Pharmacokinetics of Thalidomide in an Elderly Prostate Cancer Population

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Abstract □ Thalidomide, a glutamic acid derivative, has recently been shown to inhibit in vitro angiogenesis, the process of formation of new blood vessels. This Phase II study examined the pharmacokinetics of thalidomide in patients with clinically progressive hormone-refractory prostate cancer. Patients (aged 55 to 80 years) were randomized to two different arms, low dose versus high dose. Patients in the low-dose group were given 200 mg of thalidomide and patients in the high-dose group received 200 mg of thalidomide, with subsequent dose escalations to 1200 mg. Serial serum or blood samples were obtained for pharmacokinetic assessment after administration of a single oral dose or multiple daily dosing of thalidomide and were assayed by reversed-phase HPLC. Pharmacokinetic parameters for both the single and multiple dosing were calculated with ADAPT II. A one-compartment model best fit the data. After single dosing, the oral clearance and apparent volume of distribution for the low-dose regimen ($n = 13$) were 7.41 ± 2.05 L/h and 66.93 ± 34.27 L, respectively, whereas for the high-dose regimen ($n = 11$), these values were 7.21 ± 2.89 L/h and 165.81 ± 84.18 L, respectively. The elimination half-lives for the low and high dose were 6.52 ± 3.81 and 18.25 ± 14.08 h, respectively. After the multiple dosing of thalidomide, the oral clearance and apparent volume of distribution for the low-dose group ($n = 10$) were 6.35 ± 1.64 L/h and 64.63 ± 23.20 L, respectively, whereas for the high-dose group ($n = 11$), these values were 7.73 ± 2.27 L/h and 167.85 ± 82.08 L, respectively. The elimination half-lives for the low and high dose were 7.08 ± 1.87 and 16.19 ± 9.57 h, respectively. For both the single and multiple dosing of thalidomide, the apparent volume of distribution and half-life were significantly higher for the high-dose group than those for the low-dose group. The higher apparent volume of distribution may be attributable to several factors, such as change in absorption, protein binding, etc. A dose-proportional increase in thalidomide steady-state concentrations was seen after multiple daily dosing of thalidomide.

Introduction

Prostate carcinoma is currently the most common cancer in American men. The initial therapy for metastatic prostate cancer is androgen deprivation; that is, medical or surgical castration with or without an androgen receptor antagonist. Once metastatic prostate cancer progresses in the face of hormonal therapy, it is classified as being hormone refractory. Therapeutic options for hormone-refractory prostate cancer are extremely limited, and cytotoxic chemotherapy has not been successful in prolongation of survival.

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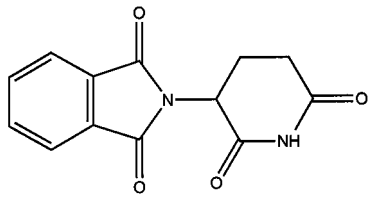

Figure 1—Structure of thalidomide.

Thalidomide (*N*-phthalidoglutarimide; $C_{13}H_9O_4N_2$; Figure 1) was initially introduced in 1954 as a sedative but was withdrawn from the market in the early 1960s because of its teratogenic effects. During the following years, this drug was found to be extremely effective in lepromatous leprosy and is currently being evaluated as an experimental drug in the treatment of a variety of diseases with an autoimmune character, including human immunodeficiency virus (HIV) infection and graft versus host disease.[1,2,3,8] Folkman and colleagues recently reported that thalidomide inhibited angiogenesis in the rabbit cornea micropocket assay.[4] Bauer et al. went on to show that a metabolite of thalidomide was responsible for the antiangiogenic properties.[5] Based on those data, four phase II clinical trials using thalidomide were initiated in solid tumors (Kaposi's sarcoma, glioblastoma, breast cancer, and prostate cancer). Herein, we characterize the pharmacokinetics of thalidomide from an open-labeled, phase II, randomized study (comparison of two dosing regimens) in an elderly population of men with hormone-refractory prostate cancer.

Patients and Methods

Patient Eligibility—Patients with clinically progressive hormone-refractory prostate cancer documented for at least 1 month and who had not undergone a radical prostatectomy or received radiation therapy, with a life expectancy of >3 months and an Eastern Cooperative Oncology Group performance status of 0 to 2, were eligible. Refractory disease was demonstrated after the withdrawal of the antiandrogen (i.e., flutamide). Patients were required to have a granulocyte count of >1000/mm^3, a platelet count of >75 000 mm^3, a measured creatinine clearance of >40 mL/min, and a total bilirubin of ≤1 mg/dL. At least 4 weeks must have elapsed from receipt of any form of anticancer therapy, and patients must have recovered from all toxicities related to the prior therapy.

Drug Administration—All eligible patients were randomized to two different arms, low dose or high dose. Patients on the low-dose arm were given 200 mg of oral thalidomide in the morning as the first dose and, thereafter, 200 mg of thalidomide orally every evening starting on day 2. Treatment was continued provided that there was no dose-limiting toxicity or progression of the disease. Patients on the high-dose arm were given 800 mg of oral thalidomide in the morning on day 1 and, thereafter, thalidomide was

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administered orally every evening starting at 200 mg/day on day 2 and increasing by 200 mg/day every 2 weeks to a maximum dose of 1200 mg/day. Dose increases were continued only if no side effects were noted. Treatment was continued provided there was no dose-limiting toxicity or disease progression. Patients took thalidomide at approximately the same time daily.

Pharmacokinetic Sampling—Blood samples were obtained from all patients for pharmacokinetic assessment. Samples (7 mL) were drawn in heparinized tubes immediately prior to the dose on day 1 (pre-level) and then at 0.5, 1, 1.5, 2, 3, 4, 5, and 7 h on day 1 and at 24, 27, and 31 h on day 2. Samples were also obtained in the morning at each clinic visit throughout the study. The instability of thalidomide requires that the plasma be harvested within 1 h of obtaining the blood samples.[6,7] After centrifuging the blood samples, the plasma was drawn off and stored at −70 °C until analysis. Plasma levels of thalidomide were determined using high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection.

Analytical Method—A Hewlett-Packard 1090 Series II Liquid Chromatograph equipped with a photodiode-array detector was used for the chromatographic analysis of total thalidomide. A Waters Nova-Pak C-18 (3.9 × 300 mm) column was used, and a gradient mobile phase of water, acetonitrile, and a 0.5 M NaH_2PO_4 buffer (pH 3.0) was run at a flow rate of 1 mL/min. Thalidomide and phenacetin, the internal standard were isolated from the plasma by solid-phase extraction and detected at UV wavelengths of 220 and 248 nm, respectively, with a run time of 16 min. Ten percent H_2SO_4 was added to the plasma to prevent the nonenzymatic degradation of thalidomide (rate constant for degradation of thalidomide is ~0.175/h[8]). Standard curves were found to be linear in the range of 25 to 10 000 ng/mL, with the coefficient of determination (r^2) ≥0.995. The intraassay as well as inter-assay precision and accuracy errors were <10%.[6]

Pharmacokinetic Analysis—Plasma samples were obtained for pharmacokinetic assessment after administration of a single oral dose or multiple daily dosing of thalidomide. Pharmacokinetic parameters for both the single and multiple dosing of thalidomide were calculated by weighted nonlinear least-squares analysis fitting a one-compartment and two-compartment open linear model computed by ADAPT II (Biomedical Simulations Resource, University of Southern California, Los Angeles, CA). Model selection was determined based on Akaike's Information Criterion (AIC) and visual examination of the difference between the measured and fitted concentration. Pharmacokinetic parameters determined from single-dose studies were used as priors for determination of multiple-dosing parameters. In the present pharmacokinetic analysis, outlier points (points ≥2 standard deviations outside the fitted line) were not disregarded and all the data points were included in the fitting of the data. The r^2 values reported are the actual values and not the skewed values.

Statistical Analysis—The two-tailed Wilcoxon rank sum test was used for comparison of pharmacokinetic parameters.

Results

Pharmacokinetics—Data were obtained from 24 patients for the single dosing of thalidomide, out of which 13 patients received the low dose (200 mg) and 11 received the high dose (800 mg). Weighting with least-squares fitting as the estimator provided the best fit for 23 patients, whereas maximum likelihood gave the best fit in one patient. In addition, a one-compartment model fit the data best. Figure 2A shows a concentration versus time profile (mean ± SD) for patients on the low dose (200 mg), who received a single dose of oral thalidomide and Figure 2B shows a concentration versus time profile (mean ± SD) for patients on the high dose (800 mg), who received a single dose of oral thalidomide. Pharmacokinetic parameters obtained after the single dose are listed by dose level in Table 1. The t_{max} of thalidomide ranged between 2.01 and 7.09 h, with a median value of 3.32 h for the low-dose regimen (200 mg of thalidomide on day 1). For the high dose (800 mg of thalidomide on day 1), the t_{max} ranged from 1.35 to 7.12 h, with a median value of 4.40 h. Median C_{max} values of 1.97 μg/mL (range of 1.15 to 3.79) and 4.42 μg/mL (range of 2.41 to 8.41) were reported for the initial low-dose (200 mg) and the initial high-dose (800 mg) groups, respectively. The oral clearance and apparent volume of distribution for the low-dose regimen were 7.41 ± 2.05 L/h and 66.93 ± 34.27 L, respectively, whereas for the high-dose regimen, these values were 7.21± 2.89 L/h and 165.81 ± 84.18 L, respectively. The elimination half-lives for the low and high dose were 6.52 ± 3.81 and 18.25 ± 14.08 h, respectively (p = 0.0037). In general, an increase in the half-life of thalidomide was seen for the high-dose group. Also, there was a significant difference in the apparent volume of distribution between the low and the high-dose groups (p = 0.0039), with the high-dose group having a higher apparent volume of distribution.

Data were obtained from 21 patients for the multiple dosing of thalidomide. Ten patients received the low dose and 11 were randomized to the high-dose arm. In the low-dose arm, one patient was removed from the study because of unresolved grade 2 neuropathy. In the high-dose arm, 10 patients either had dose held for a period of time or

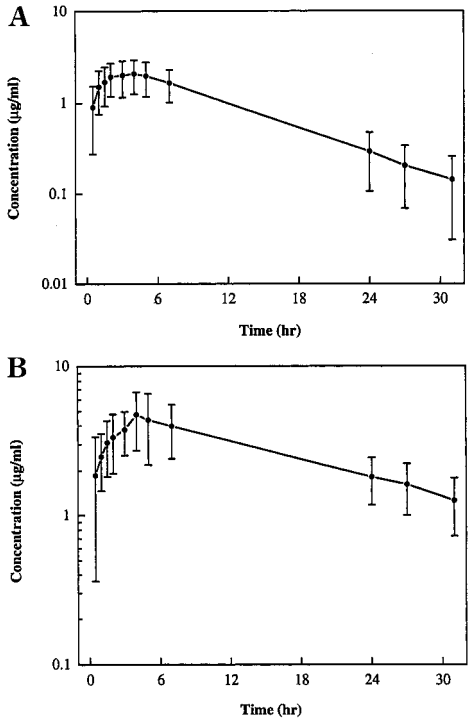

Figure 2—Plasma concentration versus time curves. (A) Plasma concentration versus time curve (mean ± SD) for patients in the low-dose group after a single oral dose of 200 mg of thalidomide. (B) Plasma concentration versus time curve (mean ± SD) for patients in the high-dose group after a single oral dose of 800 mg of thalidomide.

Table 1—Pharmacokinetic Parameters for the Low- and the High-Dose Level after a Single Oral Dose of Thalidomide

statistic	K_e (h^{-1})	Vd/F (L)	K_a (h^{-1})	CL/F (L/h)	$t_{1/2}$ (h)	r^2
			high dose (800 mg, n = 11)			
mean	0.0596	165.81	0.9075	7.21	18.25	0.835
SD	0.0431	84.18	0.8964	2.89	14.08	0.126
median	0.0561	155.10	0.7106	7.17	12.35	0.904
max	0.1410	284.60	3.345	13.43	55.44	0.945
min	0.0125	35.07	0.1405	3.49	4.91	0.625
			low dose (200 mg, n = 13)			
mean	0.1314	66.93	0.7148	7.41	6.52	0.897
SD	0.0679	34.27	0.4531	2.05	3.81	0.092
median	0.1242	62.64	0.6303	7.59	5.58	0.926
max	0.3359	158.80	1.5050	11.73	18.33	0.975
min	0.0378	24.89	0.1409	3.76	2.06	0.685

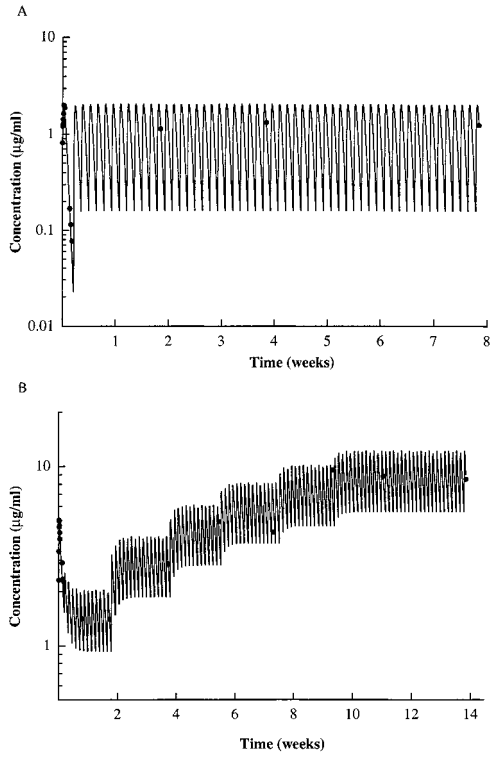

Figure 3—Plasma concentration versus time curves. (A) plasma concentration versus time curve for a patient in the low-dose group during daily oral dosing of 200 mg of thalidomide. (B) Plasma concentration versus time curve for a patient in the high-dose group during daily oral dosing of thalidomide with dose escalations after every 2 weeks.

received no dose escalations because of complications. The first patient had drug held for 24 days because of a pulmonary embolism, after which the dose was reduced to 200 mg of thalidomide followed by escalation every 2 weeks up to 1200 mg. The second patient had drug held for 7 days because of neutropenia and subsequently there was no dose escalation above 200 mg of thalidomide. The third patient had his dose held at 800 mg for 4 weeks because of shortness of breath, after which the dose was escalated to 1000 mg and subsequently to 1200 mg of thalidomide. The fourth patient had no dose escalation beyond 200 mg because of sedation, and the fifth patient had dose held at 400 mg for 5 weeks and subsequently there was no dose escalation beyond 600 mg. The sixth and seventh patients received no dose escalation beyond 800 mg of thalidomide, and thalidomide was discontinued after a dose of 200 mg for the eighth and ninth patients. The tenth patient had drug discontinued after a dose of 400 mg of thalidomide.

Figure 3A shows a representative concentration versus time profile for a patient on the low-dose arm (200 mg per day) who received multiple daily doses of oral thalidomide, and Figure 3B shows a representative concentration versus time profile for a patient on the high-dose arm (200 mg per day increasing by 200 mg every 2 weeks to a maximum of 1200 mg per day) who received multiple daily doses of oral thalidomide. Patients on the low-dose arm of the study were maintained on thalidomide for a mean of 67 days (median = 62 days), ranging from 55 to 123 days. Pharmacokinetic parameters and the average maximum concentrations at steady state ($C_{max\ ss}$) after the multiple dosing are listed by dose level in Tables 2and 3, respectively. The oral clearance and apparent volume of distribution for the low-dose regimen were 6.35 ± 1.64 L/h and 64.63 ± 23.20 L, respectively, whereas for the high-dose regimen, these values were 7.73 ± 2.27 L/h and 167.85 ± 82.08 L, respectively ($p = 0.31$ and 0.0028). The elimination half-lives for the low- and high dose groups were 7.08 ± 1.87 and 16.19 ± 9.57 h, respectively ($p = 0.013$). Similar to the single-dosing results, the apparent volume of distribution and half-life were significantly higher for the high-dose group than those for the low-dose group.

Table 2—Pharmacokinetic Parameters for the Low- and the High-Dose Level after Multiple Daily Dosing of Thalidomide

statistic	K_e (h^{-1})	*VdlF* (*L*)	K_a (h^{-1})	*CL/F* (L/h)	$t_{1/2}$ (h)	r^2
			high dose[a]			
mean	0.0656	167.85	0.9462	7.74	16.19	0.809
SD	0.0538	82.08	0.8157	2.27	9.57	0.129
median	0.0492	153.70	0.7027	6.81	14.09	0.834
max	0.1756	281.70	3.0010	12.56	36.67	0.956
min	0.0189	38.13	0.1663	4.97	3.95	0.587
			low dose (200 mg, $n = 10$)			
mean	0.1044	64.63	0.7994	6.35	7.08	0.883
SD	0.0287	23.20	0.4542	1.64	1.87	0.058
median	0.1001	60.52	0.7102	6.44	6.94	0.890
max	0.1633	97.69	1.6090	8.27	10.07	0.963
min	0.0688	33.67	0.3046	3.73	4.24	0.762

[a] Dose (*n*): 200 (11); 400 (7); 600 (6); 800 (5); 1000 (3); 1200 (3), where *n* is the number of patients that reached the corresponding dose level in the high dose group.

Table 3—Maximum Steady-State Concentrations for the High Dose After Multiple Daily Dosing of Thalidomide

	concentration (μg/mL) at:					
statistic	200 mg ($n = 11$)	400 mg ($n = 7$)	600 mg ($n = 6$)	800 mg ($n = 5$)	1000 mg ($n = 3$)	1200 mg ($n = 3$)
mean	1.81	3.43	5.56	7.57	9.18	11.07
SD	0.81	0.73	1.77	1.83	1.95	2.47
median	1.57	3.15	5.23	8.05	10.10	12.17
max	4.02	4.28	8.50	9.90	10.50	12.80
min	0.98	2.61	3.90	5.55	6.94	8.24

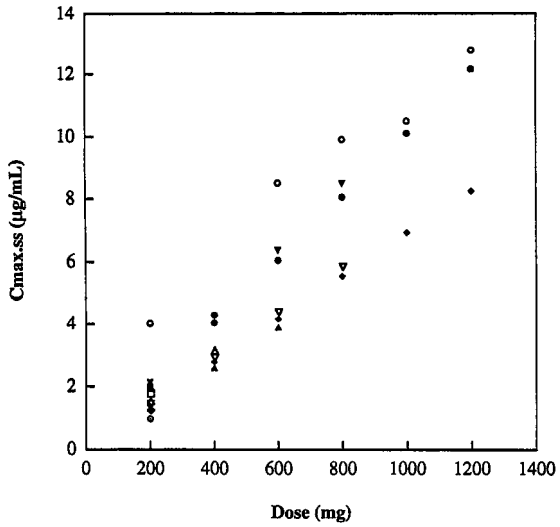

Figure 4—Maximum steady-state thalidomide concentrations as a function of dose after multiple daily dosing of oral thalidomide.

Figure 4 presents the model-predicted maximum steady-state concentrations of thalidomide as a function of dose. A dose-proportional increase in steady-state concentration of thalidomide was seen. Overall, the one-compartment linear model with first-order absorption fit the data well, as evidenced by the plot of observed versus fitted concentration for both single and multiple daily oral dosing of thalidomide (Figure 5A and B).

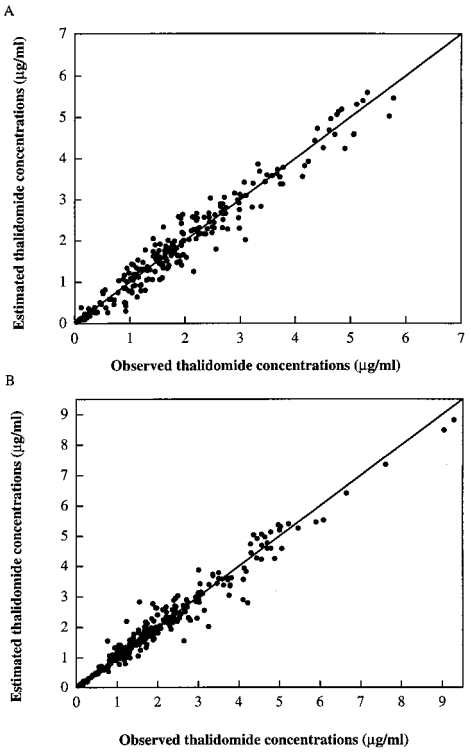

Figure 5—Estimated versus observed thalidomide concentrations. (A) Thalidomide concentrations estimated by a one-compartment model plotted against the observed thalidomide concentrations after a single oral dose. (B) Thalidomide concentrations estimated by a one-compartment model plotted against the observed thalidomide concentrations after multiple daily dosing.

Discussion

Thalidomide has been shown to inhibit tumor angiogenesis, the process of new blood vessel formation within a malignancy. Despite extensive clinical work with this compound for some 40 years, there are generally few data on the pharmacokinetics of thalidomide. Chen et al.[28] reported the pharmacokinetics of thalidomide after oral dosing in healthy male volunteers. The disposition of thalidomide in these patients was characterized by an elimination half-life of approximately 9 h, a clearance of 10 L/h, and an apparent volume of distribution of nearly 121 L. Piscitelli et al.[22] reported the pharmacokinetics of thalidomide in HIV-infected patients after a single oral dose. Thalidomide pharmacokinetics in these patients was characterized by slow absorption, with a mean t_{max} of 3.4 h, an elimination half-life of approximately 6 h, an oral clearance of approximately 8.5 L/h, and an apparent volume of distribution of approximately 85 L. For both the studies, the dose was no more than 300 mg. Our study reported nearly identical values for the low-dose arm (200 mg), but the apparent volume of distribution and the half-life were significantly different for the high-dose arm (800 mg test dose and then dose escalations every 2 weeks).

A one-compartment first-order oral absorption model provided the best fit for the data after single and multiple oral dosing of thalidomide in patients with hormone-refractory prostate cancer. In general, the model fit the data well, as evidenced by the plot of observed versus fitted concentrations. The oral clearance was comparable for the low- and the high-dose groups, but the apparent volume of distribution and half-life were significantly higher for the high-dose group. The higher volume of distribution may be attributable to several factors, such as change in absorption, protein binding, etc. Many drugs have been shown to have extended half-lives due to low aqueous solubility. The pH 7 solubility of thalidomide is 50 μg/mL.

Pharmacokinetic evaluation was reliable for 24 patients for the single dosing and 21 patients for the multiple dosing of thalidomide, (patients ranged in age from 55 to 80 years). No significant age dependency was observed in plasma clearance and elimination half-life. No dose-related changes in oral clearance were seen.

The pharmacokinetics of thalidomide have not been clearly characterized in men. Our study described the pharmacokinetic profile of thalidomide, after single as well as multiple oral dosing in an elderly population of men with cancer. Low- and high-dose groups were studied and pharmacokinetic parameters were determined for both. Patients in this study were diagnosed with hormone-refractory prostate cancer, but did not have active opportunistic infections or concomitant diseases. Additional studies are necessary to determine if age affects the clearance of thalidomide and whether the formation of the active metabolite of thalidomide that inhibits angiogenesis is altered by changes in clearance.

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