

Thalidomide in Advanced Hepatocellular Carcinoma with Optional Low-Dose Interferon- α 2a upon Progression

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Key Words. Hepatocellular carcinoma • Liver neoplasms • Thalidomide • Interferon-alpha
Hepatitis C virus • Angiogenesis inhibitors

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Identify the etiologic factors contributing to the increasing incidence of hepatocellular carcinoma in the U.S.
2. Explain the rationale for antiangiogenic therapeutic strategies in the treatment of hepatocellular carcinoma.
3. Describe the clinical features associated with a particularly poor prognosis in unresectable hepatocellular carcinoma.

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ABSTRACT

Purpose. To evaluate thalidomide in advanced hepatocellular carcinoma (HCC) and to evaluate combined thalidomide and low-dose interferon- α 2a (IFN- α 2a) after tumor progression on thalidomide. Systemic therapy is minimally effective in HCC and tumor angiogenesis is a potential therapeutic target.

Patients and Methods. Patients with unresectable HCC were eligible if they had preserved hepatic and renal function. The initial thalidomide dosage was 200 mg daily and was adjusted for toxicity. Upon progression, patients could continue thalidomide with additional low-dosage (one million units twice daily) IFN- α 2a.

Results. Thirty-eight enrolled patients were predominantly hepatitis C virus infected (53%), Child-Pugh class A (79%), and Eastern Cooperative Oncology Group performance status 0–1 (92%); 60% had extrahepatic metastasis. Confirmed disease control was seen in seven

patients (18%) and included one complete and one partial response (5% response rate). The median progression-free survival was 2.1 months, and median overall survival was 5.5 months. Tumor invasion of the portal vein or vena cava, large (>10 cm) tumor, and younger age were associated with shorter overall survival. Toxicity included fatigue in 74% of patients. Six patients stopped therapy because of side effects, including two patients (5%) with grade 4 arteriothrombotic events. Five patients continued thalidomide upon progression with the addition of IFN- α 2a; there was no disease control and 80% had grade 3 toxicity.

Conclusions. Thalidomide is not well tolerated and confers limited disease control in advanced HCC. Combination thalidomide and low-dose IFN- α 2a is neither safe nor efficacious in this population. *The Oncologist* 2005;10:718–727

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a common neoplasm worldwide. Annual global incidence and mortality is estimated to exceed 500,000 cases [1]. The highest HCC incidence occurs in SubSaharan Africa and Southeast Asia [2, 3]. Although HCC occurs less frequently in Northern Europe and the U.S., the incidence in the U.S. has increased in recent years, largely because of chronic hepatitis C virus (HCV) infection (estimated at nearly 4 million cases in the U.S.) [4]. HCC occurs most frequently in patients with cirrhosis from chronic hepatitis B virus (HBV) and HCV infection and long-standing alcohol abuse [2, 5].

HCC confers a limited prognosis. Many patients present at a stage in which potentially curative surgery or orthotopic liver transplant (OLT) is not feasible. Tumor recurrence following hepatic resection or OLT is frequent; many series report a 5-year progression-free survival (PFS) rate of 30% or less [6, 7]. In patients with unresectable HCC and preserved liver function, transarterial chemoembolization (TACE) has been shown to prolong survival [8, 9]. TACE is rarely curative, and survival beyond 24 months is infrequent [10]. For patients with advanced disease, systemic chemotherapy is of marginal benefit and associated with significant toxicity [11].

Tumor angiogenesis presents a compelling target in HCC. HCC is a highly vascular neoplasm. Carcinogenesis is characterized by the development of arterial capillaries and arterioles [12, 13]. The proangiogenic cytokines basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) are overexpressed in experimental and human HCCs, and overexpression has been associated with more aggressive tumor characteristics [14–18]. High microvessel density has been associated with rapid progression following surgical resection [19].

Thalidomide (Thalomid®; Celgene Corporation, Warren, NJ, <http://www.celgene.com>) is a glutamic acid derivative best known for teratogenicity reported after initial clinical experiences [20, 21]. Potential mechanisms of thalidomide's anticancer activity are several-fold. Antiangiogenic effects, which are well demonstrated in vivo, are believed to result from metabolite-initiated inhibition of activity of the cytokines bFGF and VEGF [22, 23]. Immunomodulatory properties have also been described [24, 25]. Thalidomide has activity in multiple myeloma [26]. Limited disease-modifying activity has been demonstrated in renal cell carcinoma, Kaposi's sarcoma, and high-grade glioblastoma [27–29].

Interferon-alpha (IFN- α) has also been shown to inhibit angiogenesis both in vivo and in human neonatal hemangiomas [30]. IFN- α inhibits blood vessel growth

at doses significantly lower than those used for antiviral purposes [31]. IFN- α has been shown to diminish the primary and secondary incidence of HCC in patients with preserved liver function; however, the clinical use of IFN- α as an anti-HCC therapy has been limited by toxicity [32, 33].

Patt et al. [34] reported a thalidomide-associated response (duration 12 months) in a patient with advanced, refractory HCC. Preliminary reports suggested response rates of 4%–10% and disease control rates of 8%–57% [35–39]. Hsu et al. [40] and Wang et al. [41] have recently published results of phase II studies investigating thalidomide in predominantly HBV-infected patients with advanced HCC. Those Taiwanese investigators reported response rates of 6% and 7%, respectively, with manageable toxicity and minimal high-grade side effects.

Because tumor-related angiogenesis contributes to HCC development and because of the limited chemotherapeutic options in HCC, we tested oral thalidomide in 38 patients with unresectable HCC. Upon disease progression, patients had the option of continuing thalidomide, with the addition of low-dose IFN- α 2a, to assess synergy between these potential angiogenesis-inhibitory agents [42]. We report the results of the first trial of thalidomide in HCC in a predominantly HCV-infected population at a North American center and report our experience with thalidomide and IFN- α in HCC.

PATIENTS AND METHODS

Eligibility and Exclusion Criteria

HCC was documented either by histology or by the combination of a characteristic liver mass, chronic HBV or HCV infection, and a serum alpha-fetoprotein (AFP) level >500 ng/ml. Patients had measurable disease (at least one non-bone tumor >2 cm) and were not candidates for surgical resection. Other criteria included absolute neutrophil count >1,200/mm³, hemoglobin \geq 8 mg/dl, platelets \geq 25,000/mm³, bilirubin \leq 5 mg/dl, transaminases fewer than five times the upper limit of normal, and creatinine \leq 1.5 mg/dl. Additional requirements were an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2, no prior anticancer therapy with thalidomide or interferon, no more than one prior anticancer systemic therapy, and no history of malignancy during the prior 5 years other than curatively resected skin cancer. Pregnant or lactating women were excluded. All patients were counseled regarding the teratogenic risks of thalidomide and were required to use contraceptive methods if sexually active and to demonstrate written comprehension regarding contraception. Informed consent was obtained

from each patient. The protocol was approved a priori by both hospitals' Institutional Review Boards in accordance with the ethical guidelines of the 1975 Helsinki Declaration.

PROCEDURES PERFORMED AT SCREENING AND DURING THE STUDY

All patients underwent a history and physical examination within 2 weeks prior to study entry and every 2 weeks while receiving therapy. Female patients underwent a serum pregnancy test within 24 hours of commencing therapy and every 2–4 weeks during treatment. Phlebotomy was performed within 2 weeks of study entry for complete blood count and serum chemistries, including liver function, creatinine, and AFP, and was repeated every 2 weeks during the study. Additional serum was isolated for the evaluation of circulating VEGF and bFGF every 4 weeks during the initial 8 weeks of therapy. A bone scan and computed tomography scan of the chest were required within 8 weeks of beginning therapy (and, if abnormal, after 8 weeks of treatment and thereafter every 12 weeks). Dynamic contrast enhanced-magnetic resonance imaging of the liver was performed within 2 weeks of beginning therapy and after 8 weeks of treatment, and thereafter, every 12 weeks.

Treatment Plan

Therapy involved oral thalidomide, 200 mg daily, given prior to bedtime. The thalidomide dose was adjusted weekly in 50- to 100-mg increments based on fatigue, neuropathy, or other side effects. At the time of tumor progression, patients were offered the option of remaining on thalidomide at their time-of-progression dose with the addition of IFN- α 2a given s.c. at a dosage of one million units twice daily.

Criteria for Evaluation of Efficacy

Assessment of tumor response was determined via the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [43]. The designation of stability or response required radiographic confirmation no fewer than 4 weeks following the initial determination.

Statistical Analysis

The primary end point was overall rate of disease control (response and stability). A two-stage minimax design targeted a disease-control rate of 20% and a maximum rate of no interest of 5%. An initial cohort of 29 patients was tested; because disease control was observed in more than one of these patients, an additional nine patients were accrued to a total enrollment of 38. The sample size

was determined assuming an alpha of .05 (probability of accepting an ineffective agent) and a beta of .10 (probability of rejecting an effective agent).

Immunoassays

Assays for bFGF and VEGF were performed on serum (bFGF) and plasma (VEGF) isolated from a subset of patients prior to treatment and every 4 weeks during initial therapy. Assays involved a standard sandwich enzyme-linked immunosorbent assay (ELISA) using a monoclonal antibody to either human bFGF or VEGF (R&D Systems, Minneapolis, <http://www.rndsystems.com>). Assays were performed in duplicate. Absolute values from each ELISA assay plate were adjusted to a standard curve generated using bFGF or VEGF proteins at concentrations of 0–2,000 pg/ml (VEGF) and 0–640 pg/ml (bFGF) as controls.

RESULTS

Thirty-eight patients were enrolled between July 2000 and July 2003. Patient characteristics at baseline are detailed in Table 1. The median age was 56 (range, 32–81). Approximately three fourths were male, and 55% were white. The predominant etiology of liver disease was HCV infection, present in 53% of patients; HBV infection accounted for liver disease in 18%. More than three fourths (79%) had Child-Pugh class A liver dysfunction, and 92% had an ECOG performance status score of 0–1 at baseline. More than one half (60%) had metastatic disease (Table 2), and an additional 32% had stage IIIA tumor (multiple tumors >5 cm or invasion of major portal or hepatic vein branch). The median Cancer of the Liver Italian Program (CLIP) score was 3 (range, 0–5). More than one half (53%) of the patients had not received prior surgical or medical therapy for HCC.

Side Effects

Toxicity is detailed in Table 3. Fatigue or somnolence occurred in 74% of patients and was grade 3 in 21%. Tremor/sensory neuropathy (47%), constipation (34%), neutropenia (21%), and dry mouth (18%) were also common, although 5% or fewer experienced grade 3 toxicity in these categories.

Tolerability

The median maximum-tolerated dosage was 250 mg/day (range, 50–500 mg/day). Six patients (16%) had toxicity requiring cessation of therapy, including one nonfatal myocardial infarction and one stroke. One patient discontinued therapy because of a syndrome of fever, rash, and hypotension that recurred after premedicated rechallenge. Other

toxicities causing refusal to continue treatment were vertigo (one patient) and peripheral neuropathy (two patients). Three of the five patients (60%) over the age of 70 discontinued therapy secondary to neurologic effects.

Table 1. Patient characteristics

		No.	(%) of <i>n</i> = 38	Comment
Age	>50	25	66%	Range, 32–81 Median, 56
	≤50	13	34%	
Gender	Male	29	76%	
	Female	9	24%	
Race/ ethnicity	Black	6	16%	
	White	21	55%	
	Hispanic	3	8%	
	Asian	7	18%	
	Middle Eastern	1	3%	
Etiology	HCV	20	53%	
	HBV	7	18%	
	Etoh	6	16%	
	Etoh & Hchm	2	6%	
	None	6	16%	
Child-Pugh classification	Class A	30	79%	
	Class B	8	21%	
ECOG performance status score	0	11	30%	
	1	23	62%	
	2	3	8%	
TNM stage	II	3	8%	
	IIIA	12	32%	
	IV	23	60%	
CLIP stage	0	3	8%	Median, 3
	1	8	21%	
	2	8	21%	
	3	8	21%	
	4	10	26%	
	5	1	3%	
Prior HCC therapy	Pharmacologic	3	8%	
	Resection	3	8%	
	Liver transplant	1	3%	
	Embolization	7	18%	

Abbreviations: CLIP, Cancer of the Liver Italian Program; ECOG, Eastern Cooperative Oncology Group; Etoh, alcohol use; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; Hchm, hemochromatosis; TNM, tumor-node-metastasis.

Table 2. Sites of metastasis at study entry

Disease site	No.	(%) <i>n</i> = 23
Lung	10	(43)
Retroperitoneal lymph node	8	(35)
Bone	5	(22)
Adrenal	5	(22)
Mediastinal lymph node	2	(9)
Omentum	1	(4)
Soft tissue	1	(4)

Efficacy

There was one complete response (3%) and one partial response (3%); five patients (13%) had confirmed disease stability. The median duration of disease control (response or stability) for these seven patients was 7 months (range, 5–24 months). For the entire cohort, the median PFS was 2.1 month and the median overall survival (OS) was 5.5 months (Fig. 1). The PFS rates at 6 and 12 months were 19% and 4%, respectively. The OS rates at 6 and 12 months were 41% and 22%, respectively. This analysis includes three patients (8%) with rapid clinical deterioration and death within 4 weeks of beginning treatment and two patients (5%) who refused participation after the initial 2 weeks of thalidomide because of side effects.

The incidence of disease control, median PFS, and median OS did not differ significantly for patients with or without extrahepatic metastases (Table 4). All of the seven patients with confirmed disease control had tumors that did not invade the main portal vein or inferior vena cava (IVC), and none of the 15 patients with portal or IVC tumor invasion had a response or stability. The median PFS was also significantly greater in patients without portal/IVC invasion (2.8 months versus 1.8 months; $p = .008$), as was the median OS (8.8 months versus 3.8 months; $p = .0002$; Fig. 2). Disease control occurred exclusively in patients older than age 50 (7 of 25, 28%); no disease control was observed in the 13 patients under the age of 50. Additional factors on univariate analysis that were associated with better outcome include lower CLIP score (Fig. 3), unilateral tumor, focal (encapsulated) tumor, and tumor <10 cm. Factors that did not appear associated with PFS or OS include thalidomide dose, Tumor-Node-Metastasis (TNM) score, AFP elevation, gender, Child-Pugh class, ECOG performance status score, etiology of liver disease, and baseline serum bilirubin or transaminase levels (Table 4).

Combination Therapy

Five patients received IFN- α in conjunction with continued thalidomide upon progression. For the 33 patients who did not continue treatment on-study, reasons were as follows: lost to follow-up, two patients; poor performance status, seven patients; death, seven patients; refusal, six patients; thalidomide toxicity, four patients; unknown, seven patients.

Four of the five patients receiving combined interferon/thalidomide had progression of disease within 12 weeks; one patient had unconfirmed stability but discontinued therapy secondary to toxicity. Grade 3 toxicity was seen in four of five patients (80%) and included neutropenia (three of five patients, 60%), fatigue/somnolence (one of five patients, 20%), and depression with severely decreased

Table 3. Adverse events

Toxicity	Incidence	Grade			
		I	II	III	IV
Fatigue/somnolence	28 (74%)	8 (21%)	12 (32%)	8 (21%)	
Constipation	13 (34%)	5 (11%)	6 (16%)	2 (5%)	
Tremor/sensory neuropathy	18 (47%)	12 (32%)	4 (11%)	2 (5%)	
Decreased concentration/other central nervous system side effects, including insomnia	4 (11%)	1 (3%)	3 (8%)		
Dry mouth	7 (18%)	7 (18%)			
Rash	5 (13%)	2 (5%)	3 (8%)		
Hematologic (neutropenia)	8 (21%)	2 (5%)	5 (13%)	1 (3%)	
Cardiovascular	3 (8%)			1 (3%)	2 (5%)
Dyspnea ^a	4 (11%)	2 (5%)	2 (5%)		

^aDyspnea occurred in four patients without objective evidence of bronchospasm, congestive heart failure, cardiac ischemia, pleural effusion, infiltrate, or pulmonary embolism.

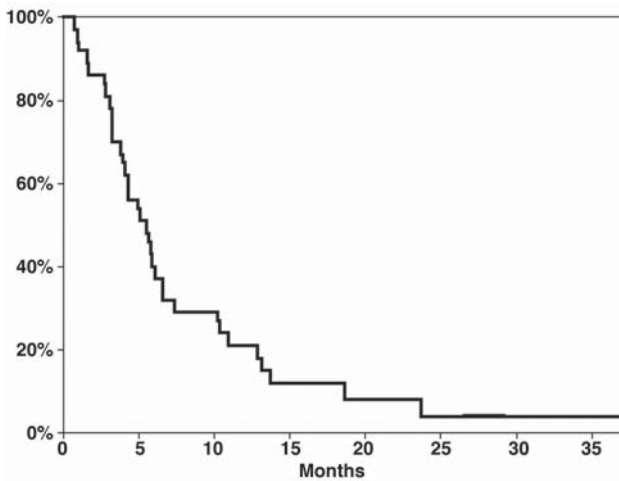


Figure 1. Overall survival (Kaplan-Meier estimate) for 38 patients receiving thalidomide for unresectable hepatocellular carcinoma.

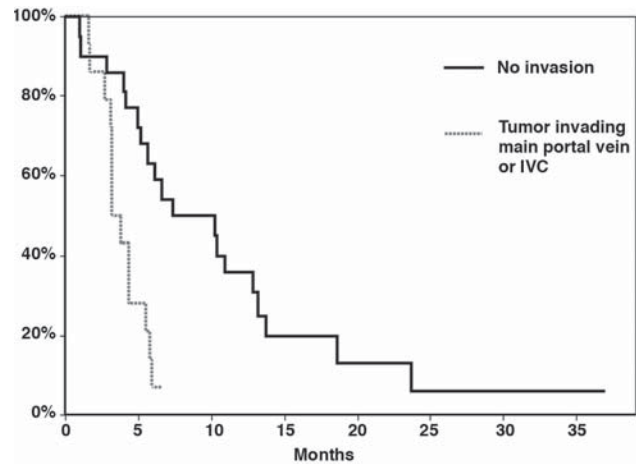


Figure 2. Overall survival (Kaplan-Meier estimate) for patients with tumor invasion of the main portal vein or inferior vena cava (IVC) ($n = 15$, dashed line) versus those without this degree of vascular invasion ($n = 22$, solid line).

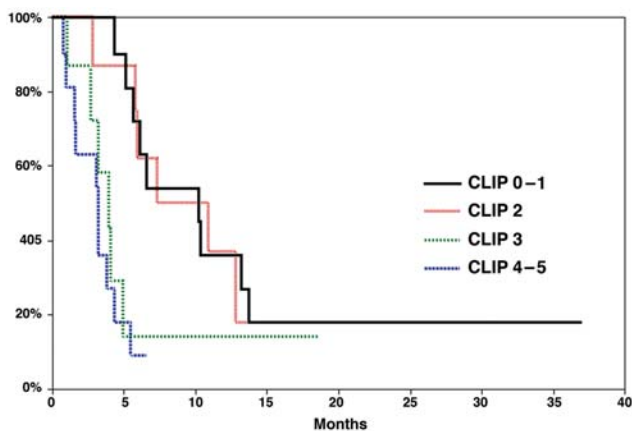


Figure 3. Overall survival (Kaplan-Meier estimate) by Cancer of the Liver Italian Program (CLIP) score. CLIP 0–1 ($n = 11$, solid line); CLIP 2 ($n = 8$, short dash), CLIP 3 ($n = 8$, dash), CLIP 4–5 ($n = 11$, long dash).

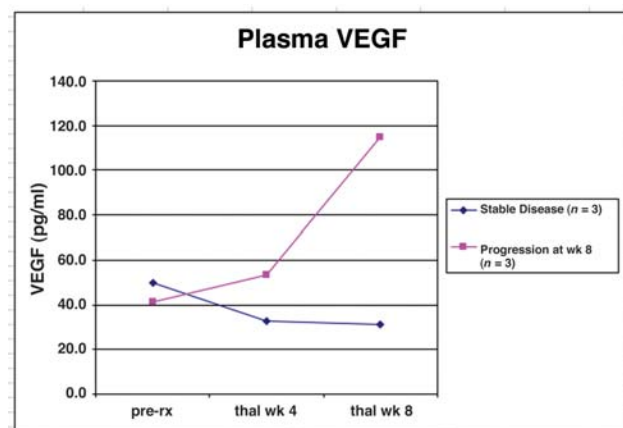


Figure 4. Mean plasma vascular endothelial growth factor (VEGF) prior to thalidomide (thal) and after 4 and 8 weeks of therapy in three patients with disease progression at 8 weeks of therapy (squares) and three patients with disease stability at 8 weeks of therapy (diamonds).

Table 4. Univariate analysis of prognostic factors associated with progression-free survival and overall survival

Variable	No.	Progression-free survival median (months)	<i>p</i> value (log-rank)	Overall survival median (months)	<i>p</i> value (log-rank)
Tumor distribution					
Unilateral (or no hepatic tumor)	9	7.2	.007	10.3	.053
Bilateral	29	1.9		5.0	
Tumor pattern					
Diffuse	18	1.8	.002	3.2	.0002
Focal or encapsulated	16	2.8		8.8	
Vascular invasion (main portal vein or IVC)					
Yes	15	1.8	.008	3.8	.0002
No	22	2.8		8.8	
Metastasis					
Yes	23	2.1	.58	5.5	.94
No	15	2.2		5.8	
Gender					
Male	29	2.1	.81	5.1	.19
Female	9	2.2		9.6	
Child-Pugh classification					
Class A	30	2.1	.80	5.8	.17
Class B	8	2.8		3.2	
ECOG performance status score					
0	11	2.7	.79	5.0	.77
1–2	26	2.1		5.8	
Etiology of liver disease					
Nonviral	11	1.9	.27	4.3	.74
HBV	7	1.8		5.9	
HCV	20	3.1		5.7	
Age					
≤50 years	13	1.8	.023	4.1	.002
>50 years	25	2.8		6.6	
TNM stage					
II–III	15	2.2	.58	5.8	.94
IV	23	2.1		5.5	
CLIP stage					
0–1	11	2.2	.066	10.2	.0002
2	8	3.2		9.1	
3	8	1.8		3.9	
4–5	11	1.8		3.2	
Thalidomide maximum dose (mg/day)					
200–250	20	1.9	.003	5.5	.36
≥300	18	2.8		5.3	
AFP at entry					
<400 ng/ml	16	3.1	.52	6.0	.47
>400 ng/ml	22	1.8		5.0	

Abbreviations: AFP, alpha-fetoprotein; CLIP, Cancer of the Liver Italian Program; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; IVC, inferior vena cava; TNM, tumor-node-metastasis.

concentration (one of five patients, 20%). Two patients discontinued combination therapy secondary to side effects.

Measurement of Circulating Cytokines

Adequate serum and plasma for bFGF and VEGF assessment were available for six patients at both pre- and

post-treatment time points. Circulating bFGF was undetectable in five of the six patients. Circulating VEGF was detectable at baseline and after 4 and 8 weeks in six patients. The mean plasma VEGF concentration for three patients with stable disease at 8 weeks of treatment remained near baseline levels, with a moderate

reduction (50 pg/ml at baseline versus 31.3 pg/ml after 8 weeks of thalidomide). The mean plasma VEGF concentration for three patients with progression at 8 weeks of treatment rose from a baseline of 41.4 pg/ml to 114.9 pg/ml (Fig. 4).

DISCUSSION

Thalidomide is poorly tolerated and minimally effective in advanced HCC patients. We observed a response rate of 5% and disease-control rate (response/stability) of 18%. The median PFS (2.1 months) and median OS (5.5 months) are also consistent with limited efficacy. Toxicity was significant, with fatigue observed in nearly 75% and severe fatigue in more than 20% of patients. Additional toxicities, including sensory neuropathy and constipation, occurred frequently, although these were rarely severe. Nonetheless, three patients who developed grade 2 neurologic side effects (vertigo and neuropathy) refused to continue thalidomide administration at any dose. Overall, 16% of patients discontinued treatment secondary to side effects, including two patients (5%) with grade 4 cardiovascular events (myocardial infarction and stroke). The high rate of toxicity-related cessation seemed especially prevalent in the elderly; the majority of patients aged 70 or older discontinued treatment because of side effects.

The limited efficacy and significant toxicity suggest that thalidomide should not be considered a viable agent in the treatment of HCC outside of investigational purposes. Univariate analysis suggests that it is particularly ineffec-

tive in patients with HCC invasion of the portal vein or IVC. The 18% disease-control rate noted and the duration of response of up to 24 months are encouraging and suggest that antiangiogenic or immunomodulatory therapy in HCC represents a viable antitumor strategy. Additional investigation—particularly with less toxic thalidomide derivatives—is warranted [44].

With respect to efficacy, our results are consistent with those reported recently by two Taiwanese groups treating predominantly HBV-infected subjects. Hsu et al. [40] reported a 6% overall response rate and a somewhat higher 32% rate of stable disease. Wang et al. [41] noted a 7% overall response rate and did not report on stability. The median survival duration in both trials was fewer than 5 months. Two recently published North American studies report 3%–4% response rates [45, 46]. Grade 3 fatigue or somnolence was not observed in the Taiwanese trials but was 26%–35% as reported by Lin et al. and Patt et al. (Table 5)[45, 46]. None of these authors noted any significant arteriothrombotic events. Thrombosis is a known side effect of thalidomide and other antiangiogenic therapies. Thrombosis in myeloma has been seen predominantly when thalidomide is used with cytotoxic therapies [47]. Our findings suggest that, in the setting of liver disease and HCC, thalidomide monotherapy may be more thrombogenic than previously recognized.

The limited number of patients in whom adequately isolated and preserved serum and plasma from multiple time points was available prevents definitive statistical conclusions. We nonetheless observed a trend suggesting

Table 5. Clinical trials of thalidomide in hepatocellular carcinoma

Study	No.	Efficacy			Median overall survival (months)	Toxicity	
		Response rate	Stable disease	Disease control		Grade 3/4 fatigue or somnolence	Other serious adverse events
Hsu et al. [40]	68	6%	32%	38%	4.3	0%	Not observed
Wang et al. [41]	99	6%	N/R	N/R	0.8 ^a 2.5	0%	Not observed
Lin et al. [45]	27	4%	7%	11%	4.1	26%	30% neuropathy (grade 1–2) 41% instability or dizziness (grade 1–2)
Patt et al. [46]	37	3%	31%	34%	6.8	35%	8% early grade 4 rash requiring discontinuation
Schwartz et al. (this study)	38	5%	13%	18%	5.5	21%	5% grade 4 arteriothrombotic events (MI, CVA)

^aMedian overall survival in the study by Wang et al. was reported for two separate groups based on whether patients had received a cumulative thalidomide dose <5 g (*n* = 22) or ≥5 g (*n* = 77).

Abbreviations: CVA, stroke; MI, myocardial infarction; N/R, not reported.

that increasing plasma VEGF levels appears to be associated with disease progression and that disease stability may be accompanied by stability or reduction in circulating VEGF. Circulating bFGF does not appear detectable in the serum of patients with advanced HCC. We are currently nearing completion of studies in which more rigorous isolation and storage of serum and plasma in patients with unresectable HCC has been performed; the hope is that this will provide more conclusive information regarding the relevance of circulating cytokines (including VEGF and bFGF) in this disease.

Few patients were able to receive ongoing thalidomide with low-dose IFN upon progression. Although some did not continue therapy because of thalidomide-related effects, many were unable to continue because of disease progression and concomitant reduction in performance status. These results suggest that second-line therapy in advanced HCC is difficult, even in a cohort of patients who begin treatment with preserved hepatic function and performance status.

The combination of thalidomide and low-dose IFN- α was poorly tolerated and did not result in disease control. This combination is not safe or feasible in a cirrhotic population, even at the lowest possible IFN dose. Our findings are consistent with earlier reports suggesting the potential hazards of thalidomide/IFN combinations. These include a 39% incidence of severe toxicity (neurologic events and Stevens-Johnson reaction) associated with thalidomide and IFN- α 2a given at nine million IU three times per week in renal cell carcinoma; other investigators reported severe myelosuppression and increased fatigue and myelosuppression from combined thalidomide and pegylated-IFN [48–50]. Some authors noted tolerability of IFN- α 2a and thalidomide at modified doses [51]. However, our experience suggests that, in advanced HCC patients, even dose-limited combinations of these agents are not tolerated.

A univariate analysis of patient and tumor characteristics (Table 4) suggests that one of the strongest predictors of rapid progression is tumor invasion of the portal vein or IVC. The median OS of 3.8 months for this subset of 15 patients is consistent with our prior observations and those reported by investigators from Barcelona and Japan (median OS of 2.7 months and 3.9 months, respectively) [52, 53]. None of the seven patients with confirmed disease control in our study had this level of HCC vascular invasion. These observations lead us to recommend that patients with portal or caval invasion be studied sepa-

rately in future HCC investigations given the limited survival and low likelihood of any agent conferring response in this population.

Patients with bilateral or diffuse tumors had more rapid progression and more limited overall survival. The etiology of liver disease (HBV versus HCV versus nonviral) did not confer any difference in prognosis, nor did gender, Child-Pugh class, or the presence of extrahepatic metastases.

We observed more rapid progression and limited survival in HCC patients aged 50 years or younger. All of the patients with significant disease control were over the age of 50, and the median PFS and OS were significantly higher in the older patients. Our sample size precludes meaningful multivariate analysis; hence, the younger patients may have had more advanced disease at the time of presentation. Nonetheless, the possibility exists that HCC may be more aggressive in younger patients. This has not been previously reported; the hope is that future investigations will clarify this finding.

CONCLUSION

Thalidomide confers a limited response rate (5%) and modest disease-control rate (18%) in advanced HCC patients. Toxicity includes frequent low-grade events (fatigue, constipation, and neuropathy) and a low but significant (5%) incidence of high-grade arteriothrombotic complications. Although toxicity was significant and responses infrequent, this investigation suggests that noncytotoxic agents have the potential to confer disease control in advanced HCC. Initial reports using less toxic, more targeted antiangiogenic and other therapies have been encouraging [54, 55]. These findings suggest that other less toxic antiangiogenic or immunomodulatory agents should be studied in this disease.

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DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicate no potential conflicts of interest.

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