

Activity of Thalidomide in AIDS-Related Kaposi's Sarcoma

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Purpose: To assess the toxicity and activity of oral thalidomide in Kaposi's sarcoma (KS) in a phase II dose-escalation study.

Patients and Methods: Human immunodeficiency virus (HIV)-seropositive patients with biopsy-confirmed KS that progressed over the 2 months before enrollment received an initial dose of 200 mg/d of oral thalidomide in a phase II study. The dose was increased to a maximum of 1,000 mg/d for up to 1 year. Anti-HIV therapy was maintained during the study period. Toxicity, tumor response, immunologic and angiogenic factors, and virologic parameters were assessed.

Results: Twenty patients aged 29 to 49 years with a median CD4 count of 246 cells/mm³ (range, 14 to 646 cells/mm³) were enrolled. All patients were assessable for toxicity, and 17 for response. Drowsiness in nine and depression in seven patients were the most fre-

quent toxicities observed. Eight (47%; 95% confidence interval [CI], 23% to 72%) of the 17 assessable patients achieved a partial response, and an additional two patients had stable disease. Based on all 20 patients treated, the response rate was 40% (95% CI, 19% to 64%). The median thalidomide dose at the time of response was 500 mg/d (range, 400 to 1,000 mg/d). The median duration of drug treatment was 6.3 months, and the median time to progression was 7.3 months.

Conclusion: Oral thalidomide was tolerated in this population at doses up to 1,000 mg/d for as long as 12 months and was found to induce clinically meaningful anti-KS responses in a sizable subset of the patients. Additional studies of this agent in KS are warranted.

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K APOSI'S SARCOMA (KS), a multicentric angioproliferative tumor, occurs frequently in patients infected with human immunodeficiency virus (HIV).^{1,2} Patients with KS often present with cutaneous and oral lesions, and they may have lymph node or visceral involvement. KS can be disfiguring, cause pain and edema, and impair quality of life. In the absence of effective therapy, visceral disease, particularly that involving the lungs, can be rapidly fatal.³ The past several years have seen several important advances in the treatment of KS, including the use of liposomal anthracyclines and paclitaxel.⁴⁻⁹ However, these approaches are not curative, and all are associated with cumulative toxicity, including bone marrow suppression. Thus, there is an interest in pathogenesis-based approaches that may be more selective for the tumor.

KS lesions are highly vascular and are microscopically characterized by spindle cells.¹⁰ Although advanced KS may involve monoclonal proliferation,¹¹ there is evidence that proangiogenic factor-driven hyperproliferation is important at all stages of the disease.¹²⁻¹⁵ Spindle cells produce and respond to proangiogenic factors such as basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF).^{12,16,17} In 1994, a novel herpesvirus called KS-associated herpesvirus (KSHV) or herpesvirus-8 (HHV-8) was discovered, and this virus has been shown to be an important etiologic factor for KS.¹⁸⁻²¹ KSHV/HHV-8 can induce the production of a number of virally-encoded and cellular angiogenic factors that are believed to play an

important role in KS pathogenesis.²²⁻²⁵ Antiangiogenic approaches are thus worth exploring in this disease.

Recently, D'Amato et al²⁶ showed that a metabolite of thalidomide inhibits angiogenesis induced by bFGF. This antiangiogenic activity was related to the drug's teratogenic effects but was distinct from its sedative characteristics.^{26,27} With this background, we hypothesized that thalidomide's antiangiogenic activity might stabilize KS lesions or induce tumor remission. To explore this possibility, we initiated a clinical trial to assess the activity of thalidomide in KS.

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PATIENTS AND METHODS

Study Population

Patients infected with HIV who were at least 18 years of age with biopsy-proven KS were eligible if they had at least five assessable lesions and objective evidence of tumor progression over the previous 2 months. Patients were required to be either on a stable regimen of antiretroviral therapy for at least 4 weeks or off all antiretroviral therapy for at least 2 weeks. Additional entry criteria included a Karnofsky performance status ≥ 70 , hemoglobin level greater than 8.0 g/dL, absolute neutrophil count ≥ 750 cells/mm³, platelet count greater than 70,000 cells/mm³, aspartate transaminase less than 3.6-fold times the upper limit of normal, and intact renal function. Patients were excluded if they had moderate peripheral neuropathy, unless it was related to mechanical compression. Patients could not have received cytotoxic chemotherapy, systemic anti-KS therapy, systemic steroids (except replacement hormones or noncorticosteroids used to treat wasting syndrome), or local anti-KS therapy within 4 weeks. Pregnancy was an exclusion criterion, and both hormonal and barrier birth control methods were required for all female participants at risk for pregnancy. Patients gave written informed consent using documentation approved by the National Cancer Institute (NCI) Institutional Review Board.

Treatment Regimen

Thalidomide was provided by the Cancer Therapy Evaluation Program, NCI through an agreement with EntreMed, Inc, Rockville, MD. Patients were administered oral thalidomide beginning at 200 mg/d, with dose escalation by 200 mg/d every 14 days up to a maximum of 1,000 mg/d. This dose-escalation method was selected based on evidence that the 200 mg was tolerated as a starting dose²⁸ and on preliminary data that suggested that patients can tolerate higher doses if the thalidomide dose is gradually escalated. Dose reductions or delays in dose escalation were permitted for toxicity. Patients were evaluated at least every 2 to 4 weeks. Patients were kept on their entry anti-HIV regimens whenever possible, but modifications were permitted for regimen failure or toxicity.

Evaluation of Patients and Response Assessment

History and physical examinations and routine laboratory assessments were performed at each visit. Toxicity was graded using the NCI common toxicity criteria.²⁹ Patients were assigned into good or poor prognostic groups based on assessment of tumor extent (T), immunologic status (I), and systemic illness (S; TIS) for KS.³⁰ Response assessments were made using a minor modification of the AIDS Clinical Trials Group method.^{31,32} Only lesions that had never received locally administered therapy were assessed. Patients were considered assessable for response if they received 5 or more weeks of therapy. A partial response was defined as no progressive disease and at least a 4-week persistence of either a 50% decrease in the sum of the cross products of the lesions, a 50% reduction in the total number of lesions, or flattening of 50% or more of the nodular lesions. A complete response was defined as the absence of any evident disease for 4 weeks with confirmation by biopsy. Progressive disease was defined as either an increase from baseline of 25% or more in the parameters used to define a partial response or the development of new or increasing tumor-associated edema or effusion that interfered with the patient's normal activities. Duration of response was defined as the interval between first achievement of response until documentation of progres-

sion of disease.³³ Stable disease was defined as disease that did not meet any of the above criteria.

Analysis of Immunologic, Virologic, and Angiogenic Parameters

Lymphocyte subsets were assessed by fluorescent activated cell sorting and plasma HIV-1 mRNA plasma levels measured by quantitative RNA (Roche Amplicor HIV-1 monitor kits, Roche Diagnostic Systems, Inc, Branchburg, NJ) polymerase chain reaction at entry and at least every 8 weeks. The lower limit of detection of the latter test was 200 virions/mL. KSHV/HHV-8 viral load was assessed in frozen stored peripheral-blood mononuclear cells (PBMC) obtained at entry and at week 8. DNA was extracted from the PBMC using the PureGene DNA Isolation Kit (Gentra Systems, Inc, Minneapolis, MN), which yielded a final DNA volume of 100 μ L per specimen. Polymerase chain reactions were performed in triplicate, each of which contained 10 μ L of the DNA extract. Quantitative, real-time amplifications were performed against two KSHV gene targets, ORF22 (primers, 5'-CACCTTGCGC-GATTGGGATC-3' and 5'-ACGCCATGACAATCATTGGG-3'; and probe, 5'-CGCGTCTGGTACTGGGTGATATCTTCGC-3') and K6 (primers, 5'-CGCCTAATAGCTGCTGCTACGG-3' and 5'-TG-CATCAGCTGCCTAACCCAG-3'; and probe, 5'-CACCCACCGC-CCGTCCAAATTC-3'), using a Perkin Elmer/ABI Prism 7,700 (Perkin Elmer, Norwalk, CT).³⁴ The number of HHV-8 copies detected in the K6 and ORF22 triplicates were averaged and normalized to the number of PBMC as determined by parallel quantification of the human *ERV-3* gene.

Serum was collected from patients at entry and at periodic time points after enrollment for assessment of tumor necrosis factor alpha (TNF- α), bFGF, interleukin-6, and VEGF levels. The serum was then analyzed in batch for these factors using enzyme-linked immunosorbent assays (R&D Systems, Minneapolis, MN). Because the platelet count can affect serum VEGF levels, these were normalized to 150,000 platelets/mm³.

Clinical Pharmacology

Plasma samples for assessment of steady-state thalidomide levels were obtained during clinic visits approximately 14 hours after a dose of thalidomide. The concentration of thalidomide in these samples was determined by a reversed-phase high-performance liquid chromatography method using ultraviolet detection.³⁵

Statistical Analysis

This was a two-stage minimax phase II study³⁶ with inpatient dose escalation. It was designed to target a response rate of $\geq 30\%$ and rule out a response rate of $\leq 10\%$. If two or more of the initial 15 patients entered had tumor responses (as occurred), then a total entry of 25 patients was targeted. Because of the two-stage study design, the 95% confidence interval (CI) of the observed response proportion was constructed using a method appropriate to the design.³⁷ Accrual was somewhat lower than anticipated, in part because of the increased availability of thalidomide outside of a research protocol, and by February 1, 1999, 20 patients were entered. The primary end point was tumor response in assessable patients. Because it was hypothesized that antiangiogenesis therapy might simply slow disease progression, disease stabilization was also assessed and was considered a potentially favorable outcome. Results presented here are up to April 7, 1999.

The probabilities of response duration, treatment failure, and progression as functions of time were estimated by the Kaplan-Meier

Table 1. Characteristics of Patients at Entry

Characteristic	No. of Patients
Sex	
Male	20
Female	0
Age, years	
Median	39.2
Range	29-49
CD4 cell count, cells/mm ³	
Median	246
Range	14-646
HIV-1 mRNA, log ₁₀ copies/mL	
Median	2.95
Range	< 2.30-5.13
Antiretroviral therapy	18
Highly active antiretroviral therapy	17
TIS tumor stage*	
Overall good/poor	4/16
T ₁ (extensive tumor)	10
I ₁ (< 200 CD4 cells/mm ³)	13
S ₁ (clinically advanced HIV disease)	6
≥ 50 cutaneous lesions	13
Prior KS therapy	12
Local only	5
Systemic	7
Cytotoxic chemotherapy	4
Prior opportunistic infections	3

*The TIS staging system for KS classifies patients as having good or poor prognosis based on tumor extent (T), immunologic status (I), and systemic illness (S).³⁰ Patients are classified as having good (0) or poor (1) prognosis for each parameter; overall, they are classified as poor prognosis if they are T₁, I₁, or S₁.

method. In the absence of treatment failure or progression, follow-up times were censored at the end of treatment because of the confounding effect of subsequent therapies. The change from baseline was determined for logarithmically transformed viral loads and for serum cytokine and angiogenic factors. The significance of changes from baseline were determined using the Wilcoxon signed rank test; associations between tumor response and several parameters were evaluated using Fisher's exact test or the Wilcoxon rank sum test as appropriate. All *P* values were two-sided and are presented without correction for the number of end points.

RESULTS

Accrual and Study Population

Twenty male patients with AIDS-associated KS, aged 29 to 49 years, were enrolled between April 1, 1996, and February 1, 1999 (Table 1). According to the AIDS Clinical Trials Group TIS staging system for KS,³⁰ 16 of the patients had poor-prognosis KS. Ten of the poor-prognosis patients had extensive tumor (T₁); of these, eight had tumor-associated edema, two had ulceration, three had oral nodular lesions, and two had visceral nonnodal disease.

The median baseline CD4 cell count at entry was 246 cells/mm³ (range, 14 to 646 cells/mm³). Three patients had a history of opportunistic infections, but none had active infections at the time of enrollment. All but two of the patients were on a stable regimen of antiretroviral therapy for a median of 22.5 weeks (range, 7.6 to 82.5 weeks) before entry. Of these, 17 were on a highly active antiretroviral regimen that contained either a protease inhibitor (16 patients) or efavirenz (one patient), whereas one patient was receiving two nucleoside analogs. The median HIV viral load at entry was 2.95 log₁₀ copies of HIV per milliliter (range, undetectable to 5.13 log₁₀ copies of HIV per milliliter).

Tumor Responses

Seventeen patients were assessable for response. None achieved a complete response. Eight patients achieved a partial response, for an overall major response rate of 47% (95% CI, 23% to 72%) (Table 2). Each of the eight patients who responded met the criteria of a 50% decrease in the number of nodular lesions in the assessed skin, and two also had a 50% decrease in the total number of lesions. Photographs of a representative patient before and during therapy are shown in Fig 1. The median time from entry to response was 8 weeks (range, 4 to 16 weeks). Two patients (12%) had stable disease, and seven (41%) had progressive disease. When all 20 patients are assessed on an intent-to-treat

Table 2. Tumor Responses in the 17 Assessable Patients

Tumor Response	No. of Patients (n = 17)		Prior Cytotoxic Chemotherapy (n = 3)		CD4 (cells/mm ³)				Prior Anti-HIV Therapy (months)			
	No. of Patients	%	No. of Patients	%	< 150 (n = 5)		≥ 150 (n = 12)		< 6 (n = 8)		≥ 6 (n = 9)	
					No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Complete	0	0	0	0	0	0	0	0	0	0	0	0
Partial	8	47	1	33	3	60	5	42	5	63	3	33
Stable disease	2	12	0	0	0	0	2	16	1	12	1	11
Progressive disease	7	41	2	66	2	40	5	42	2	25	5	55

NOTE. The overall major response rate for the 17 patients assessable for response (partial plus complete responses) was 47% (95% CI, 23% to 72%). Based on all 20 patients, with intent to treat, the response rate was 40% (95% CI, 19% to 64%).

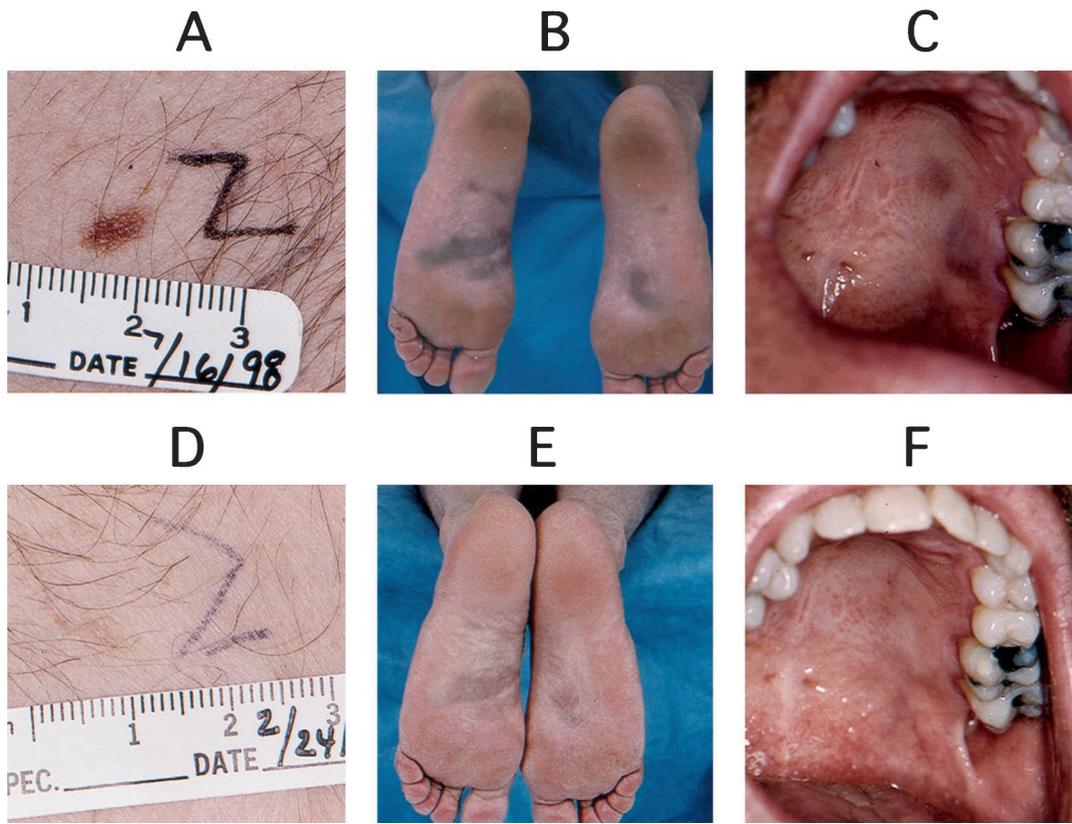


Fig 1. Photographs of KS lesions from a representative patient at entry (A, B, C) and after 32 weeks of therapy (D, E, F). Shown are lesions on his left abdomen (A, D), the soles of his feet (B, E), and the upper palate (C, F).

basis, the response rate (partial and complete responses) is 40% (95% CI, 19% to 64%).

Three (33%) of 10 patients with clinically significant edema at baseline had a beneficial decrease in edema, and two of these patients reported improved function and a decrease in edema-associated pain. However, none of these patients who responded had severe baseline edema. The patient with the most clinically significant edema at baseline had no evidence of response to thalidomide and was removed from study for progressive disease. One patient with painful foot lesions that interfered with ambulation had reduced pain and was able to walk without difficulty after treatment with thalidomide (Fig 1).

With a median follow-up time of 34.8 weeks, seven of the 17 assessable patients (41%; 95 CI, 18% to 64%) showed no evidence of disease progression at the end of the observation period. For all 20 patients, the estimated median time from entry to progression was 7.3 months (Fig 2). The estimated response duration for the eight responding patients was 7.1 months (Fig 3). Overall, the estimated median time from entry to treatment failure, including patients for

whom treatment was terminated for toxicity or disease progression, was 6.3 months (Fig 4).

The median thalidomide dose at the time of response was 500 mg/d (range, 400 to 1,000 mg/d). The median sustained

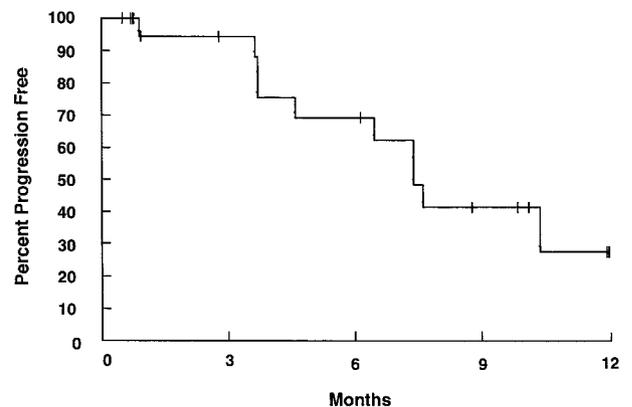


Fig 2. Kaplan-Meier curve showing the progression-free survival on thalidomide from entry in all 20 patients entered onto the study. The maximum period of observation for any patient was 12 months.

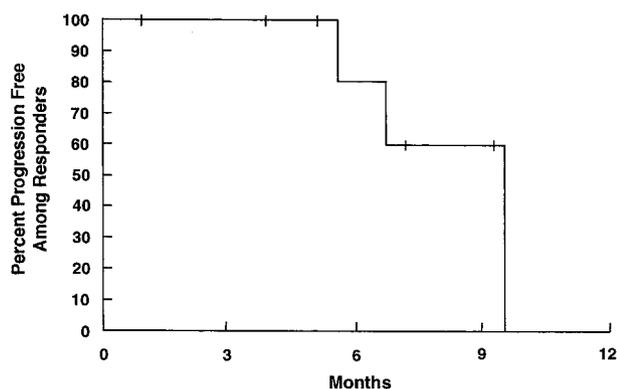


Fig 3. Kaplan-Meier curve showing the time from attainment of response to progression of disease. The maximum period of observation for any patient was 12 months.

thalidomide dose was 600 mg/d, and there was no association between this and the tumor response. Similarly, there was no relationship between either the TIS category or the presence of more than 50 KS lesions at entry and the likelihood of response. Finally, although there was a trend toward a lower baseline CD4 count in responders versus nonresponders (median, 243 v 344 cells/mm³; $P_2 = .23$, Wilcoxon rank sum test), this difference was lost by week 8 (285 v 271 CD4 cells/mm³; $P_2 = 1.0$).

Anti-HIV Therapy and Tumor Responses

Of the 17 patients assessable for response, 14 received combination antiretroviral therapy that contained either a protease inhibitor or efavirenz at entry. One patient received a regimen of only two nucleoside analogs. Two patients were not receiving antiretroviral therapy at the time of study entry: one of these had received a short course of zidovu-

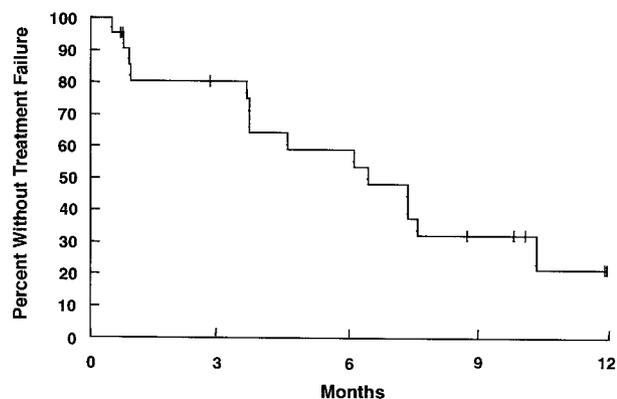


Fig 4. Kaplan-Meier curve showing the time from entry to treatment failure (either disease progression or toxicity) in all 20 patients entered onto the study. The maximum period of observation for any patient was 12 months.

dine several years previously, and the other was antiretroviral naïve. There was no statistical difference in the prior duration of highly active antiretroviral therapy between the patients who achieved a response (median, 14.9 weeks) and those who did not (median, 22.5 weeks; $P_2 = .58$). Because preliminary information suggests that generally 6 months or more of anti-HIV therapy is required to observe an anti-KS effect of HAART,³⁸ we compared the response rates according to duration of HAART and found no statistically significant difference. Of the eight patients who achieved a response, 63% had been on antiretroviral therapy less than 6 months and 33% had been on antiretroviral therapy 6 months or more at the time of response ($P_2 = .35$, Fisher's exact test). Among patients who achieved a partial response, no changes in antiretroviral therapy were made before the time a response was achieved, with the exception of one patient with undetectable viral load, in whom zidovudine was substituted for stavudine because of neuropathy. Four of the eight patients who achieved a partial response and four of the nine who had progressive or stable disease had a sustained viral load below the limit of detection. Finally, there was no association between achieving a response and having a detectable viral load at entry ($P_2 = .64$), having a detectable viral load at the time a response was attained ($P_2 = .35$), or having a greater than 0.5 log₁₀ increase in viral load between entry and the time of response ($P_2 = 1.0$, Fisher's exact test).

Toxicity and Other Clinical Parameters

Seven of the 20 patients achieved the maximum dose of 1,000 mg thalidomide daily, for a median of 19.9 weeks (range, 7.8 to 34.7 weeks). In all, seven patients (35%) discontinued thalidomide before completion of the 12 months of dosing: two discontinued use early after achieving a partial response; one was removed after he began therapy with hydroxyurea, which was prohibited by the protocol; and one, who had only 4 weeks left on protocol, thought it unnecessary to continue treatment for his KS. Five (23%) of the 20 patients discontinued thalidomide because of toxicity: two for depression (both at ≤ 200 mg/d), one for fever and rash, one for neuromotor weakness, and one for sensory neuropathy. Toxicities that were grade 2 or above or that required dose modifications are listed in Table 3. It was noteworthy that seven patients developed depression, each of whom had a prior history. Five of these were able to remain on study; in four, the depression responded to a dose reduction of thalidomide, whereas in one, it responded to a resumption of antidepressant medication.

Only one patient developed AIDS-related opportunistic illness (*Pneumocystis carinii* pneumonia). Seven patients

Table 3. Toxicity \geq Grade 2 or That Required Dose Modification

Toxicity*	No. of Patients
WBC count $< 2.0 \times 10^3$ cells/mL	1
Absolute granulocyte count $< 1.0 \times 10^3$ cells/mL	7
Neuropathy	
Sensory, moderate	1
Motor, moderate	1
Depression	
Moderate	5
Severe	2
Somnolence, moderate	9
Fatigue, moderate	1
Anxiety, moderate	1
Allergic reaction†	1

*Toxicities were graded using the National Cancer Institute common toxicity criteria, version 1.0.²⁹

†One patient developed what appeared to be an allergic reaction to thalidomide with fever, generalized skin rash, and vomiting.

had evidence of an improvement in HIV-associated conditions: one had healing of aphthous ulcers, and six had improvement in diarrhea. There was no evidence of significant weight gain among the patients with cachexia.

Clinical Pharmacology

Assays were performed on plasma samples obtained approximately 14 hours after dosing to assess steady-state thalidomide concentrations. The mean \pm SD concentration in patients who took 200-mg doses was $0.82 \pm 0.17 \mu\text{g/mL}$. There was a linear relationship between the plasma concentration and the thalidomide dose over the range of 200 to 1,000 mg/d (mean \pm SD concentration, $5.61 \pm 2.43 \mu\text{g/mL}$ at 1,000 mg/d). Responses were observed at measured concentrations that ranged from 0.94 to $5.43 \mu\text{g/mL}$, and there was no apparent relationship between the plasma levels of thalidomide attained with a given dose and the tumor responses. Similarly, there was no apparent relationship between the levels attained and the development of toxicity.

Circulating Cytokines and Growth Factors

At baseline, the median serum concentrations of bFGF and normalized VEGF (22.7 and 147 pg/mL, respectively, in the 15 patients tested) were somewhat elevated compared with published values, whereas serum levels of TNF- α and interleukin-6 (5.88 and 3.99 pg/mL, respectively) were not.³⁹⁻⁴² At week 4, there was a transient increase in the TNF- α level compared with baseline ($P_2 = .039$, Wilcoxon signed rank test) but not in the other factors (Fig 5).

KSHV/HHV-8 Viral Load in PBMC

KSHV/HHV-8 viral DNA was assessed in PBMC collected from the 17 assessable patients at entry and at week

8 (Fig 6). KSHV/HHV-8 DNA was detected at entry in 10 patients and at week 8 in eight patients. The value remained undetectable at both time points in five patients, decreased in eight, and increased in four; overall, with the use of a Wilcoxon signed rank test, there was no statistically significant change from baseline in the whole group of 17 patients ($P = .52$) or in the subsets of responders ($P = .375$) or nonresponders ($P = 1.00$).

DISCUSSION

KS is an excellent tumor in which to consider antiangiogenesis-based treatment approaches because the lesions are highly vascular and because there is an accumulated body of evidence that suggests that cellular and viral angiogenic factors are involved in its pathogenesis.^{12-15,22-25} However, previous pilot or phase I trials of experimental antiangiogenesis agents in KS have not shown consistent antitumor effects. Studies of pentosan polysulfate yielded no responses,^{43,44} and two phase I trials of the fumagillin analog TNP-470 yielded response rates of 0% and 18%, respectively.^{45,46}

In the present phase II study, thalidomide was tested primarily because of its potential antiangiogenesis activity. With the use of a dosing scheme in which patients started at 200 mg/d and escalated up to a maximum of 1,000 mg/d as tolerated, major tumor responses were observed in eight (47%) of 17 assessable patients, and another two patients had stable disease. Overall, the results suggest that thalidomide has activity against KS at doses that can be tolerated for 6 months or more in a sizable proportion of patients. The response rate and duration of response are comparable to those obtained with some cytotoxic chemotherapy regimens.^{7,47} However, response rates in KS can be affected by a variety of factors, including potent antiretroviral therapy,³⁸ and meaningful comparisons with other therapies can only be made in the context of a randomized trial.

KS may wax and wane spontaneously and may respond to potent antiretroviral therapy in some cases,^{2,38,48,49} and thus, it is worth considering whether the tumor responses observed in this study may have occurred in the absence of specific anti-KS therapy. Our group did not document any partial or complete KS responses in earlier trials of pentosan polysulfate, all-*trans*-retinoic acid, or TNP-470 using tumor response criteria similar to those in the present study.^{43,45,50} In those trials, however, patients did not receive HIV protease inhibitors, and there are anecdotal reports of KS patients responding to highly active antiretroviral therapy alone.^{51,52} Because of our concern for this factor, we required patients on the present study to be on a stable antiretroviral regimen (or to have been off therapy for at least 2 months) and to have disease progression before

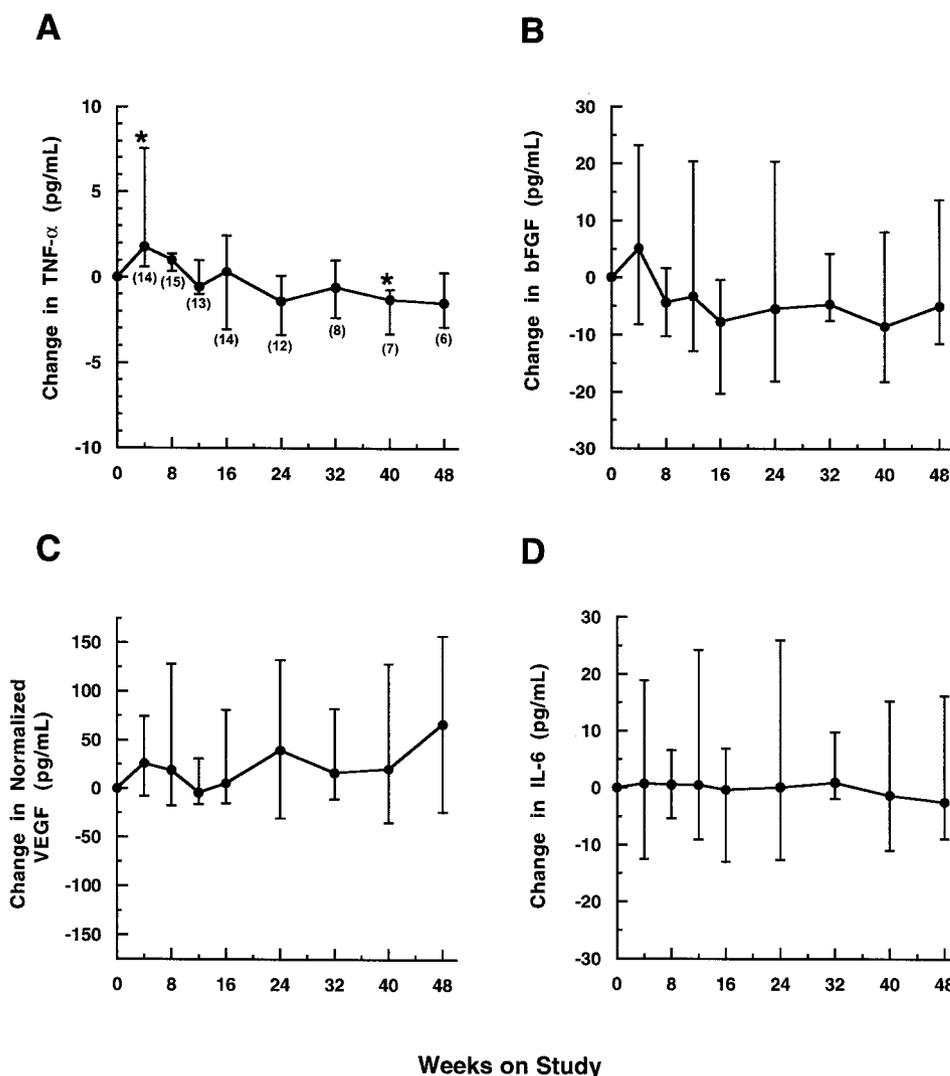


Fig 5. Changes from baseline of serum (A) TNF- α , (B) bFGF, (C) normalized VEGF, and (D) interleukin-6. Shown are the median and upper and lower quartiles. Numbers in parentheses in (A) show the numbers of patients tested, and asterisks denote time points from entry at which $P_2 < .05$. Abbreviation: IL-6, interleukin-6.

entry. Also, only one patient had changes in his antiretroviral therapy before response (because of toxicity, not regimen failure). Finally, there was no difference in the HIV viral load between the responders and nonresponders. Thus, it is unlikely that the responses observed were simply the result of antiretroviral therapy. However, it is possible that the control of HIV was a favorable prognostic factor.

It is unclear whether the observed KS responses were a result of the antiangiogenesis activity of thalidomide or some other property. Thalidomide has immunomodulatory activities that are thought to be the basis for its utility in treating erythema nodosum leprosum and HIV-associated aphthae.^{28,53-56} In vitro studies have shown that it inhibits the production of TNF- α , can suppress HIV replication in macrophages, and can suppress type 1 T-cell responses

while simultaneously enhancing type 2 responses.⁵⁵⁻⁵⁸ Whether such effects occur in patients, however, is unclear, and there is one report that it can enhance type 1 immunity in HIV-infected patients when antiretroviral therapy is used.⁵⁹ There is evidence that TNF- α and HIV replication can enhance the growth of KS,^{16,60,61} and it is conceivable that thalidomide's suppression of these factors might have contributed to the anti-KS effect. However, TNF- α levels transiently increased during the first 6 months of therapy. Such a paradoxical increase in blood TNF- α levels was also observed in a short-term trial of thalidomide for the treatment of HIV-associated oral aphthae.²⁸ Antiviral effects of thalidomide were most likely negligible, because nearly all patients on the current trial were on potent antiretroviral therapy and no consistent change in the HIV viral load

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