-, 6-, and 10-month survival rates were 92.3%, 46.2%, and 30.8%, respectively. The longest survival time was 16.7 months and patient still alive. In HCC group, the average and median survival time were 12.5 and 5.0 months; The 3-, 6-, and 12-month survival time rates were 77.4%, 38.7%, and 29.0%, respectively. The longest survival time was 84.2 months. In LC group, the 6 months, 1-, 2- and 5-year survival time rates were 33.9%, 19.1%, 14.3% and 4.2%, respectively. Meanwhile, in lung cancer group, once the survival time was over 6 months, the average and median survival time were 29.98 and 14.8 months; and the 1-, 2- and 5-year survival time rates were up to 56.1%, 42.1% and 12.3%, respectively. Meanwhile, the most common drug-related adverse event was gastrointestinal, especially dyspepsia, and just a low percentage of patients reported fatigue or diarrhea. No hematology side-effect, which was up to grade 2, was observed.

In summary, early involvement of palliative care can lead to less utilization of useless care caused by severe side-effects. Not only, in 2012, the American Society for Clinical Oncology (ASCO) has made a recommendation for 'combined standard oncology care and palliative care consideration early in the course of illness for any patient with metastatic cancer and/or high symptom burden [24, 25], but also Chinese herbal medicine(CHM) may be considered as an add-on to conventional medicine in the management of pain, constipation, anorexia and fatigue in cancer patients. Thus, early palliative care was not ought to be recognized as a final method, and it was equally important to chemotherapy. This study makes an important contribution to the body of evidence on the efficacy of herbal extractive medicine that acted as an alternative method in late-stage lung, pancreatic and liver cancer which could be recommended as an initial treatment as second line or later treatment. Future RCTs should improve outcome measurement and report detailed safety outcomes.

Conclusion

CHM can be considered as complementary and alternative medicine that provide moderate effective and low toxicity for advanced cancer.

Acknowledgment

None.

Conflict of Interest

The authors declare that there is no conflict of interest.

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