Chinese-German Journal of Clinical Oncology August 2010, Vol. 9, No. 8, P452–P458
DOI 10.1007/s10330-010-0629-y

Efficacy and safety of viscum fraxini-2 in advanced hepatocellular carcinoma: a phase II study

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Received: 27 May 2010 / Revised: 19 June 2010 / Accepted: 5 July 2010

Abstract ***Objective:*** New systemic therapies are needed to improve the prognosis of patients with advanced-stage hepatocellular carcinoma. The study was conducted to determine the efficacy and safety of viscum fraxini-2 in advanced Hepatocellular carcinoma. ***Methods:*** A phase II study with a two-stage design that enrolled a total of 120 patients with chemotherapy naïve advanced hepatocellular carcinoma. The mistletoe preparation for the study is an aqueous injectable solution that contains one milliliter of viscum fraxini. Two ampoules of viscum fraxini were administered subcutaneously once weekly. ***Results:*** Chronic hepatitis C virus infection was the predominant cause of liver disease (60%) in studied cases. According to the response evaluation criteria in solid tumors 24 patients (20%) achieved objective response (including 2 complete responses) and 40 patients (33.3%) achieved stable disease. The median progression free survival for all patients was 4 months (range 1–28 months; 95% CI 3.3:4.7 months). The median overall survival for all patients was 8 months (range 1–28 months; 95% CI 6.3:9.7 months). The median survival for patients who achieved responsive or stable disease was 16 months. The toxicity was generally mild and well tolerated, mainly in the form of local reaction and fever. There were no drug related discontinuation or toxic deaths. ***Conclusion:*** Viscum fraxini-2 is an effective, safe treatment for patients with advanced hepatocellular carcinoma. Further randomized controlled trials are recommended.

Key words viscum; fraxini-2; HCC; phase II

Hepatocellular carcinoma (HCC) is a major health problem with a rising incidence all over the world [1]. It is the fifth most common neoplasm in the world, and the third most common cause of cancer-related mortality [2].

Several treatment modalities are available for patients with HCC, including resection, liver transplantation, local ablation, transarterial therapy, systemic chemotherapy, hormonal therapy, immunotherapy and radiation therapy. Surgical resection, local ablation and liver transplantation are the mainstay of treatment of localized HCC. Unfortunately, only 25% of patients will present with localized disease and can receive such a potentially curative therapy [3]. So the majority of patients with HCC present at an intermediate or advanced stage where, effective systemic chemotherapy agents are needed [4].

Large numbers of controlled and uncontrolled clinical studies have been performed with most of the major classes of cancer chemotherapy, given intravenously as single agent or in combination. The consensus was that no single agent or combination of agents given systemically reproducibly leads to more than 25% response rates or has any effect on survival. No combination of these drugs had been associated with survival beyond that of untreated controls [4–7]. Recently a large randomized phase III study, the SHARP trial [8], was conducted and in this study, 602 patients with biopsy-proven advanced HCC were randomized to receive either sorafenib (400 mg twice daily, $n = 299$) or a placebo ($n = 303$). This trial represents the first randomized systemic therapy trial that demonstrates the overall survival benefit of systemic treatment in patients with advanced HCC, and proofs that development of novel agents will improve the management of HCC.

Viscum album L. is a semi parasitic plant growing on different host trees [9]. The extracted mistletoe preparations are among the most widely used unconventional cancer therapies in Central Europe. Viscum Fraxini is an aqueous extract of mistletoe [10]. It has many biologically active substances, the best investigated include: Lectins inhibit tumor growth and metastasis by increasing apoptosis, direct cytotoxicity and inhibiting angiogenesis. Vis-

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cotoxins cause membranolysis. Polysaccharides activate natural killer cells. Vesicles enhance T-cell proliferation especially helper cells [11, 12].

In a systematic review on controlled clinical trials, 23 studies were identified: 16 randomized, 2 quasi-randomized and 5 non-randomized. Cancer sites included breast, lung, stomach, colon, rectum, head and neck, kidney, bladder, melanoma, and genital. Among these studies, statistically significant positive outcomes were reported for survival (n = 8), tumor remission (n = 1), overall quality of life (n = 3), and quality of life in relation to side effects during cytoreductive therapy (n = 3) [10]. A more recent review evaluated the therapeutic effectiveness of viscum album extract on gynecological and breast cancer. The review included 19 randomized, 16 non-randomized controlled studies, and 11 single-arm cohort studies. Nine randomized controlled trials and 13 non-randomized controlled studies assessed survival; 12 reported a statistically significant benefit, the others either a trend or no difference. Single-arm cohort studies investigated tumor behavior, and safety. Tumor remission was observed after high dosage and local application. The treatment was well tolerated [13]. These positive results and the need for effective safe systemic agents for patients with advanced HCC prompted this phase II study to determine the response rate to viscum fraxini-2 in advanced HCC. The secondary objectives were to evaluate the safety of the drug, the predictive factors of tumor response, and to estimate the progression free and overall survival in studies patients.

Patients and methods

This was a prospective uncontrolled phase II trial in patients with advanced HCC. The protocol was approved by the institutional review board. Informed consent was obtained from each patient.

Patient characteristics

The study population consisted of patients with advanced-stage HCC. The diagnosis of HCC was confirmed by pathological analysis or α-fetoprotein > 400 ng/mL with a hepatic tumor highly suggestive of HCC by imaging studies. Patients were classified as having advanced disease if they were not eligible for surgical or locoregional therapies. Patients were required to have at least one target lesion that could be measured in one dimension.

Exclusion Criteria included: (1) Eastern Cooperative Oncology Group (ECOG) performance status > 2; (2) Advanced hepatic decompensation (Child-Pugh class C); (3) Advanced medical co-morbidity; (4) Previous systemic therapy; (5) Other malignancy or concomitant anti-tumor therapy including tamoxifen and interferon.

Treatment schedule and toxicity assessment

The mistletoe preparation for the study is an aqueous injectable solution. It contains one milliliter of viscum fraxini in dilution stage-2 (15 mg extract of 20 mg mistletoe herb from ash tree, diluted in di-natrium-monohydrogen phosphate, ascorbic acid and water) which is equivalent to 10 000 ng/mL injection ampoules. Two ampoules of viscum fraxini-2 were administered subcutaneously once weekly. The treatment was administered till unacceptable toxicity or documented progression or if the patient chose to discontinue treatment. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria, version 3.0.

Pretreatment, follow-up, and response evaluation

Prior to treatment all patients provided a complete history and underwent thorough physical examination. Laboratory studies included a complete blood count, biochemical liver function tests, serum creatinine, electrolyes and AFP. Radiological evaluation included chest X-ray, ultrasonography (US) and triphasic computerized scan (CT) of the abdomen, and a nuclear bone scan when needed.

Patients were seen on a weekly basis during treatment for history taking and physical examination. A complete blood count serum creatinine and liver functions were performed every 4 weeks. The tumor was assessed by CT scan of the abdomen every 8 weeks. Responses were evaluated by independent staff radiologists and confirmed by CT after 4 weeks. Tumor response was classified on the basis of the response evaluation criteria in solid tumors guidelines (RECIST) [14].

Statistical analysis

A phase II study designed with a 90% power to exclude a true response rate of < 10% and detect a true response rate of ≥ 20%. The study progressed using the Simon's two-stage design [15], recruiting a total of 42 patients in the first stage; the trial will be terminated if 4 or fewer patients respond. If the trial goes on to the second stage, a total of 120 patients will be studied. If the total number responding is less than or equal to 17, the drug is rejected. The first interim analysis suggested potential activity (10 patients responded); therefore, patient enrollment was permitted to continue.

Data were analyzed on a personal computer running SPSS© for windows (Statistical Package for Social Scientists) Release 15. All tests are considered significant if (P< 0.05). For descriptive statistics of qualitative variables the Frequency distribution procedure was run with calculation of the number of cases and percentages. For descriptive statistics of quantitative variables the Mean, Range and Standard Deviation were used to describe central

Table 1 Patient characteristics

	n	%
Sex		
Male	83	69.2
Female	37	30.8
Performance Status (ECOG)		
0	3	2.5
1	59	49.2
2	58	48.3
Ascites		
Absent	56	46.7
Present	64	53.3
Hepatitis		
HCV (+)	72	60.0
HbsAg (+)	26	21.7
Both (+)	10	8.3
Virology (–)	12	10.0
Child-pugh class		
A	37	30.8
B	83	69.2
Number of lesions		
Single	48	40.0
Multifocal	72	60.0
Okuda stage		
I	30	25.0
II	90	75.0
Metastasis/macro-vascular invasion		
Absent	53	44.2
Present	67	55.8
Age		
Mean (SD)	56.0 (9.0)	
Range	38.0–81.0	
Bilirubin (mg/dL)		
Mean (SD)	2.4 (2.1)	
Range	0.3–12.0	
Albumin (gm/dL)		
Mean (SD)	3.2 (0.5)	
Range	2.2–4.7	
INR		
Mean (SD)	1.5 (0.3)	
Range	1.0–2.3	
AFP (ng/mL)		
Mean (SD)	1508 (3329)	
Range	4–22040	

tendency and dispersion. Association between categorical variables was tested by the Chi Square Test. Survival and time to progression analyses were calculated by the Kaplan-Meier Product-Limit Estimator. Progression free survival was calculated from the date of entry to the date of objective disease progression or death. Overall survival was measured from the date of entry to the date of last follow up or death. The study outcomes were assessed according to the intention-to-treat principle. All statistical tests were two-sided.

Table 2 Tumor response*

	n	%	95% CI	
			Lower	Upper
Complete response	2	1.7	0.0	4.2
Partial response	22	18.3	11.7	25.0
Stable disease	40	33.3	25.0	42.5
Progressive disease	50	41.7	32.5	50.8
Not Assessed	6	5.0	1.7	9.2

* Intention-to-treat analysis

Results

Patient characteristics

A total of 120 patients were enrolled between June 2007 and January 2009. Baseline characteristics are shown in (Table 1); the mean age of studied cases was 56 years with a male to female ratio of 2.2/1. Chronic hepatitis C virus infection was the predominant cause of liver disease (60%), followed by hepatitis B (22%). The diagnosis of HCC was based on fine needle cytology in 55 patients (46%). The remaining 65 patients (54%) were diagnosed by marked elevation of α-fetoprotein level and imaging studies indicating HCC. Distant metastasis were present in 37 cases (31%), 18 cases (15%) lymph node metastasis, 11 cases (9%) bone metastasis, and 8 cases (7%) lung metastasis. Thrombosis of the main portal vein or one of its two major branches was present in 51 cases (43%).

All patients were chemotherapy naive. The median duration of treatment on viscum fraxini-2 is 17 weeks (range 2–121 weeks).

Response

According to the RECIST 24 patients (20%) achieved objective response, 2 patients (1.7%) achieved complete response and 22 patients (18.3%) achieved partial response. Forty patients (33.3%) achieved stable disease. Progressive disease has been shown in 50 patients (41%). 6 patients (5%) did not have evaluation of response due to early death (Table 2).

The overall objective response rate was significantly higher in cases with: good PS (32% in patients with PS 0–1 vs. only 7% in patients with PS 2), well compensated cirrhosis (32% in Child-Pugh class A vs. 15% in Child-Pugh class B), and earlier tumor stage (47% in Okuda Stage I vs. 11% in Okuda stage II) (Table 3). On multivariate regression analysis only PS 0-1 and Okuda Stage I was associated with better response to treatment (Table 4).

Survival

By the end of follow up 20 patients (20%) remained progression free, the median progression free survival for all patients was 4 months (range 1–28 months; 95% CI 3.3:4.7 months) (Fig. 1). The median overall survival for all patients was 8 months (range 1–28 months; 95% CI

Table 3 Univariate analysis of factors that could predict response to treatment with viscum

	RR				χ^2	P
	Response		No Response			
	n	%	n	%		
Sex						
Male	19	22.9	64	77.1	1.4	0.24
Female	5	13.5	32	86.5		
Performance status						
0–1	20	32.3	42	67.7	12.0	0.001
2	4	6.9	54	93.1		
Ascites						
Absent	12	21.4	44	78.6	0.1	0.71
Present	12	18.8	52	81.3		
Underlying Liver Disease*						
Viral	22	20.4	86	79.6	*	0.76
Other	2	16.7	10	83.3		
Child-Pugh Class						
A	12	32.4	25	67.6	5.2	0.023
B	12	14.5	71	85.5		
Number of lesions						
Single	12	25.0	36	75.0	1.3	0.26
Multifocal	12	16.7	60	83.3		
Metastasis/Macro-vascular Invasion						
Absent	13	24.5	40	75.5	1.2	0.27
Present	11	16.4	56	83.6		
AFP (at the median cut-off)						
< 300	16	26.7	44	73.3	3.3	0.68
> 300	8	13.3	52	86.7		
Okuda stage						
I	14	46.7	16	53.3	17.8	< 0.001
II	10	11.1	80	88.9		

* Fisher's exact test

Table 4 Multivariate analysis of variables with significant relation to the response to viscum

	Odds ratio	95% CI		P
		Lower	Upper	
PS	0.25	0.066	0.95	0.041
Child	5.54	0.630	48.66	0.123
Okuda	0.07	0.008	0.62	0.017

6.3:9.7 months) (Fig. 2). The median survival for patients who achieved disease control (responsive + stable disease) was 16 months (95%CI 8–24 months), while the median survival for cases who suffered progressive disease was 4 months (95% CI 3–5 months), the difference was statistically significant (Log-Rank 70, $P < 0.001$) (Fig. 3).

Toxicity

No hematologic toxicity has been encountered; the spectrum of non-hematologic toxicity was generally mild and well tolerated. Pain and erythema at the injection site developed in 94 patients (78.3%). Analgesics and anti-inflammatory drugs were used in 10 patients (8.3%) to alleviate severe pain and erythema. The treatment was postponed for 1–2 weeks till resolution of the local reaction and the dose had to be reduced to one ampoule in subsequent courses in 3 patients (2.5%). The local reactions gradually abate with subsequent injections to be nearly painless after a median of 5 injections. Drug related fever developed in 39 patients (32.5%). It fever was grade 1 in most patients, only two patients suffered grade 2 fever that was alleviated by administration of paracetamol. Drug related fever gradually abate with subsequent injection. There were no drug related discontinuation or toxic deaths.

Discussion

HCC is a major, and often therapeutically frustrating oncologic problem with a rising incidence of all over the world [1]. Studies carried out on HCC in Egypt presumed an increasing trend [16, 17]. HCC is a relatively chemo-resistant tumor and is highly refractory to cytotoxic chemotherapy. This resistance is partly related to its tumor biology, pharmacokinetic properties, and both intrinsic and acquired drug resistance. In addition to intrinsic re-

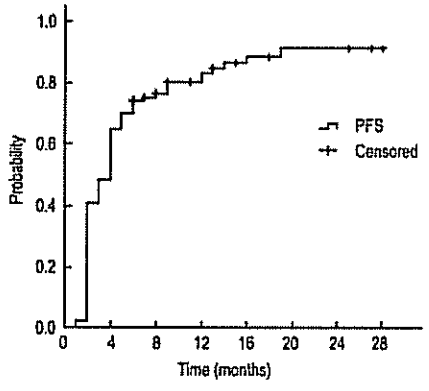

Fig. 1 Progression free survival in studied cases

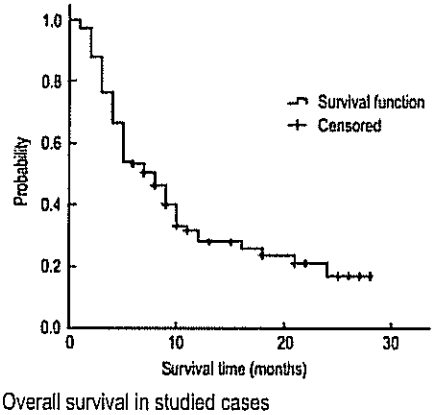

Fig. 2 Overall survival in studied cases

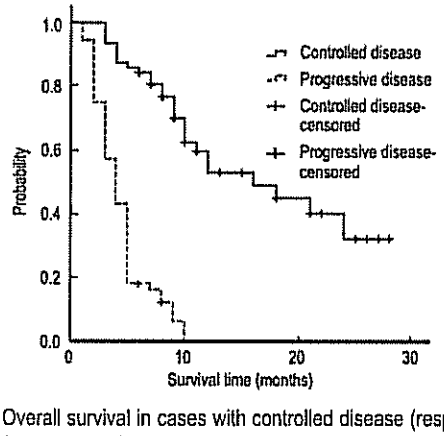

Fig. 3 Overall survival in cases with controlled disease (responsive or stationary) vs. progressive disease

sistance, underlying liver cirrhosis most often precludes the use of several cytotoxic agents [4].

Extracts from European mistletoe or Viscum album L have been reported to exert direct cytotoxic and immunomodulatory effects in vitro and in vivo. The mechanism of its anti-tumoral activity is largely related to immunostimulatory effects, increasing apoptosis, direct cytotoxicity and inhibition of angiogenesis [18–23].

Several reviews are available on controlled and uncontrolled trials aiming to determine the effectiveness, tolerability and safety of mistletoe extracts given either as monotherapy or as an adjunct to conventional cancer treatments. The most recent and authoritative systematic review was conducted by Horneber *et al* [24]. Outcome measures considered included survival times, tumor response, quality of life, adverse effects of cancer therapies and safety of mistletoe extracts. Twenty one randomized clinical trials met all the inclusion criteria, 13 provided data on survival, 7 on tumor response, 16 on measures of quality of life or reduction of adverse effects of chemotherapy, 12 on side effects of mistletoe treatment; overall comprising 3484 randomized cancer patients. Of the 13 trials investigating survival, 6 showed some evidence of a benefit, but none of them was of high methodological quality. Of the 16 trials investigating the efficacy of mistletoe extracts for either improving quality of life, or the reduction of adverse effects of chemotherapy, 14 showed some evidence of a benefit, but only 2 of them were of higher methodological quality. Data on side effects indicated that mistletoe extracts were usually well tolerated and had few side effects.

With a disease control rate of 53%, an overall response rate of 20%, a median progression free survival of 4 months, our result compares favorably with other systemic therapies for HCC. One of the most frequently used single agents, doxorubicin, has a response rate of less than 20%. Single agents such as 5- fluorouracil, cisplatin, paclitaxel, raltitrexed, irinotecan, and nolatrexed have been evaluated but all have shown disappointing results [5, 6, 25–27]. Combination chemotherapy regimens such as PIAF (cisplatin, interferon, doxorubicin, and 5-fluorouracil) achieved an overall response of 21% however, have not shown to improve survival when compared to single-agent doxorubicin in a randomized phase III study [28].

These positive effects on tumor response confirm the results of a previous phase II study on the efficacy and safety of mistletoe in advanced HCC. The study included 23 patients with chemotherapy-naive, advanced HCC. The drug was administered by subcutaneous injection once weekly. Three patients (13.1%) achieved CR, and two patients (8.1%) achieved a PR. The median survival was 5 months [29].

The recent introduction of single agent sorafenib, in the treatment of advanced HCC patients, indeed represents an important advance in this challenging disease [8]. However, one has to be reminded that this study included patients with mostly pristine liver function (95% or more with Child-Pugh A score in both groups) and excellent performance status (mainly ECOG 0–1). Added to this, the low response rate reported for this novel agent (only 2%) prompted a modified response criteria for HCC tak-

ing into account the viability of hepatic tumors rather than tumor shrinkage. The subsets of patients in the current study presenting with similar criteria (early stage of the disease with minimal or no symptoms) gained the best benefit from palliative treatment with viscum fraxini-2. The overall objective response rate was significantly better in cases with: good PS (32% in patients with PS 0–1), and earlier tumor stage (47% in Okuda Stage I).

The treatment in the current study was well tolerated; the most common drug-related adverse events were pain and erythema at the injection site and drug related fever. The adverse events were generally mild, manageable and gradually abate with subsequent injections. There were no drug related discontinuation or toxic deaths.

The median overall survival was 8 months; this cannot be compared to other studies due to differences in study design, selection criteria and etiology of cirrhosis. However in our study a remarkable median overall survival of 16 months was recorded in patients who achieved a disease control on treatment.

On the basis of the study results, it can be concluded that, Viscum Fraxini-2 is an effective treatment for patients with advanced HCC. It can achieve a disease control rate of 53% including a 20% overall response, with some occasional complete responses. The response is higher in patients with good performance status and earlier stage of the disease (Okuda Stage I). Cases who achieve a disease control are expected to obtain a significantly higher overall survival. Given the high safety of viscum fraxini-2 and the previous reports on its ability to reduce the side effects of chemotherapy, further phase II trials in combination with other active agents in HCC are highly indicated. Analysis with a larger number of patients in a controlled phase III clinical trial is clearly warranted.

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