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• LIVER CANCER •

Salvage therapy for hepatocellular carcinoma with thalidomide

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Abstract

AIM: To evaluate the clinical benefit of thalidomide in patients with advanced hepatocellular carcinoma (hepatoma).

METHODS: From March 2000 to July 2002, patients who had advanced hepatocellular carcinoma and failed to or were unsuited for aggressive treatment, were enrolled and took thalidomide 150 to 300 mg/d. All cases were followed till April 2003. Data collection included viral hepatitis, grade of cirrhosis, total dosage of thalidomide, side effect, stage of hepatoma by Okuda and CLIP classification, and prognosis. The subjects were divided into A and B groups, depending on 5 000 mg dosage of thalidomide. Survival time of all cases and in the two subgroups was evaluated.

RESULTS: Ninety-nine patients with hepatoma were enrolled, 81 men and 18 females with median age 58±14.1 years. Eighty-six percent had viral hepatitis and one case was alcoholism. Hepatoma was diagnosed with histology, alpha-fetoprotein (aFP) >400 ng/mL, or image examination, there were 30, 33 and 36 cases respectively. At the time of thalidomide therapy, more than 81% had cirrhotic status. Twenty-two patients were in group A (<5 000 mg) with median survival time about 25 days, for 77 cases in group B (⩾5 000 mg) the median survival time was about 109 days. Six subjects had partial response. Most adverse effects were skin rush, neuropathy, somnolence, and constipation.

CONCLUSION: Several patients responded to thalidomide therapy. As a single drug therapy, thalidomide might not have good therapeutic effect for all cases, but a small ratio of patients had exciting response, the resistance or tumor escape would develop after long-term use. Up to now, no defined facts could be used to predict response. The effect of thalidomide on hepatoma might be associated with the dosage. As salvage therapy, thalidomide has its value. Combination or adjuvant therapy will be the next trial.

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INTRODUCTION

Hepatocellular carcinoma (hepatoma) is a major cause of death in the world, especially in the endemic areas of viral hepatitis B and C, such as Taiwan, China. Taiwan is a high prevalence area of hepatocellular carcinoma, more than 6 900 people died of hepatocellular carcinomas at Taiwan in 2002. Although the incidence rate of small hepatoma was increased in the last few years, but most patients had severe liver cirrhosis that made them lose the opportunities to receive curative therapy. Therapy of hepatocellular carcinoma in chronic liver disease patients is challenging also. Local treatments, such as surgical resection, ethanol intratumor injection, ablation with high frequency, or transhepatic artery embolization have been improved, but these procedure might cause new problems and the curative and survival rates of these patients are still low[1]. The average survival time is shorter than 6 months if metastasis occur. However, to seek new effective therapy for hepatoma, to prolong the patient life or improve their life quality with later stage of hepatoma are major issues at Taiwan.

Anti-angiogenesis is a new concept for cancer therapy, in the 1970' s, Dr Folkman launched out the theory[2]. Neoplasm' s growth depends on angiogenesis, angiogenesis inhibitors could block the process and treat neoplasm, especially vascularized ones. Many antiangiogenic agents are developed and some are going in clinical trials. Thalidomide is one of them and has been studied for its anti-angiogenic activity in last several years.

Hepatoma is a hypervascular tumor that has been proved by angiography and histology. For this reason, antiangiogenesis therapy may be effective for hepatoma. Up to now, few papers described the antiangiogenesis therapy for hepatoma. The first success case of hepatoma treated with thalidomide, was reported in 2000. A 67- year-old man had a 6 cm large tumor. Unfortunately, the tumor continued to grow after 5FU and interferon therapy, chemoembolization and chemotherapy. Thalidomide therapy was used. The tumor was shrunk, aFP was diminished, and the patient was alive in 2000[3]. Henceforward, some might had exciting results, some were disappointed, Although a few patients would get benefit from thalidomide therapy[4-8]. No final conclusion was made. In this study, we report our experience in using thalidomide as a salvage drug for the patients with hepatoma, who were unsuitable for other managements.

MATERIALS AND METHODS

One hundred and six patients with hepatocellular carcinoma were entered into the study between Mar 2000 and July 2002. A diagnosis of hepatoma was made by histopathology, alpha fetoprotein (AFP) more than 400 ng/mL or image plus clinical manifestation. All of them were poor candidates for more aggressive treatment. Those patients were required to receive a risk-benefit counseling, to sign an informed-consent agreement, to use forms of birth control. The Institutional Ethics Committee of the Mackay Memorial Hospital and Department of Public Health in Taiwan approved the study protocol and the informed consent form.

They were given oral thalidomide table, containing 50 mg (Taiwan Tung Yang Biopharm Co. Ltd), at a dosage of 150 to 300 mg/day according to clinical reactions and adverse effects for a variable period. The drug was given 2 dosages in the morning and bedtime. The subjects were followed to April 2003. Ninety-nine patients were evaluated.

Depending the total dosage used, the patients were divided into two subgroups, group A took thalidomide less 100 tablets

(5 000 mg), and group B had more than 100 tablets. Data collected included viral hepatitis, grade of cirrhosis, total dosage of thalidomide, side effect, stage of hepatoma by Okuda and CLIP classification[9], and prognosis. The trial was prompted by the observation of response and survival times in all case and in the two subgroups. Survival time was calculated with SPSS 10 software and observation time interval was one week.

RESULTS

General data

Ninety-nine patients were valuable for evaluation (Table 1). The ratio of men and women was 81:18. The median age of the patients was 58 years (range, 21-86 years, S=14.1 years). Fifty-eight patients were chronic hepatitis B, 22 patients had hepatitis C, and five patients were infected with viral hepatitis B and C. Six cases were confirmed with non-B and non-C hepatitis. Seven cases had an underminted condition. One was alcoholic cirrhosis without viral hepatitis. Among them, another 12 patients had alcohol consumption. At the time of hepatoma diagnosed, 81%(80 cases) of the patients had cirrhosis diagnosed with histology or image studies, 14 cases had chronic parenchyma disease, and only 5 patients had normal texture of liver. The hepatoma diagnosis was dependent on either histopathology, aFP >400 ng/mL or image and clinical manifestations. There were 33, 30 and 36 cases respectively. They were followed up, with median follow-up time about 6 months (average 177 days) to April 2003 in this study. Group A had 22 patients and group B had 77 patients.

Table 1 Description of cases

Age (yr)	
Median	58±14.1
Range	21-86
Sex	
Male	81
Female	18
Modality of diagnosis	
Cytological / histological	33
Imaging + AFP > 400 ng / mL	30
Imaging + AFP < 400 ng / mL or unknown	36
Cirrhosis	
Absent	5
Present	80
Chronic parenchymalds'	14
Causes of liver disease	
Hepatitis B	58
Hepatitis C	22
Hepatitis B +C	5
Non B and Non C	6
Alcoholic	1
Child-Pugh stage (unknown = 2)	
A	43
B	33
C	21
AFP (ng / mL) (unknown =10)	
10 <	17
11-400	33
400	39
Portal vein thrombosis (unknown=3)	
No	46
Yes	50
Pre ThalidomideTreatment (unknown=7)	
No	30
Yes	72
Surgery	11
PEI	16
TACE	49
Radiation	6
Chemotherpay	3

Laboratory data

The pretreatment median platelet count was $187\times10^3/mm^3$, leukocyte count was about 6 820/mm^3. Analyzed the liver function by Child' s classification, 43, 33 and 21 patients belong to grades A, B and C, respectively. Two cases were unclassified at the beginning of medication because of incomplete data record. Both of them were grade A when hepatoma was diagnosed. One had bone and lung metastasis and one was followed up at other hospital. Fifty-two percent of the patients had alpha-fetoprotein level more than 400 ng/mL. According to hepatoma stage Okuda (Table 2) and CLIP (Table 3), the numbers of patients and survival time in the both groups are shown in Table 4 and Table 5. There were no confirmed complete responses. Although no scheduled image evaluation was done, six patients having partial response were observed, yielding a rate of 7% at least. Four responded patients had a high serum aFP initially, which was decreased after treatment.

Table 2 Okuda staging for HCC

Point	0	1
Size of tumor	<50% of liver	> 50 %
Ascites	No	Yes
Albumin	>=3	<3
Bilirubin	<3	>=3
Stage I: 0	II: 1 or 2	III: 3 or 4

Table 3 CLIP scoring system

Scores Variables	0	1	2
Child-pugh stage	A	B	C
Tumor morphology	Unninodular and extension <=50%	Multinodular and extension <=50%	Massive or extension > 50%
AFP	<400	>=400	
Portal vein thrombosis	No	Yes	

Table 4 Hepatocellular carcinoma stage and survival time, Okuda stage and survival time

Group		Stage			MSD
		I	II	III	
A (*n*=19)	Case No.	5	9	5	
	Survival days	161	26.8	10.5	25.2
B (*n*=76)	Case No.	19	41	16	
	Survival days	171.5	136.5	47.3	108.5

MSD: medium survival day.

Table 5 Hepatocellular carcinoma stage and survival time, CLIP classification and survival time

Group		Score						
		0	1	2	3	4	5	6
A (*n*=20)	Case	0	2	2	2	8	5	1
	Survival days		220.5	49	42	35	12.3	11
B (*n*=76)	Case	1	8	20	20	15	9	3
	Survival days	>345	301	150.5	106.8	96.2	59.5	19.3

Response and survival

Overall, the median survival time was about 80 days to Apr 2003. Twenty-one of 22 patients in group A had expired, only one survived to Dec 2000 then lost follow-up. The median survival time in group A was 25 days. Most of them had a

poor condition for aggressive treatment and died due to liver function decompensation. Thirty-six percent patients of group A has Child-pugh' s grade C, compared only 16% in group B. One third patients died with hepatic failure and 4 patients died with massive esophageal varices bleeding in group A. Fifty percent cases had multiple lesions in liver or distal metastasis. Some of them liked to try TAE again and other alternative therapies. One patient had grade 3 dermatologic toxicity. These were major causes the withdrawal of thalidomide. Seventy-seven patients were group B, 61 patients died, and 16 patients experienced disease progression or partial responses. The median overall survival time in group B was 108.5 days.

Toxicity

The most common treatment-related toxic effects were skin itching, rush and urticaria. Twenty patients were relieved by antihistamine, two patients with severe dermatitis prompted discontinuation of thalidomide treatment. Other adverse effects included neuropathy, somnolence, and constipation and six had ith others side effect, such as gastrointestinal symptom. Most of them took laxative, therefore the rate of constipation was not real. Toxicity of thalidomide in our patients was tolerable.

Table 6 Response rate of hepatoma treated with thalidomide

	Tumor response		Stabilization rate		
	N	CR / PR	SD	PD	(PR + SD)
Patt *et al*. '00[6]	21	0 / 1	11	9	12 (57%)
Chen *et al*. '00[8]	42	0 / 2	15	25	17 (43%)
Kong *et al*. '01[5]	11	0 / 1	4	6	5 (45%)
Lin *et al*. '02[4]	27	0 / 1	1	25	2 (8%)
Schwartz *et al*. '02[7]	20	1 / 1	7	11	9 (45%)
Total	121	1 / 6	38	76	45 (37%)
Wang *et al*. '03	99	0 / 6	Survival 16 upto Apr 31 '03		

CR: complete response, PR: partial response, SD: stable disease, PD: Progressive disease.

DISCUSSION

Thalidomide was developed in the 1950' s and originally marketed as a sedative but was withdrawn after its teratogenic effects were recognized in 1964. FDA approved thalidomide for erythema nodosum leprosum in 1999, which stimulated new interests[10]. Thalidomide has been shown to be effective in treating cutaneous lupus erythematosus, idiopathic oral and oropharyngeal apthous ulceration in HIV-1 positive patients. It has subsequently been used in the treatment of graft versus host disease, rheumatoid arthritis, inflammatory bowel disease, and the malignancy diseases in phase II or phase III, such as multiple myeloma, renal cell carcinoma, prostate cancer, breast cancer, ovary cancer, *etc*. The effects may come from its potent inhibitor of angiogenesis and immune response-modifying properties, which are essential to many physiologic and pathologic pathways. Thalidomide could inhibit the production of tumor necrosis factor-alpha[11,12] and alter multiple cytokines. Several other immunomodulatory effects have been reported, such as down-regulation of T-lymphocyte surface molecules, inhibition of lymphocyte proliferative responses to alloantigens and mitogens, and lowering of CD4:CD8 peripheral T-lymphocyte ratios[13,14]. It could induce a shift from T helper cell type 1(Th1) to Th2 T-cell responses and modify various cell surface receptors[15].

Hepatoma is a hypervascular tumor, blood support comes from new branch vessels of hepatic artery. Presumably, chemoembolization intercept the vessels has become one of standard treatments for hepatoma. We can speculate that anti-angiogenetic agents can inhibit hepatoma growth, such as thalidomide. Thalidomide was believed to be species-specific antiangiogenesis drug[16,17]. That is the most likely reason for its reported effectiveness against some solid tumors involving neoformation of blood vessels in early days. In addition, angiogenesis inhibitor TNP-470 can inhibite both the growth of primary tumors and the formation of liver metastases from gastric and colon cancer xenografts in nude mice. In a rat hepatoma model, it also enhanced apoptosis in hepatic metastases and improved survival[18]. Again, inhibition of tumor necrosis factor-alpha (TNF-alpha) is one important action of thalidomide, which could be used to treat human hepatoma.

To treat hepatoma with thalidomide will be feasible. Some papers have actually discussed this issue since 1999, most were reported with case studies or in academic meetings[4-8] (Table 6). The complete response was rare, partial response rate was 5% to 10%, stable disease was about 37%, the variant was depending on the duration of observation, cancer stage of patients and definition of stability. In our study, no patient had complete remission, the initial partial response was 7%.

The effect of thalidomide on cancer is still mysterious. We surmised that interaction between the drug, patient immunity and heterogeneous cancer was very complex. The impact factors of response are multiple. However, there are some other antitumor mechanisms in addition to antiangiogenesis and TNF suppression. For example, degradation of tumor necrosis factor-alpha mRNA in human monocytes was modulated by thalidomide[12]. On the contrary, TNF-alpha production in IL-1beta-stimulated or PMA-stimulated hepatocyte cultures was not altered following the addition of thalidomide[19]. Thalidomide can augment natural killer cell cytotoxicity. The number of NK cells increased in multiple myeloma after medication, but only those patients who responded to treatment showed an increase in the percentage of NK cells. Thalidomide for multiple myeloma might trigger the NK cells[20]. Same phenomena might occur in hepatoma. The exact mechanism of thalidomide is not fully clear, lot of effect wait to discover.

Why thalidomide for hepatoma does no work as a targeted therapy? Hepatoma was heterogeneous in genotype and phenotype[21]. Animal experiments showed that angioarchitecture and blood flow velocity in liver cancer were heterogeneous[22]. Adhesion molecular, E-cadherin, revealed various expressions among tumor samples[23]. These could explain why not all the solid tumors or patients had no response to thalidomide therapy, even in treatment of hepatoma. Although a few hepatomas had very good response to thalidomide beyond expectancy. At present, we still lack a landmark to select the suitable patients and specific parameters to predict the response to thalidomide treatment. Host may be another important factor affecting the response to thalidomide. All these need more researches to answer.

It seems that thalidomide may offer hepatocellular carcinoma stabilization, but has no significant antitumor activity. Most papers discussed the rate of response only. The survival time may be one of the major destinations in clinical trails of thalidomide therapy. A few phase I and II studies showed survival times slightly increased in hepatoma patient, but the survival time of those patients was also unpredictive and thalidomide did not significantly prolong the life of all patients. Our patients survived average of 25 and 108 days in groups A and B, respectively. The survival time appeared shorter than reported[9,24]. We thought the time was calculated from the day of thalidomide therapy, not the day of hepatoma diagnosed. In group A, the general condition of them was poor, they seemed not get any benefit from thalidomide therapy. All the response cases in our study were belong to group B with a large total dosage. Chen found the average survival time in patients with responded or stable disease was 269 days,

significantly longer than 74 days in the patients with progression[8]. Neben Kai reported the cumulative 3-month dosage was the remaining factor for overall survival rate in treating multiple myeloma[25]. At the same time, that might occur in HCC and the anticancer effect of thalidomide was associated with cell cycle and total dosage, as other chemotherapy. So, thalidomide might not be suitable for patients with too terminal status because they do not have chance to take enough dosage of thalidomide. It is the issue to be studied.

Besides, this study might have a worth finding. We usually think there is no drug resistance to antiangiogenetic therapy, but it did occur. We revealed a case with high aFP and lung metastasis had a good response. His serum level of aFP dropped and lung lesions became small and disappeared after thalidomide therapy. Unfortunately, the aFP increased again and lung lesion regrew after 9 months thalidomide continuous therapy. That means the resistant may develop if patients take thalidomide for enough long time. These need more case observations to confirm.

However, patients with hepatoma at later stage do not have time to wait for a new therapy. Most hepatomas develop in patients with cirrhosis. In this study, the ratio of cirrhosis was more than 80%. Lot of patients are poor candidates for aggressive treatment. Moreover, the prognosis of patients with metastatic or refractory HCC was very poor, to cure the patients was almost impossible. The aim of therapy was to improve their life quality and prolong their survival time[26]. Overall, as a single medication, thalidomide has the response rate about 5 to 10%.

At one time, thalidomide was notorious for its side effect that has been under control in last few years. Phocomelia is the most severe adverse effect that did not cause any problem in patients with hepatoma. The other adverse effects were sedation, constipation, and skin rash in our study. These effects were usually dose-related and mild, and could be treated except few patients who must discontinue medication. Peripheral axonal sensory neuropathy caused by thalidomide appeared only after a large dose accumulation. In our study, even at the later stage of cirrhosis, only few patients discontinued thalidomide. Another unusual adverse effect of thalidomide is vascular thrombosis. Deep venous thrombosis may occur, especially in patients with multiple myeloma and renal cell carcinoma, but has not seen in patients with hepatoma. Our results showed that thalidomide was tolerated in cirrhotic patients with hepatoma. Thalidomide is convenient for oral intake. It can be used as a salvage therapy before more powerful antiangionetics or other combinated or adjuvant methods are developed. Several pilot studies have been on going[27], such as combination therapy of thalidomide plus interferon alfa in phase II[28]. A combination of capecitabine and thalidomide, celecoxib and escalating doses of thalidomide in patients with unresectable HCC revealed few response patients[29,30].

In conclusions, thalidomide is a drug with multifunctions, may be useful in some of patients with advanced hepatocellular carcinoma and it produces durable stability disease in approximately one third of patients, with a partial response rate not beyond 10%. Most side effects of thalidomide are minimal, it could be administered to patients with even significant liver cirrhosis and poor candidates for other therapies. However, thalidomide as a single drug formula for hepatoma is no so good, resistance will be appear after long-term use. If it is used as a salvage therapy in patients with hepatoma, some patients get benefit[27]. A controlled trial of thalidomide in selected patients with cirrhosis and hepatoma is warranted. The combination therapy with other drugs or adjuvant therapy in different stage hepatoma will be the next step studies. Thalidomide analogues have been under investigation. Hopefully, this will be the beginning of the development of a new therapeutic modality for hepatoma.

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