

Thalidomide in the Treatment of Patients with Hepatocellular Carcinoma

A Phase II Trial

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Supported in part by a grant from Celgene Corporation and by a grant from McKinley Medical LLP.

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Received June 14, 2004; revision received October 20, 2004; accepted October 20, 2004.

BACKGROUND. The treatment of patients with hepatocellular carcinoma (HCC) presents a major challenge, because associated cirrhosis limits the choice of chemotherapeutic agents. However, the abundant vascularity of HCC presents an attractive target for antiangiogenic therapy that potentially may be tolerated by cirrhotic patients. The current study was conducted to assess the antitumor activity, treatment tolerance, treatment-related toxicity, and patient survival after the administration of thalidomide in a Phase II trial.

METHODS. Thirty-seven HCC patients were accrued between March, 1999, and March, 2000. Initially, the dose of oral thalidomide was escalated from 400 mg per day during the first week to 1000 mg per day by the fifth week, delivering one-third of the dose in the morning and the remaining two-thirds of the dose in the evening prior to bedtime. Changes in the daily drug administration schedule were allowed based on tolerance. Response was assessed at 8-week intervals.

RESULTS. Thirty-two of 37 registered patients were evaluable for response. One patient had a partial response (PR), 1 patient had a minor response (MR), 10 patients had stable disease (SD) (31%; 95% confidence interval [95%CI], 16–51%), and 20 patients (61%; 95%CI, 42–78%) had disease progression. The most commonly encountered toxicity was somnolence, with Grade 3–4 somnolence (≥ 4 hours of sleep during normal waking hours) in 9 patients (35%) and Grade 2 somnolence (≤ 3 hours) in 30% of patients. In fact, only 48% of patients tolerated a daily dose > 800 mg if it was delivered at bedtime. Grade 3–4 skin reactions were observed in 20% of patients, and exfoliative dermatitis was observed in 1 responding patient. The overall median survival was 6.8 months.

CONCLUSIONS. With a 5% PR rate, a 5% MR rate, and a 31% SD rate, the results indicate that thalidomide mostly may offer HCC patients disease stabilization. It is possible that, at a different dosage, or combined with other chemotherapy agents, or with the use of a different thalidomide analogue, longer patient survival may be achieved. However, in view of the significant neurologic toxicity encountered among these commonly cirrhotic HCC patients, thalidomide monotherapy at the high doses studied cannot be recommended for the treatment of HCC. *Cancer* 2005;103:749–55. © 2005 American Cancer Society.

KEYWORDS: hepatocellular carcinoma, HCC, thalidomide, antiangiogenic therapy, cirrhosis.

Thalidomide (d-phthalimido glutarimide) was introduced in Europe in the 1950s as a sedative and an antiinflammatory agent.¹ Due to its teratogenic effects, most notably phocomelia,² thalidomide was never released or marketed in the United States. Laboratory studies have demonstrated down-regulation of peptide signals, such as interleukin 6 (IL-6), basic fibroblast growth factor (bFGF), vascular

endothelial growth factor (VEGF), and tumor necrosis factor α (TNF- α) by thalidomide; the inhibition of the latter through accelerated degradation of mRNA coding for it.³ The ability of thalidomide to down-regulate overproduction of TNF- α confers therapeutic importance to this drug in malignancies that are distinguished by overproduction of TNF- α . In addition, thalidomide may inhibit bFGF-induced and VEGF-induced angiogenesis in the *in vivo* rabbit cornea micropocket assay.^{4,5}

Thalidomide has demonstrated activity against multiple myeloma⁶ and myelodysplastic disorders⁷ and, among the solid tumors, against renal cell carcinoma^{8,9} and acquired immunodeficiency syndrome-related Kaposi sarcoma.¹⁰ Neither low-dose thalidomide (100 mg) nor high-dose thalidomide (600 mg) thalidomide had significant single-agent activity against melanoma.¹¹ However, when combined with temozolomide, thalidomide was associated with 5 responses among 12 patients with melanoma who were treated on a Phase I trial. It is noteworthy that increased toxicity was observed when higher doses were used among patients age > 70 years.¹²

Hepatocellular carcinoma (HCC), the most common primary liver malignancy, often develops among patients who have cirrhosis. It is estimated that approximately 60% of all patients with HCC have underlying cirrhosis.¹³ In some patients, cirrhosis associated with portal hypertension and thrombocytopenia makes cytotoxic chemotherapy for HCC extremely precarious and contributes to the poor prognosis associated with HCC. In fact, a study of 753 patients with HCC in the United States who were seen at The University of Texas M. D. Anderson Cancer Center showed that cirrhosis significantly increased the hazard ratio (HR) of earlier death from HCC (HR, 1.8; 95% confidence interval [95%CI], 1.5–2.3; $P < 0.0001$).¹⁴

Like many other solid tumors, HCC is dependent on preexisting vasculature for its development and on neovascularization and angiogenesis for its growth. In cirrhotic livers, the organ parenchyma is replaced by fibrotic tissue. Under the influence of hepatocyte growth factors, regenerative nodules develop. The number of unpaired blood vessels that are not associated with portal triads increases as the nodules become more dysplastic,¹⁵ suggesting that neoangiogenesis plays an important role in the progression from cirrhosis to regenerative nodules, to dysplastic nodules, and ultimately to HCC. Therefore, antiangiogenic therapy is an attractive approach to the treatment of HCC, particularly in the presence of cirrhosis.

Indeed, hepatic artery chemoembolization, which induces tumor ischemia along with increased local drug concentration, may be appropriate for the man-

agement of HCC confined to the liver.¹⁶ However, this approach may be precarious in patients who have severe liver dysfunction due to advanced cirrhosis. Furthermore, we previously reported on a patient who had refractory HCC who received escalating doses of oral thalidomide.¹⁷ A dramatic response in the primary HCC and the metastases was observed that was correlated highly with a significant drop in the serum levels of α -fetoprotein (AFP). Based on the case report described above, the vascular nature of HCC, and the paucity of treatment options for cirrhotic patients with advanced HCC, we conducted an open-label Phase II trial of thalidomide in patients with HCC who were referred to The University of Texas M. D. Anderson Cancer Center.

MATERIALS AND METHODS

Patient Selection

This Phase II study was initiated after approval was obtained from the Institutional Review Board (IRB). All patients signed an IRB-approved informed consent form attesting to the fact that they were aware of the investigational nature of the study. Patients were eligible if they had histologically confirmed, radiologically measurable HCC with evidence of disease progression. All patients had a performance status ≤ 2 on the Zubrod scale, a life expectancy ≥ 16 weeks, an absolute granulocyte count $\geq 1000/\text{mL}$, and a platelet count $\geq 40,000/\text{mL}$. Other inclusion criteria included a serum creatinine level ≤ 2 mg/dL, a serum bilirubin level ≤ 3 mg/dL, and a serum albumin level ≥ 2.8 g/dL. These hematologic and biochemical inclusion criteria were used to allow the inclusion of patients with advanced cirrhosis.

Cirrhotic as well as noncirrhotic patients were eligible for the study. A clinical diagnosis of cirrhosis was based on the presence of stigmata of portal hypertension frequently evidenced by splenomegaly, ascites, esophageal varices demonstrated endoscopically or radiologically, and/or clinical findings, such as spider angiomas and palmar erythema. A cirrhotic contour of the liver as seen on a computed tomography scan also supported a diagnosis of cirrhosis.

Prior systemic therapy with drugs other than thalidomide was allowed. Women who were pregnant or breast-feeding were excluded from this trial.

Birth-Control Requirement

All female patients with childbearing potential had to have been practicing proper birth-control methods for 1 month prior to receiving thalidomide. Two methods of birth control were required, one hormonal and one barrier. Women who had a contraindication to hormonal contraception were required to use two barrier

methods. All male patients were instructed to use barrier contraceptives, such as condoms. Contraception was continued for at least 1 month after the discontinuation of thalidomide treatment. Sexually active patients who did not practice adequate birth control were excluded from this trial.

Thalidomide Supply

Thalidomide was provided by Celgene Corporation (Warren, NJ).

TREATMENT PLAN

Thalidomide was given orally on an outpatient basis. In an attempt to improve tolerance, the daily dosage was increased gradually from 400 mg per day during the first week, to 600 mg per day during the second week, to 800 mg per day during the third week, to 1000 mg per day during the fourth week, to 1200 mg/day during the fifth week, and onward. This weekly dose escalation was contingent on tolerance of the thalidomide dose during the preceding week. The intention was to treat patients at the highest tolerable dose, allowing dose adjustment and adjustment of dose timing to minimize drowsiness. The initial plan was to give 50% of the dose at night, 25% in the morning, and 25% in the afternoon. However, lethargy among the first 10 patients prompted a change in dosing, with 35% of the dose given in the afternoon and 65% given at bedtime (10 patients). This schedule still was soporific; therefore, all remaining patients received the entire dose at bedtime.

Response Evaluation

Antitumor response was assessed at 8-week intervals, and the best response was used to classify the antitumor effect. The following criteria were used: 1) A complete response was defined as the disappearance of all radiologic and clinical evidence of the tumor and absence of all tumor-related symptoms and radiologic evidence of the tumor for at least 4 weeks. 2) a partial response (PR) was defined as a decrease $\geq 50\%$ in the product of the 2 greatest perpendicular dimensions of measurable tumors measured at least 4 weeks apart. No simultaneous increases in the size of any lesions or appearance of new lesions could occur. 3) A minor response (MR), for the purpose of this particular protocol, was defined as a decrease $\geq 50\%$ in the serum AFP level, even without any change in radiologic tumor measurements on computed tomography scans or magnetic resonance images. 4) Stable disease (SD) was defined as no change in radiologic tumor measurements without a change or a decrease $< 49\%$ in the serum AFP level. 5) Progressive disease was defined as an increase $\geq 25\%$ in any measured lesions

and/or the appearance of new lesions. The entity of an MR was introduced and was defined arbitrarily, as described above, to make sure that even minor evidence of antitumor activity was not ignored and could trigger continuation of the trial.

Statistical Methods

Simon's design of Phase II trials¹⁸ was used to determine the study sample size. A p_0 and p_1 defined as a true response probability that is uninteresting (p_0); and a true response probability that is of definite interest (p_1) were set at 5% and 20% respectively. For the purpose of this study, any evidence of biologic activity was considered to be of interest, and even 1 MR in the first 12 patients was sufficient to trigger the second stage of the study. Accordingly, 12 patients were to be entered initially into the trial, and the next cohort of 25 patients would be accrued if there were any objective responses in the first cohort, bringing the total number to 37 patients. This plan was designed to have both a false-positive error rate and a false-negative error rate of 10%, with a probability rate of early termination at the end the first of stage of 54%.

The first patient was registered in March, 1999, and the 37th patient was registered in February, 2000. For data management and statistical analyses, the Statistical Package of Social Science was used (SPSS, Inc., Chicago, IL). Baseline laboratory markers were expressed as medians and ranges. To assess changes in AFP levels among patients, a Friedman analysis of variance was applied for all repeated measurement parameters, and a Wilcoxon signed-rank test was used for comparisons within patients between baseline values and subsequent measurements during follow-up. The survival curves were generated by the Kaplan-Meier method,¹⁹ and the statistical significance of differences was determined according to Gehan's modification of the Wilcoxon signed-rank test.²⁰

RESULTS

Patients Characteristics

Thirty-seven patients with HCC were included in this trial. The median patient age was 63 years (range, 32–79 years), and the median performance status on the Zubrod scale was 1 (range, 0–2). Table 1 shows the patient characteristics. Twenty-two patients (59%) had clinical and/or radiologic evidence of cirrhosis. However, histologic confirmation of cirrhosis in the underlying liver could not be ascertained in this trial. The histologic diagnosis of HCC was established using fine-needle aspiration of the tumor, thereby precluding histologic assessment of the hepatic parenchyma. Indeed, all patients had histologic confirmation of HCC. Twenty of 37 patients (54%) were reactive for

TABLE 1
Characteristics of Patients with Hepatocellular Carcinoma

Characteristic	No. of registered patients (%)
Not assessable for response	6 (16)
Assessable for response	31 (84)
Gender	
Male	24 (65)
Female	13 (35)
Age (yrs)	
Median	63
Range	32–79
Ethnicity	
White	27 (73)
African Americans	1 (3)
Hispanic	6 (16)
Asians	3 (8)
Distant metastases	
Lungs and bone	8 (22)
Lymph nodes ^a	10 (27)
Previously treated	
Yes	22 (60)
No	15 (40)
Cirrhosis	22 (59)
Median performance status (range)	1 (0–2)
Hepatitis virus markers	
HCV (anti-HCV antibodies)	5 (14)
HBV (HBsAg or anti-HBc)	9 (24)
HCV and HBV markers	6 (16)
No viruses markers	17 (46)
Disease stage	
CLIP score	
0	3 (8)
1	6 (16)
2	6 (16)
3	10 (27)
4	8 (22)
≥ 5	4 (11)
Okuda stage	
Stage I	12 (32)
Stage II	22 (60)
Stage III	3 (8)
AJCC stage	
Stage I	0 (0)
Stage II	1 (3)
Stage III	3 (8)
Stage IV	33 (89)
Prior treatment	
None	15 (40)
Surgery alone ^b	2 (6)
Surgery and others ^c	5 (13)
Chemotherapy alone ^d	10 (27)
Chemotherapy and others ^e	3 (8)
Chemoembolization	2 (6)

HCV: hepatitis C virus; HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; anti-HBc: hepatitis B core antibody; CLIP: Cancer of the Liver Italian Program; AJCC: American Joint Committee on Cancer.

^a Patients may have had lymphadenopathy at more than one site.

^b Surgical resection only.

^c Includes chemotherapy agents (see ^d below), chemoembolization, radiation, and alcohol ablation.

^d Includes different combinations of 5-fluorouracil, interferon- α , xeloda; platinum interferon, doxorubicin and fluorouracil by intravenous infusion; floxuridine, leucovorin, doxorubicin, and platinum by hepatic arterial infusion; tamoxifen, and doxil.

^e Includes radiation, surgery, and radiofrequency ablation.

TABLE 2
Pretreatment Laboratory Results

Laboratory variable	Median value (range)
Platelet count ($\times 10^3 \mu/L$)	129.0 (43.0–390.0)
Bilirubin level (mg/dL)	0.9 (0.4–3.0)
Albumin level (g/dL)	3.5 (2.8–5.0)
Alkaline phosphatase (IU/L)	136.0 (74.0–526.0)
α -fetoprotein serum level (ng/mL)	1205.0 (3.1–176,694.0)
Lactic dehydrogenase (IU/L)	618.0 (312.0–1194.0)
Alanine aminotransferase (IU/L)	42.0 (12.0–22.0)
Prothrombin time (seconds)	11.85 (10.60–14.60)

hepatitis markers as follows: antihepatitis C virus (HCV)-positive, 5 patients (14%); hepatitis B surface antigen (HBsAg)-positive or hepatitis B core antibody (anti-HBc) positive, 9 patients (24%); and HCV and hepatitis B virus (HBV) marker-positive, 6 patients (16%).

Among 22 cirrhotic patients, 15 patients (68%) were positive for hepatitis markers as follows: HCV-reactive, 5 patients; HBV-reactive (HBsAg-positive and/or anti-HBc-positive), 9 patients; and both HBV-reactive and HCV-reactive, 1 patient. Seven patients with alcoholic cirrhosis had no viral markers. Five patients who were HBV or HCV marker-reactive had no clinical or radiologic evidence of cirrhosis. All patients had Stage IV-A HCC ($n = 27$ patients) or Stage IV-B HCC ($n = 10$ patients), according to the American Joint Committee on Cancer (AJCC) Tumor-Lymph Node-Metastases (TNM) classification system, with multifocal hepatic involvement.²¹ The stage of HCC in these patients according to the Cancer of the Liver Italian Program (CLIP) score,²² the Okuda classification system,²³ and the AJCC staging system are shown in Table 1. Extrahepatic disease was present in 18 of 37 patients (49%). The pretreatment laboratory data are summarized in Table 2.

Dose Adjustments

All 37 patients were started on 8 capsules of 50 mg each or a total of 400 mg and were escalated to the 600-mg dose level. However, only 27 of 37 patients reached the 800-mg dose level, 21 patients reached the 1000-mg dose level, and 9 patients reached the 1200-mg dose level. In total, 309 weeks of treatment were given to these patients. The median length of treatment was 7 weeks (range, 2–2 weeks). The reason for dose reduction in all patients was Grade 3–4 somnolence with or without a skin reaction to the drug.

Radiologic Response Evaluation

Thirty-two patients were evaluable for treatment response. Three of the 6 patients who were not evalu-

TABLE 3
Response Evaluation

Variable	No. (%)	95% CI
Registered patients	37	
Treated patients	35	
Evaluable patients	32	
Complete response	0	
Partial response	1 (3)	0.8–17.0
Minor response	1 (3)	0.8–17.0
Stable disease	10 (31)	16.0–51.0
Progressive disease	20 (62)	42.0–78.0

95%CI: 95% confidence interval.

able for response developed a Grade 4 skin rash and discontinued treatment before their evaluation date, 2 patients never underwent treatment (1 patient developed hepatic encephalopathy unrelated to treatment) or had treatment interrupted very early and died due to disease progression before returning for the first 2-week follow-up visit (1 patient).

Table 3 shows that 1 patient (3%) had a PR, 1 patient had an MR (3%), 10 patients had SD (31%), and 20 patients had progressive disease (62%). The time to disease progression among the patients with SD could be determined clearly in only 7 patients, and the median time to disease progression was 8 weeks (range, 8–40 weeks).

Correlation with Serum AFP Level

The median baseline serum AFP level among patients with SD was significantly higher compared with the level among patients with progressive disease. A drop in the AFP level after 4 weeks of treatment was observed in 14 patients with SD, MR, or PR. The reduction ranged from 2% to 25% (median 15%) from the baseline level of the marker. However, this reduction did not reach statistical significance.

ADVERSE EVENTS

Drug-related toxicity was assessed in all 35 study patients who received thalidomide (Table 4). Drowsiness was common, and its severity was graded according to the number of sleeping hours during normal waking time. Two hours of sleep during normal waking time were considered Grade 1 drowsiness, 3 hours were considered Grade 2 drowsiness, 4–6 hours were considered Grade 3 drowsiness, and ≥ 6 hours were considered Grade 4 drowsiness. Twenty-one patients (60%) experienced Grade 1–2 drowsiness, and 11 patients (31%) experienced Grade 3–4 drowsiness. Dermatologic toxicity in the form of skin rash also was quite common and included Grade 1–2 skin rash in 10

TABLE 4
Toxicity Analysis: Toxicity Data on 35 Patients who Received Treatment

Toxic effect	No. of patients (%) (n = 35)
Hematologic	
Neutropenia	
Grade 1–2 (AGC 1.0–1.9 × 10 ³ μ/L)	14 (40)
Grade 3–4 (AGC < 0.9 × 10 ³ μ/L)	2 (6)
Anemia	
Grade 1–2 (Hgb 8.0–9.0 g/dL)	12 (34)
Grade 3–4 (Hgb < 7.9 g/dL)	1 (3)
Nonhematologic	
Diarrhea	
Grade 1–2	1 (3)
Grade 3–4	0 (0)
Nausea	
Grade 1–2	7 (20)
Grade 3–4	1 (3)
Emesis	
Grade 1–2	5 (14)
Grade 3–4	0 (0)
Fatigue	
Grade 1–2	1 (3)
Grade 3–4	0 (0)
Skin rash	
Grade 1–2	10 (29)
Grade 3–4	5 (14)
Peripheral neuropathy	
Grade 1–2	9 (26)
Grade 3–4	0 (0)
Drowsiness	
Grade 1–2	21 (60)
Grade 3–4	11 (31)

AGC: absolute granulocyte count; Hgb: hemoglobin.

patients (29%) and Grade 3–4 skin rash in 5 patients (14%). Three patients had to discontinue thalidomide therapy because of the severity of the rash. Finally, hematologic toxic effects were relatively infrequent and were mostly Grade 1–2.

Survival Analysis

All of the patients in this study were observed until February, 2001. The estimated overall median survival duration was 6.8 months (95%CI, 5.4–8.2 months) (Fig. 1). Response to treatment did not affect survival. Thus, the median survival duration in patients who had SD, a PR, or an MR was 8.9 months, which was not significantly different compared with the response among patients who had disease progression (6.3 months).

DISCUSSION

HCC is a vascular tumor that frequently evolves from dysplastic nodules encountered in cirrhotic livers.¹⁵

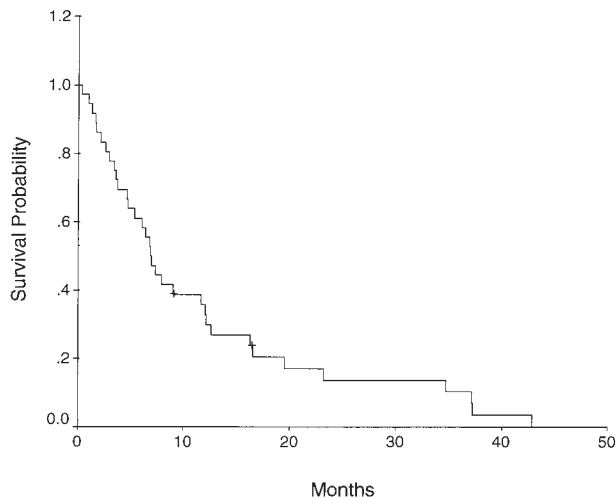


FIGURE 1. The median survival of patients with hepatocellular carcinoma was calculated with the Kaplan–Meier method.

The progression from a dysplastic liver nodule, to a highly dysplastic nodule, to HCC is associated with an increase in the number of unpaired blood vessels that are not constituents of the portal triads.¹⁵ Japanese²⁴ and Italian^{25,26} investigators have demonstrated that progression from HCV-related cirrhosis to HCC may be prevented by treatment with recombinant interferon α (rIFN- α) and that this preventive effect was independent of the antiviral activity of the agent. It is quite plausible that these preventive properties were related to the inhibition of angiogenesis. We have used a combination of continuously infused 5-fluorouracil and subcutaneous rIFN- α and observed a median survival of 15.5 months among patients with HCC,²⁷ indicating that the combination was of interest. In search of other angiogenesis inhibitors that could be given safely to cirrhotic patients, we tested thalidomide in the current Phase II trial. The agent was selected after observation of a single patient with alcoholic cirrhosis who did not respond to numerous prior treatments and, thus, was treated with thalidomide on a compassionate protocol. The patient had a dramatic radiologic response with a corresponding decrease in the serum AFP level from 109,000 ng/mL to approximately 90 ng/mL.¹⁷ That observation prompted the current Phase II trial for patients with HCC who were not candidates for higher priority protocols or who had disease that had not responded to prior therapies. Our initial analysis reported to the American Society of Clinical Oncology 2000 meeting suggested a median patient survival of 12.4 months (95%CI, 3.9–29.0 months).²⁸ However, the current updated analysis indicated a median survival of only 6.8 months with a much narrower 95%CI, and the initial data could not

be substantiated. In addition, thalidomide therapy was associated with significant sedation, resulting in a deteriorating quality of life among a few patients who refused to continue treatment. The poor drug tolerance may have been related to the frequent presence of cirrhosis among our patients with HCC. Poor tolerance of thalidomide combined with temozolomide also was observed when treating patients with melanoma age ≥ 70 years.¹² Fatigue was also a common occurrence among patients with myeloma who were treated with single-agent thalidomide (39%) or thalidomide combined with dexamethazone (55%).²⁹ Indeed, bedtime drug administration has become the standard for thalidomide therapy.¹¹ Results of other trials with thalidomide in patients with HCC have not differed substantially from the current results. Indeed, Wang et al.³⁰ and Hsu et al.³¹ observed toxicity profiles similar to those reported here, low response rates, and survival rates that were affected more by disease stage than by treatment.

Thalidomide has four major groups of active peptide signals as discussed by Eisen in a previously published editorial.¹¹ First, it down-regulates IL-6, bFGF, VEGF, and TNF- α ^{32,33} that may be released by tumors to stimulate neoangiogenesis and tumor cell growth. The down-regulation of these or some of these factors may be associated with angiogenesis. Second, thalidomide modulates immune function by inducing the proliferation of CD8-positive T cells.³⁴ Third, thalidomide modulates the cell adhesion molecules involved in metastases.³⁵ Fourth, thalidomide reduces the production of prostaglandin by suppressing cyclooxygenase-2 activity.³⁶ It is unclear which of these four activities is most important, and different activities may be of prime importance in different malignancies. TNF- α plays a role in hepatocarcinogenesis, and its down-regulation indeed would have been desirable. Unfortunately, the toxicity observed in the current trial suggested that native thalidomide is unlikely to play an important role in the treatment of HCC. It is possible that a thalidomide derivative with more specific TNF-inhibitory activity also will have less central and peripheral neurologic toxicity and may be of benefit to patients with HCC.

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