Cancer Chemother Pharmacol (2006) 58: 654–664
DOI 10.1007/s00280-006-0203-z

ORIGINAL ARTICLE

**Her-Shyong Shiah · Yee Chao · Li-Tzong Chen
Tzy-Jyun Yao · Jin-Ding Huang · Jang-Yang Chang
Pei-Jer Chen · Tsai-Rong Chuang · Yung-Hsin Chin
Jacqueline Whang-Peng · Tsang-Wu Liu**

Phase I and pharmacokinetic study of oral thalidomide in patients with advanced hepatocellular carcinoma

Received: 25 October 2005 / Accepted: 30 January 2006 / Published online: 7 March 2006

Abstract *Purpose:* To evaluate the dose-limiting toxicities (DLT), maximum tolerated dose (MTD), and pharmacokinetics of thalidomide in patients with advanced hepatocellular carcinoma (HCC). *Methods:* Patients with advanced HCC who were not feasible for definitive local therapy were eligible. Patients were enrolled in a cohort of three to receive thalidomide twice daily for 1 week to determine the MTD. Intra-patient dose escalation was permitted. Pharmacokinetic studies were performed at the first dose level and repeated at the second dose level of each patient. *Results:* Fifteen patients were accrued at four dose levels with the starting dose range 100–400 mg/day. Two patients at 400 mg/day experienced DLT (grade 3 angioedema and dyspnea, respectively). The MTD of twice-daily schedule was determined as 300 mg/day. The mean steady-state maximal blood concentration and mean steady-state area under the curve had a trend toward positive correlation, but non-linear proportionate, to the daily dose of thalidomide. Pharmacokinetic parameters are comparable for patients of Child-Pugh's A and B. Apparent mild, transient drug-induced transaminitis was early onset, self-limited, which occurred in 30.7% of patients. Serum hepatitis B or C viral titers was largely not affected. *Conclusion:* The absorption and elimination of thalidomide are not significantly different in HCC patients with compensated or decompensated hepatic dysfunction.

Keywords Cirrhosis · Maximum tolerated dose · Angiogenesis inhibitor · Hepatitis virus

Li Tzong Chen and Tsang-Wu Liu contributed equally to this work.

H.-S. Shiah · L.-T. Chen · J.-Y. Chang · T.-R. Chuang
Y.-H. Chin · J. Whang-Peng · T.-W. Liu (✉)
Divisions of Cancer Research, National Health Research Institutes, Ward 191 Veterans General Hospital, Taipei, Taiwan, ROC
E-mail: walter@nhri.org.tw
Fax: 886-2-28716467

L.-T. Chen
Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, ROC

T.-J. Yao
Biostatistics & Bioinformatics and Biotechnology & Pharmaceutical Research, National Health Research Institutes, Taipei, Taiwan, ROC

J.-D. Huang
Biotechnology and Pharmaceutical Research, National Health Research Institutes, Taipei, Taiwan, ROC

Y. Chao
Cancer Treatment Center, Taipei Veteran General Hospital, Taipei, Taiwan, ROC

J.-D. Huang
Department of Pharmacology, Medical College of National Cheng-Kong University, Tainan, Taiwan, ROC

P.-J. Chen
Graduate Institute of Clinical Medicine, Medical College of National Taiwan University, Taipei, Taiwan, ROC

Introduction

Angiogenesis has recently been demonstrated to play a crucial role in the growth, progression and even chemoresistance of a variety of tumors both in primary and metastatic forms [17–19, 23, 44, 56]. Inhibition of angiogenesis has been proposed as a potential anticancer treatment [4, 29]. Thalidomide, a glutamic acid derivative first described in 1953, was marketed as a sleeping pill, but was withdrawn from the European market 30 years ago because of its teratogenic effects [38]. The thalidomide-associated birth defect, phocomelia (stunted limb growth), might be due to the interference of blood vessel growth in a developing fetal limb bud by thalidomide [8]. Recent studies suggested that oral thalidomide treatment could inhibit the basic fibroblast growth factor (bFGF)- and vascular endothelial growth factor (VEGF)-induced rabbit corneal neovascularization [8, 31]. This leads to a revival in the

use of thalidomide in the treatment of some angiogenic tumors, including, hormone-refractory prostate cancer, high-grade glioma, breast cancer, Kaposi's sarcoma, head and neck squamous cell carcinoma, myelodysplastic syndrome and hepatocellular carcinoma [2, 7, 14, 16, 24, 35, 47, 50, 55]. Recently, single agent thalidomide therapy has been approved by Australia's Therapeutic Goods and Administration (TGA) for advanced/refractory multiple myeloma [22]. Another application of thalidomide is in the management of numerous inflammatory and autoimmune diseases, such as Crohn's disease and rheumatoid arthritis [21, 57]. Further investigation suggested that its immunomodulating effects may be derived from the inhibition of tumor necrosis factor-α (TNF-α) secretion from monocytes [48]. Nevertheless, besides teratogenicity, thalidomide management is associated with several adverse events—somnolence, constipation, asthenia, skin rash, peripheral edema, paresthesia and dizziness are the most common, while deep vein thrombosis, peripheral neuropathy and Stevens–Johnson syndrome are the most serious [10]. Those toxicities would compromise the dose intensity of thalidomide.

In preclinical in vivo studies, the bFGF-induced angiogenesis was inhibited by the oral administration of thalidomide but not by topical use [8]. Furthermore, thalidomide could inhibit human aortic endothelial cell proliferation and microvessel formation from rabbit aorta in the presence of human or rabbit liver microsomes ex vivo, whereas thalidomide inhibited neither endothelial cell proliferation nor microvessel formation without the activation by microsomes [3, 5]. These results suggested that thalidomide metabolized by liver was probably a pivotal step to form active anti-angiogenic metabolite(s) of thalidomide in humans. On the other hand, the production of 5-hydroxy compound is the major hepatic thalidomide metabolite catalyzed by cytochrome P-450 in microsomes [52]. Such a production of 5-hydroxy metabolite is very low. Thalidomide is mainly broken down through a spontaneous nonenzymatic hydrolytic cleavage at physiological pH [26]. It was even demonstrated that hepatic enzyme-inducing drugs had little effect on the metabolism of thalidomide [16]. Therefore, it gives rise to the question whether an impaired liver function has any impact on the efficacy and toxicity of thalidomide. Up to now, there has been no comprehensive study performed to evaluate the pharmacokinetics of thalidomide in patients with hepatic dysfunction, while the pharmacokinetics of thalidomide has not changed in patients with impaired renal function or on dialysis [13].

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide [58] and also the leading cause of death due to cancer among the people of Taiwan [34]. Clinically, HCC patients who present with advanced stage of diseases at the time of diagnosis as well as those who have recurrence after definitive local treatments will require a systemic therapy. Since there are issues of intrinsic multidrug resistance and the relatively poor reserve of liver function in HCC patients who are at an advanced stage, systemic chemotherapy is generally less effective and is associated with greater toxicity [32, 42]. HCC is also a well known angiogenic and angiogenesis-dependent cancer [28, 37]. Strategies aimed at inhibiting angiogenesis, i.e., oral thalidomide, were considered to be potential alternatives for treating this chemo-resistant cancer [6, 24, 45, 55, 59]. Based on the facts that the underlying reserve of liver function is relatively poor in most of HCC patients and thalidomide might not require a metabolism by liver, it is important to document the pharmacokinetics and the toxicity profiles of thalidomide treatment in such patients.

Herein, we present the first phase I/pharmacokinetic study of oral thalidomide in HCC patients with underlying hepatic dysfunction.

Patients and methods

Patient population

Patients with measurable, metastatic or locally advanced HCC whose tumors had failed to have definitive local therapy [including surgical resection, percutaneous ethanol or alcohol injection (PEI or PAI), transcatheter arterial chemoembolization (TACE), or in combination) or whose tumor was too advanced; 18–75 years of age; and an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2 were eligible. The diagnosis of HCC had to be established by cytology or histopathology. Patients were required to have a Child-Pugh's Score ≤ 8 with a serum total bilirubin ≤ 3 mg/dL, a prothrombin times ≤ 5 s above normal control, a platelet count $\geq 7.5\times10^4/mm^3$, a white cell count $\geq 3{,}000/mm^3$, and a serum creatinine < 1.5 mg/dL. Female patients of childbearing age should show a negative pregnant test. Sexually active patients, in conjunction with their partners, had to agree to practice birth control measure during and for at least 2 months after thalidomide therapy. This study has been approved by the Institutional Review Board of the hospital and by the Department of Health, Executive Yuan, Taiwan. All patients gave signed informed consent.

Phase I study

The schema of phase I study and intra-individual study was displayed in Fig. 1. For phase I study, patients were enrolled in a cohort of three to receive 1 week of thalidomide (Thado®, 50 mg/capsule, TTY Biopharm Co. Ltd, Taipei, Taiwan) therapy. Thalidomide was given orally twice daily (b.i.d.) between 0900–1000 and 2100–2200 hours. The dose of thalidomide started from 100 mg/day and escalated in the subsequent cohorts of patients, with a target dose at 1,200 mg/day. The escalation was by 100 mg while receiving dose < 400 mg/day and by 200 mg while receiving dose ≥ 400 mg/day. If no

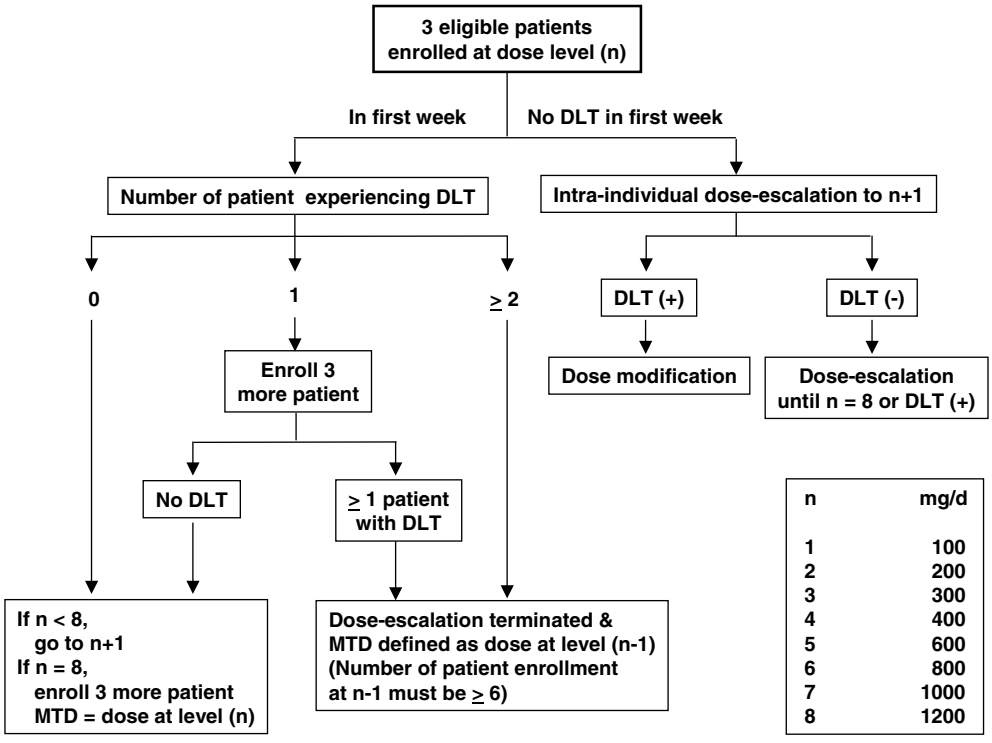

Fig. 1 Schema of phase I study and dose-escalation study of thalidomide in advanced HCC. *DLT* dose-limiting toxicity, *MTD* maximum tolerated dose

patient had a dose-limiting toxicity (DLT) at a certain dose level, the subsequent three patients would be treated with the next dose level. DLT was defined as: ≥ WHO grade 2 somnolence, ≥ WHO grade 2 peripheral neuropathy, erythema multiforme, Stevens–Johnson syndrome and/or other ≥ WHO grade 2 allergic skin eruption that was unresponsive to antihistamine (± local corticosteroid) therapy, other unmanageable ≥ WHO grade 3 non-hematological toxicity, prolonged (> 7 days) ≥ WHO grade 3 hematological toxicity and/or neutropenic fever; and repetitive, unexpected ≥ grade 2 infection. If one out of three patients developed DLT, three additional patients would be accrued to the same dose level. If none of the additional three patients developed DLT, the dose escalation would be continued. If two or more patients developed DLT at a certain dose level, the dose escalation would be terminated, and the prior dose level would be considered as the maximum tolerated dose (MTD). A minimum of six patients was required to test at the dose level of MTD.

Intra-individual dose-escalation study

Patients who did not experience DLT during the first week of therapy would have their thalidomide dose escalated by one dose level weekly until the target dose of 1,200 mg/day was achieved, the patient refused or a DLT occurred. For each patient, the dose one level below that associated with DLT or the dose that the patient refused was considered as an individual achievable dose for further escalation. Subsequent treatment for each patient was maintained at individual achievable dose until the presence of unacceptable toxicity, the patient's refusal or tumor progression.

Evaluation of patients

Physical examination and symptoms were evaluated before treatment and daily during the phase I study (the first week of treatment), and then evaluated every 2–4 weeks. The serum levels of albumin/globulin, aspartate/alanine transaminase (AST/ALT), alkaline phosphatase (Alk-p), gamma-glutamyltranspeptidase (γGT), total/direct bilirubin, alpha-fetoprotein (AFP), blood urea nitrogen (BUN), creatinine and electrolytes, and complete blood count with differential count, prothrombin time/activated partial thrombine time (PT/aPTT), and urine analysis were examined before treatment and then every 2–4 weeks throughout the whole study. Additional serum biochemistry studies were performed before each pharmacokinetic (PK) study. Indocyanine green (ICG) clearance test was performed to determine the ICG-R_{15} (indocyanine green retention rate at 15 min), which served as an indicator of hepatic function reserve [43], before every PK study. Woman of the childbearing age had urinary HCG test before treatment which was repeated every 4 weeks.

The serum HBV-DNA and HCV-RNA were quantified by the signal amplification nucleic acid probe assay (branched DNA assay, HBV DNA Assay and HCV RNA 3.0 Assay, Bayer, USA) at the central

laboratory of Hepatitis Research Center, National Taiwan University Hospital.

Chest X-rays, and abdominal ± chest CT were done before the treatment, and then repeated every 8 weeks or whenever clinically indicated; additional examinations were done 4 weeks after the first radiological evidence of tumor response. The grading of treatment toxicity as well as tumor response was evaluated according to the criteria defined by the WHO [40]. Because the baseline liver function was abnormal in most patients, the grading of hepatic (ALT) toxicity was assessed by comparison with a baseline value of individual patients rather than the upper normal limits in this study.

Pharmacokinetic study

Blood samples were obtained from all patients for pharmacokinetic studies at their their1st dose level. Two mL of blood were obtained at 0 h (0900 hours, before the first dose) then at 12 h (2100 hours, before the second dose), 24 h (0900 hours, before the third dose), 36 h (2100 hours, before the fourth dose), 48 h (0900 hours, before the fifth dose), 50, 52, 54, 56 and 60 h (2100 hours, before the sixth dose). The studies were repeated at the second dose level and at individual achievable dose (optional) in patients who received an escalating dose of thalidomide. The blood sample at the dose level of individual achievable dose was obtained when patients had received thalidomide at one level below that associated DLT for 1 week. The blood samples were immediately mixed with an equal volume of 25 mM sodium citrate buffer (pH 1.5) and stored at -70°C until analysis. The whole blood concentration of thalidomide was determined by the high-performance liquid chromatography (HPLC) with ultraviolet detection [12, 13]. The lower limit of quantification was 0.1 μg/mL. The procedure was validated through the range of 0.1–10 μg/mL, using 1 mL whole blood. The precision was $<10\%$ and the accuracy was between 90 and 110%. The urine was also collected for the determination of thalidomide concentration at the interval of 12 h during each blood sampling. Totally six 12 h-urine samples (50 mL) at 0 h, 0–12 h, 12–24 h, 24–36 h, 36–48 h and 48–60 h were measured in each patient. The urine samples were immediately mixed with an equal volume of 25 mM sodium citrate buffer (pH 1.5) and stored at -70°C until analysis.

Pharmacokinetic analysis

The blood concentration-time curve for each subject was evaluated. The area under curve ($AUC_{48–60}$) of steady-state during every dosage interval, the mean blood concentration at steady state, C_{ave} = AUC/dosage interval, the maximum blood concentration at steady state ($C_{max\text{-}ss}$), elimination half-life ($t_{1/2}$), time to achieve maximum blood concentration (t_{max}) and absorption coefficient (K_a) were calculated. The elimination half-life was determined by non-linear regression program [25]. Apparent total (oral) clearance, as a function of bioavailability (CL/F), was calculated as dose/$AUC_{48–60}$. The renal clearance (CL_r) was estimated by dividing the total amount of urinary drug elimination (X) by AUC, $CL_r = X/AUC$.

Statistical analysis

The association between discrete variables was assessed using Fisher's exact test. The two-tailed Wilcoxon rank sum test was used for comparison of pharmacokinetic parameters. The statistical difference of data from three datasets was analyzed using repeated measures ANOVA. A value of $P < 0.05$ was considered statistically significant.

Results

Demographic features

Fifteen patients (14 male, 1 female) were accrued onto this study. The median age was 57 years (range 31–75 years), and the median ECOG performance status was 1 (range 0–2). Thirteen patients had underlying cirrhosis (87%, documented by histology in 11 and by radiology in 2) with Child-Pugh's class of A in 8 and of B in 7. Twelve (80%) patients had extrahepatic metastatic diseases and 6 (40%) had major portal venous invasion. The clinicopathological characteristics of patients are presented in Table 1.

Safety evaluation and maximal tolerated dose in Phase I study

The starting daily dose for the 15 patients ranged from 100 mg to 400 mg. The patient number and the adverse events (AE) at each dose level during phase I study (the first week of treatment) were summarized in Table 2. In general, oral thalidomide was well tolerated twice daily at dose ≤ 300 mg/day (150 mg b.i.d.). One patient who had 150 mg b.i.d. suffered from esophageal varices bleeding on the fourth day of therapy and was temporarily removed from the study before his condition stabilized. One additional patient was accrued at 150 mg b.i.d. before further dose escalation.

Two of three patients at the dose level 200 mg b.i.d. developed grade 3 AE. One patient had suffered from grade 3 allergic reaction (cutaneous eruption and periorbital angioedema) from the fourth day of treatment and was off-study on the sixth day. The other patient suffered from shortness of breath on the second day of thalidomide treatment, without significant electrocardiogram and chest X-ray film changes. The dyspnea

Table 1 Clinicopathological characteristics

Age, (years)	57 (31–75)[a]
Sex	
Male	14
Female	1
ECOG performance status	
0	6
1	8
2	1
Serum albumin (gm/dL)	3.5 ± 0.6 (2.6–4.4)[b]
Serum total bilirubin, (mg/dL)	1.43 ± 0.69 (0.5–2.7)[b]
Serum ALT (IU/dL)	75 ± 53 (14–203)[b]
Ascites	
Absent	12 (80%)
Present	3 (20%)
Child-Pugh's class	
A	8 (54%)
B	7 (46%)
ICG retention at 15 min (%)	31.1 ± 19.1 (8–68)[b]
HBsAg +	8 (53%)
Anti-HCV +	5 (33%)
Both negative	2 (13%)
Primary tumors[c]	
T0	3 (20%)
T1–T2	1 (7%)
T3	1 (7%)
T4	10 (67%)
Presence of venous invasion	
Portal vein, main or first branch	6 (40%)
Hepatic vein or inferior vena cava	3 (20%)

[a]median (range), [b]mean ± SD (range), [c]based on AJCC Cancer staging Manual 5th edn, 1997

was promptly resolved after the discontinuation of thalidomide and the intravenous administration of diuretics. It recurred after he was rechallenged with the same dosage of thalidomide and resolved again after diuretics therapy. A similar attack did not happen to him after the dose of thalidomide was tapered to 150 mg b.i.d.. After two patients experienced DLT at the level of 200 mg b.i.d., three additional patients were treated with 150 mg b.i.d. without experiencing significant toxicity. Therefore, the MTD of this phase I study was 150 mg b.i.d.

Toxicity profile and individual achievable dose in intra-individual dose-escalation study and subsequent therapy

Except the two patients who experienced DLT during phase I study, the dose of thalidomide was intra-individually escalated in the other 13 patients. The individual achievable dose was listed against their starting dose in Table 3. The major DLT of intra-individual escalation was a grade 2/3 somnolence in 8 of 13 patients. The median individual achievable dose was 250 mg b.i.d. (ranged 100–600 mg b.i.d.), with 250 mg b.i.d. (ranged 100–600 mg b.i.d.) for patients of Child-Pugh's class A ($n = 8$) and 200 mg b.i.d. (ranged 150–400 mg b.i.d.) for patients of class B ($n = 7$, including the one who had grade 3 allergic reaction at 200 mg b.i.d.).

The AE that occurred during the intra-individual dose-escalation study and subsequent therapy period are listed in Table 4. Grade 1–2 somnolence occurred in 60–75% of patients at all tested dose levels. Skin rash was also frequently observed, especially at lower dose levels (100–150 mg b.i.d.). The cutaneous lesion could be improved by the oral anti-histamine ± local corticosteroid therapy and did not recur even at higher dose. The constipation of grade 1–2 was a common AE, which could be easily treated with an increased dose of laxative. Grade 1 peripheral neuropathy, which was usually manifested as mild peri-oral or digital numbness, occurred in 13–25% of patients but caused treatment interruption in none. One patient with intra-atrial tumor growth suffered from grade 3 (symptomatic) sick sinus syndrome that was considered probably related to either the tumor or thalidomide itself.

Changes in serum ALT level and hepatitis viral titer

In this study, an increase in hepatitis activity induced by drug was defined as an elevation of ALT level to more than twofolds of the pre-treatment value and greater than 100 IU/mL. The apparent mild, transient drug-induced transaminitis was found in four patients (4/13,

Table 2 Adverse events at each dose level of phase I study (per patient)

	Dose of thalidomide (mg/day)							
	100 ($n = 3$)		200 ($n = 3$)		300 ($n = 7$)		400 ($n = 2$)	
Adverse events Items	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Somnolence	2[b]				2[b]			
Dizziness			1		1			
Constipation	1		1		3		1	
Peripheral europathy			1[b]					
Cutaneous	1		1		1		1	1[a]
mucositis			1		1			
Hair loss			1					
Fever	1						1	
Dyspnea								1[a]
Hepatic[c]					1			
Hemoglobin					1			
Leucopenia					1			
Cystitis					2			

[a]dose-limiting toxicity, [b]belong to grade 1, [c]elevation of ALT as compared with baseline data rather than with upper normal limits

Table 3 Individual achievable dose in dose-escalation study

Starting dose	Individual achievable dose (mg/day)						
(case no.)	200	300	400	600	800	1,000	1,200
100 ($n=3$)	1[b]	1	1				
200 ($n=3$)			1	1			1[c]
300 ($n=7$)			2	1 + 1[b]	1 + 1[b]	1[c]	
400 ($n=2$)[a]		1					
Total ($n=15$) [a]	1	2	4	3	2	1	1

[a]one patient being off-study due to grade 3 allergic reaction at starting dose of 400 mg/day
[b]patients who refused further dose-escalation in the absence of significant toxicity (satisfactory therapeutic effects in 1, grade 1 somnolence in 1 and grade 2 cutaneous eruption in 1)
[c]patients had disease progression without dose-limiting toxicity

30.7%). It was observed in two of eight HBsAg-positive patients, in one of three anti-HCV-positive patients, and in one of two seronegative for both HBsAg and anti-HCV patients. The elevation of ALT usually occurred within the first 2 weeks of the treatment and reached its peak at the 4th week. Despite continuation of thalidomide therapy, the ALT level returned to or below the baseline value in three patients during the 8th–12th week of therapy and remained elevated in one HBsAg-positive patient during his 16 weeks of study period.

In general, thalidomide therapy seemed not to affect the serum hepatitis viral load (titers of HBV DNA [$n=8$] and HCV RNA [$n=5$]). Only two patients had an increase of serum viral titer after thalidomide therapy, with the elevation of HBV DNA titer in one and HCV RNA titer in the other one, which was not accompanied with corresponding ALT changes.

Indocyanine green clearance test before and after thalidomide therapy

The ICG-R_{15} (mean ± SD) before the first and the second weeks of therapy from 14 patients was 29.6 ± 18.9% and 27.1 ± 19.0%, respectively. The ICG-R_{15}, from 8 patients who had three sets of test, before the first and the second week of treatment, and after a median of 6 weeks therapy (ranged 5–10 weeks, during treatment at individual achievable dose level), was 19.2 ± 8.3, 18.8 ± 10.6 and 22.6 ± 15.2%, respectively.

Table 4 Adverse events at each dose level during intra-individual dose-escalation study and subsequent therapy period (per patient)

	Dose of thalidomide (mg/day)													
	200 ($n=4$)		300 ($n=6$)		400 ($n=12$)		600 ($n=11$)		800 ($n=7$)		1,000 ($n=4$)		1,200 ($n=1$)	
Adverse events	grade 1–2	grade 3–4	grade 1–2	grade 3–4	grade 1–2	grade 3–4	grade 1–2	grade 3–4	grade 1–2	grade 3–4	grade 1–2	grade 3–4	grade 1–2	grade 3–4
Somnolence	3		4		7 [1]		8 [4]		5 [2]		3 [1]		1	
Dizziness			1		3		2		2		1		1	
Constipation	3		3		7		4	1[a]	3	1[a]	1			
Neuropathy[b]	1		2		2		2		1					
Cutaneous	3		5		2		3		1		2[d]			
Bradycardia	1					1[e]								
Mucositis			1				1		1		1			
Hair loss					1		1							
Fever							1				1		1	
Dyspnea			1					2		2		1		1
Hepatic‡	2		1		4		1		1		1			
Hemoglobin	1		1											
Leucopenia	1						2							
Cystitis					2		2		1		1			

Numbers in the parentheses indicates the number of patients who had grade 2 somnolence which is considered as dose-limiting toxicity
[a]the patient also received high-dose of morphine phosphate for pain control
[b]belong to grade 1 and most of the patients experience mild perioral numbness and none required dose modification
[c]elevation of ALT as compared with baseline data rather than with upper normal limits [d]one of the patients requested dose reduction due to grade 2 skin rush
[e]Symptomatic bradycardia in a patient with intra-atrial tumor growth

There was no statistical difference within these three datasets.

Pharmacokinetic analyses

Totally, 37 sets of distinct time points of blood samples were obtained for pharmacokinetic analyses from 15 patients at various dose level, 100 mg/day in three sets, 200 mg/day in six sets, 300 mg/day in 12 sets, 400 mg/day in ten sets, 600 mg/day in three sets and 800 or more mg/day in three sets. Since the number of patients at high-dose level (800 or more mg/day) was limited, the presentation of pharmacokinetic study was focused on those on 600 or less mg/day. The pharmacokinetic parameters after multiple doses administered twice daily are listed by the dose level in Table 5. The maximum concentration at steady state ($C_{max\text{-}ss}$) and the mean area under curve at steady state ($AUC_{48–60}$, which measures the area between 48 and 60 h after first dosage) did not increase linearly proportionate as the daily dose increased, as shown in Fig. 2 ($P = 0.0065$). On the other hand, the ratio of $AUC_{48–60}$ / daily dose showed a trend toward negative correlation to the daily administration dose, as shown in Fig. 3 ($P = 0.0004$). The CLr increased from 76.71 (±24.39) mL/h at dose of 50 mg b.i.d., 99.02 (±22.68) mL/h at 100 mg b.i.d. and up to 150.33 (±40.42) mL/h at dose of 300 mg b.i.d.. The $clearance_{oral}$ at steady state (CL/Fss, clearance/bioavailability) ranged from 8.63 (±1.67) to 14.33 (±4.35) L/h at dose between 50 and 300 mg b.i.d.. The mean $t_{1/2}$ of thalidomide at dose greater than 100 mg b.i.d. was quite consistent, ranged from 7.78 to 10.7 h. The mean t_{max} of thalidomide ranged from 4 (±1.16)–7.33 (±1.33) h at dose between 50 and 300 mg b.i.d.. The effect of dose on $C_{max\text{-}ss}$, C_{ave}, $AUC_{48–60}$ and CL/F_{ss} were statistically significant ($P < 0.02$).

The influence of the severity of hepatic dysfunction (Child-Pugh's class A vs. class B) on the PK parameters of oral thalidomide was also studied. The representative data from 12 patients, Child-Pugh's class of A in 6 and of B in 6, while they were taking 150 mg b.i.d. is presented. The clinicopathological characteristics and pharmacokinetic parameters of these patients are listed against Child-Pugh's class in Table 6. The ICG-R_{15}, serum bilirubin and serum albumin were significantly different between patients of Child-Pugh's class A and of class B, P value = 0.038, 0.02 and 0.003, respectively. However, there was no significant difference in any of the tested pharmacokinetic parameters, including $C_{max\text{-}ss}$, C_{ave}, $AUC_{48–60}$, $clearance_{oral}$, elimination half-life, t_{max}, K_a and renal clearance, between the two groups of patients.

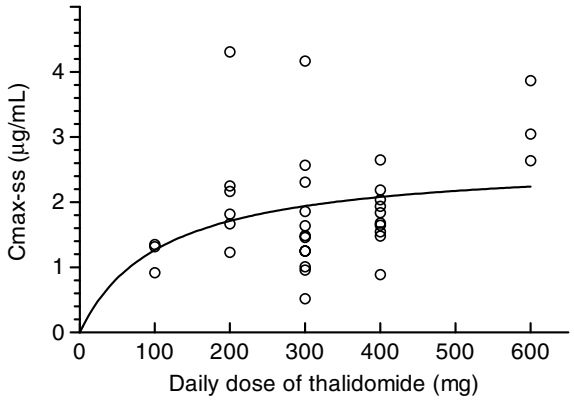

Fig. 2 The steady-state maximum blood concentration at different dose levels of thalidomide in HCC patients. The P value of correlation between concentration and dose was 0.0065

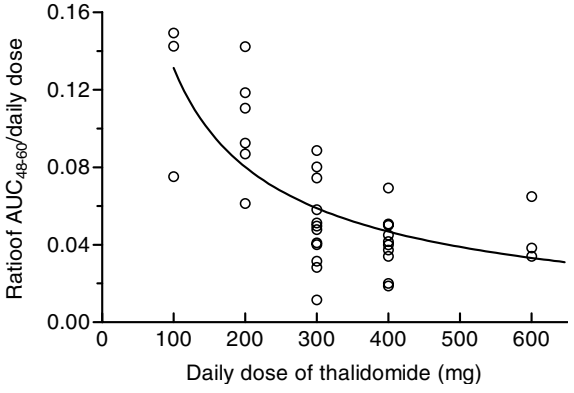

Fig. 3 The ratio of area under the curve/daily dose (AUC/D) against daily dose of thalidomide in HCC patients. The P value of correlation between AUC/D and dose was 0.0004

Table 5 Pharmacokinetic parameters of thalidomide between 48 and 60 h at each tested dose level

	$C_{max\text{-}ss}$ (μg /mL)*	C_{ave} (μg/mL)*	$AUC_{48–60}$ (mg h/L)*	CL/F_{ss} (L/h)*	$t_{1/2}$ (h)	t_{max} (h)	K_a	CL_r (ml/h)
100 mg/d, $N = 3$	1.20 ± 0.14	1.03 ± 0.20	12.3 ± 2.35	9.02 ± 3.62	33.10 ± 38.10	4.00 ± 1.16	1.57 ± 1.81	76.71 ± 24.39
200 mg/d, $N = 6$	2.24 ± 0.44	1.70 ± 0.19	20.4 ± 2.29	8.63 ± 1.67	36.90 ± 50.70	4.33 ± 0.95	4.32 ± 4.76	99.02 ± 22.68
300 mg/d, $N = 12$	1.70 ± 0.28	1.26 ± 0.16	15.1 ± 1.95	13.24 ± 4.36	10.70 ± 4.02	4.33 ± 0.41	2.80 ± 2.80	157.65 ± 36.55
400 mg/d, $N = 10$	1.81 ± 0.15	1.37 ± 0.15	16.4 ± 1.83	12.70 ± 5.27	9.53 ± 4.36	5.00 ± 0.61	1.92 ± 1.94	180.07 ± 50.59
600 mg/d, $N = 3$	3.19 ± 0.36	2.29 ± 0.48	27.5 ± 5.78	14.33 ± 4.35	7.78 ± 2.45	7.33 ± 1.33	1.17 ± 1.57	150.33 ± 40.42

Mean ± SD; $C_{max\text{-}ss}$: steady-state maximum blood concentration; C_{ave}: mean blood concentration at steady state; $AUC_{48–60}$: steady-state area under curve 48–60 h after the first dosage (0–12 h after the fifth dosage) at each dose level; CL/F_{ss}: steady-state clearance/bioavailability ($clearance_{oral}$); $t_{1/2}$: half-life; t_{max}: time to achieve maximum blood concentration; K_a: absorption coefficient. CL_r: renal clearance

*$P < 0.02$

Table 6 Pharmacokinetic parameters of oral thalidomide (150 mg twice daily) of HCC patients in Child-Pugh's class A and class B

	Child-Pugh's A	Child-Pugh's B	*P* value
Age	45.2 ± 13.0	61.0 ± 12.4	0.060
Sex (M/F)	6/0	5/1	
Liver tumor (≤ T3/T4)	4/2	0/6	
Albumin (g/dL)	3.87 ± 0.34	2.73 ± 0.15	0.003
Bilirubin (mg/dL)	0.88 ± 0.52	2.62 ± 1.26	0.02
ALT (IU/dL)	44.0 ± 15.6	196.3 ± 139.8	0.045
Alkaline phosphatase (IU/dL)	134.8 ± 52.5	267.3 ± 147.3	0.083
ICG-R_{15} (%)	16.67 ± 13.02	38.4 ± 17.6	0.038
$C_{max\text{-}ss}$ (μg/mL)	1.59 ± 0.19	1.81 ± 0.55	0.390
C_{ave} (μg/mL)	1.04 ± 0.29	1.48 ± 0.70	0.203
$AUC_{48–60}$ (mg h/L)	14.9 ± 2.23	15.4 ± 3.43	0.772
CL/F_{ss}	14.2 ± 5.67	12.3 ± 2.79	0.485
$t_{1/2}$ (h)	10.2 ± 3.31	10.8 ± 4.93	0.811
t_{max} (h)	4.33 ± 1.97	4.33 ± 0.82	1.000
K_a	2.99 ± 2.86	2.44 ± 2.94	0.750
CL_r	148.2 ± 44.9	262.2 ± 242.7	0.309

Mean ± SD; $C_{max\text{-}ss}$: steady-state maximum blood concentration; C_{ave}: mean blood concentration at steady state; $AUC_{48–60}$: steady-state area under curve 48–60 h after first dosage (0–12 h after the fifth dosage) at each dose level; CL/F_{ss}: steady-state clearance / bioavailability ($clearance_{oral}$); $t_{1/2}$: half-life; t_{max}: time to achieve maximum blood concentration; K_a: absorption coefficient. CL_r: renal clearance

Tumor response

Thirteen patients were assessed for response. One patient achieved partial response with an overall response rate of 7.7%. Four patients had a stable disease with a median response duration of 13 weeks (ranged 12–99 weeks), and eight had a progressive disease. On an intention-to-treat analysis, the response rate was 6.7%. Among the seven patients with baseline AFP > 100 ng/mL, three patients, two with SD and one with PR, had a sustained (≥4 weeks) reduction of AFP by 30, 45 and greater than 99%, respectively.

The dose of thalidomide for the patient with partial response was 50 mg b.i.d. during the first week, then maintained at 100 mg b.i.d. since the second week of therapy. Among the six patients who had PK studies at 100 mg b.i.d., the PK parameters of patient with PR were not significantly different from those of the others (data not shown).

Discussion

This is the first report of phase I/pharmacokinetic study of oral thalidomide in patients with an underlying hepatic dysfunction. The 300 mg/day (150 mg b.i.d.) of population MTD and 500 mg/day (250 mg b.i.d.) of median individual achievable dose in current study are comparable with the median achievable daily dose of thalidomide in other dose-escalating studies for HCC [30, 33, 49] as well as in some studies for other malignancies [1, 36, 39, 51]. The median individual achievable dose for our patients in Child-Pugh's class A and of class B was 250 mg b.i.d. (ranged, 100–600 mg b.i.d.) and 200 mg b.i.d. (ranged, 100–400 mg b.i.d.), respectively. These observations demonstrate the high variability of individual compliance to thalidomide and suggest that the severity of underlying hepatic dysfunction does not affect the individual achievable dose and tolerability of thalidomide in HCC patients, at least for those in Child-Pugh's A and B classes.

In this study, $C_{max\text{-}ss}$ and $AUC_{48–60}$ showed a trend toward positive correlation, but non-linear proportionate to the daily dose of thalidomide. The findings are consistent with those observed in a study of proportionality assessment of single-dose thalidomide in healthy individuals [53]. These are likely caused by the low aqueous solubility of thalidomide (≅50 mg/L) to result in an easy saturation of drug in the gastrointestinal fluid of absorption site, and further dissolution can only take place when some of the drug is absorbed across the intestinal lumen. As compared with earlier reported multiple-dose pharmacokinetic studies, the 1.81 ± 0.15 μg/mL of mean blood $C_{max\text{-}ss}$ in our patients taking 200 mg bid (400 mg/day) was similar to the 1.81 ± 0.81 μg/mL and the 1.52 ± 1.1 μg/mL of plasma values in patients of prostate cancer and of breast cancer taking 200 mg once daily [2, 15]. It suggested that the $C_{max\text{-}ss}$ was largely determined by the dose of each administration rather than by the total daily dose.

The renal clearance increased as the dose of thalidomide increased from 50 mg b.i.d. to 200 mg b.i.d.. The mean $clearance_{oral}$ (clearance/bioavailability ratio) of our patients taking 50 mg–200 mg b.i.d. of thalidomide, ranged between 8.63 ± 1.67 L/h and 12.27 ± 5.27 L/h, is similar to those observed in breast and prostate cancer patients taking either 200 mg/day or 800 mg/day [2, 15]. The mean half-life of thalidomide at various dose levels in our study was similar (ranged from 7.78 ± 2.45 h to 36.9 ± 50.7 h) and consistent with published data of

multiple daily dosage studies with half-life ranged from 7.08 h to 16.2 h [2, 15, 16]. The C_{max}, clearance$_{oral}$ and half-life of thalidomide in this study are comparable to those parameters of patients with glioma, breast and prostate cancers, suggesting that the underlying liver disease (i.e. HCC with cirrhosis) does not significantly affect the absorption and elimination of thalidomide. In our study, the ratio of $AUC_{48–60}$ to daily dose of thalidomide showed a trend of negative correlation when the daily dose was increased (Fig. 3). The known low aqueous solubility, 6–12 h of half-life, and decrease of $AUC_{48–60}$/daily dose ratio with increasing administration doses imply that thalidomide had better to be given in divided doses rather than daily administration of it once, especially when a high-dose is to be used.

In this study, although there was a significant difference of serum albumin and bilirubin levels and ICG-R_{15} between patients of Child-Pugh's class A and class B, all PK parameters including $C_{max\text{-}ss}$, C_{ave}, $AUC_{48–60}$, clearance$_{oral}$, elimination half-life, t_{max}, K_a and renal clearance were not significantly different among those patients. The data indicate that the severity of impaired liver function does not interfere the absorption and elimination of oral thalidomide in patients with compensated or decompensated cirrhosis.

The PK parameters of thalidomide at 100 mg b.i.d. of the responsive patient were not significantly different from other five non-responsive patients. Due to the limited number of cases, it is hard to draw any conclusions. Thus, we recommend incorporating pharmacokinetic studies in future prospective trials to elucidate the correlation between PK parameters and tumor response in the thalidomide-treated HCC patients.

Besides teratogenicity, the incidences of several adverse events varied and were documented, including manifestations of gastrointestinal, cutaneous, cardiovascular, peripheral and central nervous systems [reviewed in 11]. In the current study, the major toxicities comprised somnolence, constipation and skin rash, occurring in one-third or more of the patients. The adverse events in our patients were usually mild to moderate in severity and were similar to those found in healthy volunteers and other types of cancer patients [2, 14, 16, 35, 41, 50, 51, 53]. In our study, the DLTs were dyspnea, somnolence, constipation, allergic reaction and sinus bradycardia. Especially, the dyspnea was apparently the most important DLT in our patients receiving higher range of MTD (600–1,200 mg/day), which had been observed in a phase II study of advanced renal cell carcinoma as well [41]. Although the DLT of somnolence could be tachyphylatic, the dose was needed to be adjusted in our patients and patients with HIV, glioma or metastatic breast cancer [2, 16, 35]. Symptomatic bradycardia was a less common DLT, which was noted in other studies as well and might even be rescued by a device of cardiac pacemaker [2, 14, 41]. Peripheral neuropathy occurred in patients with long-term use of thalidomide and might become a DLT. In our study, this adverse event was reversible, which phenomenon was also found in acute myeloid leukemia patients [51]. One of the possible explanations was that the duration of thalidomide use was not longer enough in our patients. One unexpected finding was the relatively high incidence (30.7%, 4 of 13 patients who had 4 weeks or more of therapy) of apparent ALT elevation. The increase in ALT level was usually self-limited, not associated with hepatitis viral titer change, and returned to or below the baseline value even with continuation of thalidomide therapy. These observations suggest that the apparent mild, transient transaminitis might be an idiosyncratic reaction to thalidomide rather than by its immunomodulatory effects. In contrast, the hepatotoxicity has not been emphasized in trials of thalidomide for various malignancies, including HCC [1, 2, 9, 14–16, 27, 30, 33, 35, 36, 39, 41, 46, 49–51, 54]. One of the possibilities might be that the serum ALT level was more frequently monitored in our study than in other studies. Therefore, more early but transient events of transaminitis were observed in our study. Are patients with underlying liver illnesses, such as viral hepatitis or cirrhosis/HCC, more susceptible to thalidomide-induced hepatocellular injury, as suggested by Fowler and Imire [20], or is the fluctuation of ALT a common event in patients with such end-stage liver diseases just detected by the frequent ALT monitoring? This issue can only be answered by placebo-controlled, randomization phase III study, which is currently going on in the Taiwan Oncology Cooperative Group.

In summary, we describe the first phase I/pharmacokinetic study of oral thalidomide in patients with underlying hepatic dysfunction. Our results showed that the median individual achievable dose and all the tested pharmacokinetic parameters were equivalent in patients of Child-Pugh's class A and B. These indicate the compliance, and the absorption and elimination of thalidomide are not significantly affected by the severity of the underlying hepatic dysfunction in patients with compensated or decompensated cirrhosis. The findings of 6–12 h of half-life and decrease of $AUC_{48–60}$/daily dose ratio with increasing daily doses suggest that divided doses may be a more reasonable schedule for thalidomide administration than the conventional schedule of dosing it once daily.

Acknowledgement This work was supported by intramural grant of National Health Research Institutes, no. NHRI-89A1-CA-QOVGHWRD.

References

1. Abramson N, Stokes PK, Luke M, Marks AR, Harris JM (2002) Ovarian and papillary-serous peritoneal carcinoma: pilot study with thalidomide. J Clin Oncol 20:1147–1149
2. Baidas SM, Winer EP, Fleming GF, Harris L, Pluda JM, Crawford JG, Yamauchi H, Isaacs C, Hanfelt J, Tefft M, Flockhart D, Johnson MD, Hawkins MJ, Lippman ME, Hayes DF (2000) Phase II evaluation of thalidomide in patients with metastatic breast cancer. J Clin Oncol 18:2710–2717

3. Bauer KS, Dixon SC, Figg WD (1998) Inhibition of angiogenesis by thalidomide requires metabolic activation, which is species-dependent. Biochem Pharmacol 55:1827–1834
4. Boehm T, Folkman J, Browder T, O'Reilly MS (1997) Antiangiogenic therapy of experimental cancer does not induce acquired drug resistance. Nature 390:404–407
5. Braun AG, Harding FA, Weinreb SL (1986) Teratogen metabolism: thalidomide activation is mediated by cytochrome p450. Toxicol Appl Pharmacol 82:175–179
6. Chang JY, Ka WS, Chao TY, Liu TW, Chuang TR, Chen LT (2004) Hepatocellular carcinoma with intra-atrial tumor thrombi: a report of three cases responsive to thalidomide treatment and literature review. Oncology 67:320–326
7. Chen LT, Liu TW, Chao Y, Shiah HS, Chang JY, Juang SH, Chen SC, Chuang TR, Chin YH, Whang-Peng J (2005) Alpha-fetoprotein response predicts survival benefits of thalidomide in advanced hepatocellular carcinoma. Aliment Pharmacol Ther 22:217–226
8. D'Amato RJ, Loughnan MS, Flynn E, Folkman J (1994) Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci USA 91:4082–4085
9. Dimopoulos MA, Zomas A, Viniou NA, Grigoraki V, Galani E, Matsouka C, Economou O, Anagnostopoulos N, Panayiotidis P (2001) Treatment of Waldestrom's macroglobulinemia with thalidomide. J Clin Oncol 19:3596–3601
10. Dimopoulos MA, Eleutherakis-Papaiakovou V (2004) Adverse effects of thalidomide administration in patients with neoplastic diseases. Am J Med 117: 508–515
11. Eleutherakis-Papaiakovou V, Bamias A, Dimopoulos MA (2004) Thalidomide in cancer medicine. Ann Oncol 15:1151–1160
12. Eriksson T, Bjokman S, Fyge A, Ekberg H (1992) Determination of thalidomide in plasma and blood by high-performance liquid chromatography: avoiding hydrolytic degradation. J Chromatogr 582:211–216
13. Eriksson T, Hoglund P, Turesson I, Waage A, Don BR, Vu J, Scheffler M, Kaysen GA (2003) Pharmacokinetics of thalidomide in patients with impaired renal function and while on and off dialysis. J Pharm Pharmacol 55:1701–1706
14. Figg WD, Dahut W, Duray P, Hamilton M, Tompkins A, Steinberg SM, Jones E, Premkumar A, Linehan WM, Floeter MK, Chen CC, Dixon S, Kohler DR, Kruger EA, Gubish E, Pluda JM, Reed E (2001) Randomized phase II study of thalidomide, an angiogenesis inhibitor, in androgen-independent prostate cancer. Clin Cancer Res 7:1888–1893
15. Figg WD, Raje S, Bauer KS, Tompkins A, Venzon D, Bergan R, Chen A, Hamilton M, Pluda J, Reed E (1999) Pharmacokinetics of thalidomide in an elder prostate cancer population. J Pharm Sci 88:121–125
16. Fine HA, Figg WD, Jaeckle K, Wen PY, Kyritsis AP, Loeffler JS, Levin VA, Black PM, Kaplan R, Pluda JM, Yung WK (2000) Phase II trial of the antiangiogenic agent thalidomide in patients with recurrent high-grade gliomas. J Clin Oncol 18:708–715
17. Folkman J (1971) Tumor angiogenesis: therapeutic implication. N Engl J Med 285:1182–1186
18. Folkman J, Merler E, Abernathy C, William G (1971) Isolation of a tumor factor responsible or angiogenesis. J Exp Med 133:275–288
19. Folkman J, Watson K, Ingber D, Hanahan D (1989) Induction of angiogenesis during the transition from hyperplasia to neoplasia. Nature 339:58–61
20. Fowler R, Imrie K (2001) Thalidomide-associated hepatitis: a case report. Am J Hematol. 66:300–302
21. Gutierrez-Rodriguez O, Starusta-Bacal P, Gutierrez-Montes O (1989) Treatment of refractory rheumatoid arthritis–the thalidomide experience. J Rheumatol 16:158–163
22. Habeck M (2003) Australia approves thalidomide. Lancet Oncol 4:713
23. Holmgren L, O'Reilly MS, Folkman J (1995) Dormancy of micrometastases: balanced proliferation and apoptosis in the presence of angiogenesis suppression. Nature Med 1:149–53
24. Hsu C, Chen CN, Chen LT, Wu CY, Yang PM, Lai MY, Lee PH, Cheng AL (2003) Low-dose thalidomide treatment for advanced hepatocellular carcinoma. Oncology 65:242–249
25. Huang JD, Chen RRL, Oie S (1984). Microfit: a Basic program for non-linear regression analysis of pharmacokinetic data using a microcomputer. J Taiwan Pharmaceutical Asso 36:69–81
26. Huupponen R, Pyykko K (1995) Stability of thalidomide in human plasma. Clin Chem 41(8 Pt 1):1199
27. Hwu WJ, Krown SE, Panageas KS, Menell JH, Chapman PB, Livingston PO, Williams LJ, Quinn CJ, Houghton AN (2002) Temozolomide plus thalidomide in patients with advanced melanoma: results of a dose-finding trial. J Clin Oncol 20:2610–2615
28. Ikeda K, Saitoh S, Tsubota A, Arase Y, Chayama K, Kumada H (1993) Diagnosis and follow-up of small hepatocellular carcinoma with selective intraarterial digital substraction angiography. Hepatology 17:1003–1007
29. Kerbe RS (1991) Inhibition of tumor angiogenesis as a strategy to circumvent acquired resistance to anti-cancer therapeutic agents. BioEssays 13:31–36
30. Kong HL, Boyer MJ, Lim R, Clarke S, Millward MJ, Wong JE (2001) Phase II trial of thalidomide in unresectable hepatocellular carcinoma (HCC): a Cancer Therapeutics Research Group (CTRG) study. Proc Am Soc Clin Oncol 20:133b
31. Kruse FE, Joussen AM, Rohrschneider K, Becker MD, Volcker HE (1998) Thalidomide inhibits corneal angiogenesis induced by vascular endothelial growth factor. Graefes Arch Clin Exp Ophthalmol 236:461–466
32. Lai CL, Wu PC, Chan GCB, Lok ASF, Lin HJ (1988) Doxorubicin versus no antitumor therapy in inoperable hepatocellular carcinoma. Cancer 62:479–483
33. Lin AY, Brophy N, Fisher GA, So S, Biggs C, Yock T, Levitt L (2002) Phase II study of thalidomide in patients (pts) with unresectable hepatocellular carcinoma (HCC). Proc Am Soc Clin Oncol 21:97b
34. Lin TM, Chen CJ, Tsai SF, Tsai TH (1988) Hepatoma in Taiwan. J Natl Public Health Assoc (ROC) 8:91–100
35. Little RF, Wyvill KM, Pluda JM, Welles L, Marshall V, Figg WD, Newcomb FM, Tosato G, Feigal E, Steinberg SM, Whitby D, Goedert JJ, Yarchoan R (2000) Activity of thalidomide in AIDS-related Kaposi's sarcoma. J Clin Oncol 18:2593–2602
36. Marx GM, Pavlakis N, McCowatt S, Boyle FM, Levi JA, Bell DR, Cook R, Biggs M, Little N, Wheeler HR (2001) Phase II study of thalidomide in the treatment of recurrenct glioblastoma multiforme. J Neurooncol 54:31–38
37. Matsui O, Kadoya M, Kameyama T, Yoshikawa J, Takashima T, Nakanuma Y, Unoura M, Kobayashi K, Izumi R, Ida M (1991) Benign and malignant nodules in cirrhotic liver: distinction based on blood supply. Radiology 78:493–497
38. McBride WG (1968) Thalidomide and congenital abnormalities. Lancet 2:1358
39. Merup M, Kutti J, Birgergard G, Mauritzson N, Bjorkholm M, Markevarn B, Maim C, Westin J, Palmblad J (2002) Negligible clinical effects of thalidomide in patients with myelofibrosis with myeloid metaplasia. Med Oncol 19:79–86
40. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47:207–214
41. Motzer RJ, Berg W, Ginsberg M, Russo P, Vuky J, Yu R, Bacik J, Mazumdar M (2002) Phase II trial of thalidomide for patients with advanced renal cell carcinoma. J Clin Oncol 20:302–306
42. Nerenstone S, Friedman F (1987) Medical treatment of hepatocellular carcinoma. Gastroenterol Clin North Am 16:603–612
43. Okamoto E, Kyo A, Vamanaka N, Tanaka N, Kuwata K (1984) Prediction of the safe limits of hapatectomy by combined volumetric and functional measurement in patients with impaired hepatic function. Surgery 95:586–592
44. O'Reilly MS, Holmgren L, Shing Y, Chen C, Rosenthal RA, Moses M, Lane WS, Cao Y, Sage EH, Folkman J (1994) Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma. Cell 79:315–328

45. Patt YZ, Hassan MM, Lozano RD, Ellis M, Peterson JA, Waugh KA (2000) Durable clinical response of refractory hepatocellular carcinoma to orally administered thalidomide. Am J Clin Oncol 23:319–322
46. Patt YZ, Hassan MM, Lozano RD, Nooka AK, Schnirer II, Zeldis JB, Abbruzzese JL, Brown TD (2005) Thalidomide in the treatment of patients with hepatocellular carcinoma: a phase II trial. Cancer 103:749–755
47. Raza A, Meyer P, Dutt D, Zorat F, Lisak L, Nascimben F, du Randt M, Kaspar C, Goldberg C, Loew J, Dar S, Gezer S, Venugopal P, Zeldis J (2001) Thalidomide produces transfusion independence in long-standing refractory anemias of patients with myelodysplastic syndromes. Blood 98:958–965
48. Sampaio EP, Sarno EN, Galilly R, Cohn ZA, Kaplan G (1991) Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes. J Exp Med 173:699–703
49. Schwartz JD, Sung MW, Lehrer D, Goldenberg A, Muggia F, Volm M (2002) Thalidomide for unresectable hepatocellular cancer (HCC) with optional interferon-α upon disease progression. Proc Am Soc Clin Oncol 21:10b
50. Singhal S, Mehta J, Desikan R, Ayers D, Roberson P, Eddlemon P, Munshi N, Anaissie E, Wilson C, Dhodapkar M, Zeddis J, Barlogie B (1999) Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 341:1565–1571
51. Steins MB, Padro T, Bieker R, Ruiz S, Kropff M, Kienast J, Kessler T, Buechner T, Berdel WE, Mesters RM (2002) Efficacy and safety of thalidomide in patients with acute myeloid leukemia. Blood 99:834–839
52. Teo SK, Sabourin PJ, O'Brien K, Kook KA, Thomas SD (2000) Metabolism of thalidomide in human microsomes, cloned human cytochrome P-450 isozymes, and Hansen's disease patients. J Biochem Mol Toxicol 14:140–147
53. Teo SK, Scheffler MR, Kook KA, Tracewell WG, Colburn WA, Stirling DI, Thomas SD (2001) Thalidomide dose proportionality assessment following single doses to healthy subjects. J Clin Pharmacol 41:662–667
54. Tseng JE, Glisson BS, Khuri FR, Shin DM, Myers JN, El-Naggar AK, Roach JS, Ginsberg LE, Thall PF, Wang X, Teddy S, Lawhorn KN, Zentgraf RE, Steinhaus GD, Pluda JM, Abbruzzese JL, Hong WK, Herbst RS (2001) Phase II study of the antiangiogenesis agent thalidomide in recurrent or metastatic squamous cell carcinoma of the head and neck. Cancer 92:2364–2373
55. Wang TE, Kao CR, Lin SC, Chang WH, Chu CH, Lin J, Hsieh RK (2004) Salvage therapy for hepatocellular carcinoma with thalidomide. World J Gastroenterol 10:649–653
56. Weidner N, Semple J, Welch W, Folkman J (1991) Tumor angiogenesis correlates with metastasis in invasive breast carcinoma. N Engl J Med 324:1–8
57. Wettstein AR, Meagher AP (1997) Thalidomide in Crohn's disease. Lancet 350:1445–1446
58. WHO technical report series (1983) Prevention of Liver Cancer. World Health Organization, Geneva
59. Xia JL, Yang BH, Tang ZY, Sun FX, Xue O, Gao DM (1997) Inhitory effect of the angiogenesis inhibitor TNP-470 on tumor growth and metastases in nude mice bearing human hepatocellular carcinoma. J Cancer Res Clin Oncol 123:383–387