9-cis-Retinoic Acid Capsules in the Treatment of AIDS-Related Kaposi Sarcoma

Results of a Phase 2 Multicenter Clinical Trial

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Objective: To evaluate the safety, dose tolerance, and anti-tumor effects of 9-cis-retinoic acid in the treatment of Kaposi sarcoma (KS) related to acquired immunodeficiency syndrome (AIDS).

Design: Phase 2, open-label clinical trial of oral doses of 9-cis-retinoic acid increasing in 40-mg increments every 2 weeks from 60 mg/m² per day to a maximum of 140 mg/m² per day.

Setting: Five hospital or health maintenance organization outpatient clinics.

Patients: Fifty-seven adult male patients with human immunodeficiency virus and biopsy-proven KS.

Main Outcomes Measures: Safety was evaluated by adverse events, physical examination, laboratory test abnormalities, treatment-limiting toxic effects, and reasons for early withdrawal. Response (≥50% improvement) was evaluated by an overall KS response and by the area and height from 6 index lesions selected at baseline.

Results: Patients tolerated 60 and 100 mg/m² per day. Most patients found 140 mg/m² per day intolerable owing to headache. Common treatment-related adverse events were headache, xerosis, rash, alopecia, and hyperlipemia. The patient response rate for the overall KS disease was 19% (11/57), including 1 patient with clinically complete response. The response rate assessed by measuring 6 index lesions during treatment was 39% (22/57). Sixteen responding patients (73%) were refractory to at least 1 previous anti-KS therapy. Patients with CD4⁺ counts of 150 cells/µL or lower were as likely to respond as patients with counts of higher than 150 cells/µL. The median time to response was 8.5 weeks (range, 4.0-21.1 weeks). The median duration of treatment was 15.1 weeks (range, 0.14 to ≥62 weeks).

Conclusion: 9-cis-retinoic acid capsules have moderate activity and provide durable responses, but substantial toxic effects at higher doses limit its suitability as an anti-KS therapy.

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Although the incidence of Kaposi sarcoma (KS) in the United States and Europe is waning, it remains the most prevalent tumor associated with human immunodeficiency virus (HIV) infection. The natural history of KS is heterogeneous. Although not all patients seek treatment for early-stage disease, most will obtain medical consultation. Radiation therapy, intralesional chemotherapy, and topical liquid nitrogen have been administered to patients with cutaneous KS, and in indolent or limited-stage disease, such treatments usually achieve good results.

Various cytotoxic chemotherapeutic agents, including liposomal anthracyclines and paclitaxel, are also available for patients with more advanced disease but have the potential for appreciable toxic effects.

Retinoids have been examined as a potential new treatment for KS. These are pharmacologic compounds chemically related to retinol (vitamin A) that exert their physiologic effects by interacting with 1 or more of 6 nuclear receptors designated retinoic acid receptors (subtypes 9, 4, 8) and retinoid X receptors (subtypes 9, 4, and 8). Retinoids have antiproliferative, differentiating, and apoptotic effects in various in vitro models, including KS-derived spindle cell lines.

Moderate antitumor effects have been reported with selected retinoids in clinical trials involving patients with squamous neoplasms, renal cell cancers, and premalignant conditions of the oral cavity. All-trans-retinoic acid has significant activity in the treatment of acute promyelocytic leukemia and is capable of inducing complete hematologic and cy-
togenetic remissions. 9-cis-retinoic acid, or altretinoi
(Panretin; Ligand Pharmaceuticals Inc, San Diego, Calif), is a natural panagonist for all 6 retinoic acid and reti-
roid X receptors,9,10 so it may provide clinical benefit dis-
tinct from other retinoids (unpublished data, Ligand Pharma-
cueticals Inc).10 Clinical trials of 0.1% 9-cis-retinoic acid
gel resulted in objective response rates in KS from
27%17 in phase 1 and 2 studies to 56%18,19 in open-label
phase 3 studies. The antitumor effects, safety, and toler-
ability results of orally administered 9-cis-retinoic acid
in patients with KS related to acquired immunodefi-
ciency syndrome (AIDS) are reported here.

METHODS

STUDY DESIGN AND DRUG FORMULATION

A phase 2, open-label, dose-escalation trial of 9-cis-retinoic acid
capsules was conducted in patients with AIDS-related KS be-
tween July 1996 to December 1997. Patients were enrolled at
5 study centers to evaluate the efficacy, safety, and toler-
ability of 9-cis-retinoic acid capsules for the treatment of KS when taken
for at least 16 weeks. The protocol and informed consent were
approved by local institutional review boards. Prospective pa-
ients gave written informed consent before they were screened
for study enrollment.

PATIENT ELIGIBILITY

Patients eligible for the trial were at least 18 years old, HIV
positive by enzyme-linked immunosorbent assay, and had biopsy-proven KS. The protocol required a Kar
sky performance score of 60 or higher. Patients needed to have serum aspartate aminotransferase and serum alanine aminotrans-
ferase levels at least 1.5 times the upper limit of normal (ULN), bili-
rubin levels lower than 1.5 times the ULN, serum creatinine
levels up to 2 times the ULN, fasting serum triglyceride levels
up to 1000 mg/dL (11.3 mmol/L), serum amylase levels up to
1.5 times the ULN, hemoglobin levels of 8 g/dL or higher, neu-
rophil counts of 900/µL or higher, and platelet counts of
50,000/µL or higher.

Participants were required to have a minimum of 6
mucocutaneous index lesions (including at least 3 raised
lesions), each of which was typical of the patient’s disease,
clinically present for 30 days or longer or with at least 1
dimension 10 mm or greater. The 6 designated index lesions
could not have received local or topical treatment within 60
days prior to study entry because they were an efficacy end
point. Each investigator chose which 6 index lesions were to
be assessed, usually based on accessibility and distinct bor-
ders for serial measurements. The protocol required patients
who were undergoing stable antiretroviral therapy to be
clinically stable on the regimen for a minimum of 6 weeks
prior to study entry with an intention to continue it through
the first 16 weeks of the study. Patients agreed to use barrier
contraceptives for the entire treatment period and for at least
16 weeks. The protocol required patients to use barrier
contraceptives for the entire treatment period and at least
16 weeks (ACTG) criteria.20 The overall KS disease se-
verity assessment depended on more stringent criteria. For ex-
ample, a patient with a clinically complete response (CCR) or
patient quality-of-life questionnaire, designed to collect sub-
jective information including the patient’s own assessment of

PATIENT QUALITY-OF-LIFE ASSESSMENTS

A patient quality-of-life questionnaire, designed to collect sub-
jective information including the patient’s own assessment of

TREATMENT REGIMEN

Treatment was initiated with 9-cis-retinoic acid capsules at a dose
of 60 mg/m² once daily for 2 weeks, as was determined from re-
sults of phase 1 and 2 trials in adults with various solid tumors
(unpublished data, Ligand Pharmaceuticals Inc). Patients who toler-
ated their dose during the initial 2 weeks had their dose increased
to 100 mg/m² per day for at least the next 2 weeks. If this dose was
also tolerated for 2 weeks or longer, it was increased again, to a
maximum of 140 mg/m² per day. The highest dose, however (140
mg/m² per day), was associated with substantial headache and dry,
erthematous, exfoliative skin during the trial. The maximum dose
of 9-cis-retinoic acid was therefore reduced by protocol amend-
ment to 100 mg/m² per day after 31 patients enrolled and 11 had
been advanced to the 140 mg/m² per day dose.

Treatment of each patient was to be maintained at the max-
imum tolerated dose for at least 16 weeks. Treatment could be
continued as long as the patient might benefit from it without
experiencing unacceptable toxic effects. Protocol guidelines on
dose-limiting toxic effects provided that the daily dose could be
adjusted down by 40 mg/m² at the discretion of the inves-
tigator. Patients who did not tolerate the lowest study dose of
60 mg/m² per day were withdrawn from the trial.

EFFECTIVENESS ASSESSMENTS

Overall KS Disease Assessment

The overall extent of KS disease was evaluated at baseline (study
day 1) and compared with baseline every 4 weeks thereafter for
total number of visible KS lesions, total number of raised
KS lesions, number of new lesions, presence of new or pro-
gressive tumor-associated edema or effusions, and new or pro-
gressive KS visceral disease.

KS Index Lesion Assessment

Six index mucocutaneous lesions, including at least 3 raised le-
sions, were assessed at baseline (study day 1) and every 2 weeks
thereafter. Photographs of these lesions were obtained every 4
weeks. Lesion assessments were based on the lesion area, height,
color, pain, and edema. Lesion area (square centimeters) was mea-
sured by the product of the 2 longest perpendicular lesion diam-
eters, and lesion height was assessed using a 3-point scale (macu-
lar, 0 mm; plaque-like, ≤5 mm; and nodular, ≥2 mm). Lesion
color was graded on a 4-point scale, ranging from 0 (natural skin
color) to 3 (deep purple to gray-black); lesion-associated pain/
discomfort was graded on a 4-point scale, ranging from 0 (ab-
sence of pain/discomfort) to 3 (severe pain); and lesion-
associated edema was graded on a 4-point scale, ranging from
0 (no edema) to 3 (severe edema).

KS Objective Response Classification

Responses for the overall KS disease severity and for KS index
lesion assessments were classified according to the AIDS Clini-
cal Trials Group (ACTG) criteria.20 The overall KS disease se-
verity assessment depended on more stringent criteria. For ex-
ample, a patient with a clinically complete response (CCR) or
partial response (PR) as measured by the response of all index
lesions would nonetheless have “progressive disease” accord-
ing to overall KS severity of disease assessment if 1 new lesion
developed anywhere at any time during therapy.

Patient Quality-of-Life Assessments

A patient quality-of-life questionnaire, designed to collect sub-
jective information including the patient’s own assessment of

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KS disease, was to be completed at baseline (study day 1) and every 4 weeks thereafter. The questionnaire was derived from the National Institute of Allergy and Infectious Disease ACTG 286 instrument used in other HIV trials and included a KS module with 3 questions on pain, appearance, and sentiment related to KS. This instrument has not yet been formally validated. The patient completed this assessment alone after minimal administrative instructions from the study staff. The questionnaire included an assessment of the overall feeling of well-being, with scores ranging from 1 (“the very worst I ever felt”) to 10 (“the very best I ever felt”). The level of satisfaction with physical appearance was evaluated on a 5-point scale ranging from 1 (“much more satisfactory”) to 5 (“much less satisfied”). The effect of disease was measured on performance abilities and on emotional perception with a 6-point scale ranging from 1 (“none of the time”) to 6 (“all of the time”). The level of satisfaction with physical appearance was evaluated on a 5-point scale ranging from 1 (“much more satisfactory”) to 5 (“much less satisfied”). The effect of disease was measured on performance abilities and on emotional perception with a 6-point scale ranging from 1 (“none of the time”) to 6 (“all of the time”).

SAFETY AND TOLERABILITY ASSESSMENTS

Safety and tolerability of 9-cis-retinoic acid capsules were evaluated twice monthly throughout the study by the frequency and type of adverse events, toxic effects, physical examination, and laboratory abnormalities. At each patient visit, resting vital signs (temperature, blood pressure, heart rate, and respiratory rate) and changes from the findings of the prior physical examination were noted. CD4+ and CD8+ T-lymphocyte cell counts were obtained every 4 weeks. A hematologic panel and complete metabolic panel, including amylase, lipase, cholesterol, and triglyceride levels, were done every 2 weeks. Any adverse events were documented at each visit and rated by the investigator as serious or not serious, and mild, moderate, moderately severe, or severe. Adverse events were encoded using both a Ligand-modified Coding Symbols for the Thesaurus of Adverse Reaction Terms (COSTART 5)<sup>21</sup> dictionary and National Cancer Institute (NCI) toxicity terms.

DATA EVALUATIONS

Efficacy data were evaluated using the KS index lesion assessments, the KS overall disease severity assessment, and the answers to the patient quality-of-life questionnaire. The primary efficacy end points were the tumor responses (CCR + PR) for overall severity and for all index lesions during at least 16 weeks of treatment. Responses were based on the ACTG criteria adapted to each end point. The secondary efficacy end points included time to response (ie, time from first day of study drug administration to first day of meeting criteria for CCR or PR), time to relapse (ie, time from study day 1 until first day of losing response), and answers to the quality-of-life questionnaire.

Serial CD4+ and CD8+ T-lymphocyte counts and ratios were evaluated by analysis of variance methods. The use of antiretroviral agents and tumor response were analyzed using a χ² test or Fisher exact test, as appropriate.

All patients enrolled comprised the intent-to-treat population and were assessable for efficacy and safety. Descriptive statistics were generated (sample sizes, medians, minima, and maxima) for major safety parameters.

RESULTS

STUDY POPULATION PROFILE

Fifty-seven HIV-seropositive men with early or advanced-stage KS were enrolled in this study and constituted the intent-to-treat patient population. Patient characteristics are listed in Table 1. Twenty-two of the patients (38/57) were tumor in situ stage 1 (ie, at poor risk) by revised ACTG staging criteria, as defined by a CD4+ count lower than 150 cells/µL, a history of AIDS-defining illness, or presence of visceral KS or KS-caused edema or ulceration.<sup>22</sup> Most patients (42/57; 74%) had previously received local (10/57; 18%), systemic (17/57; 30%), or both treatments (15/57; 26%) for KS. Local therapies for KS included external beam radiation (n=16), intralesional vinblastine (n=7), liquid nitrogen (n=4), bexarotene retinoid gel (Targretin; RP Scherer, Basking Ridge, NJ) (n=4), and excisional surgery (n=1). Prior systemic therapy for KS consisted of doxorubicin (including liposomal formulations) (n=15), bleomycin (n=10), vincristine (n=12), interferon alfa (n=3), combination chemotherapy (ABV [Adriamycin (doxorubicin hydrochloride); Pharmacia Corporation, Phoenix, Ariz], bleomycin, and vinblastine; n=3), and off-label foscarnet (n=1).

The protocol required study patients to be treated with an approved antiretroviral therapy. Fifty-one patients were treated with 3 or more antiretroviral agents at baseline, of whom 48 received a protease inhibitor in conjunction with nucleoside analogues, and 3 were treated with 2 nucleoside analogues coupled with a nonnucleoside reverse transcriptase inhibitor.<sup>23</sup> Fifty patients underwent antiretroviral therapy that included at least 1 protease inhibitor. Five were taking a combination of 2 nucleoside analogues, including 2 who were main-
Objective Response Rates

Patient responses to 9-cis-retinoic acid by stage, prior KS therapy, antiretroviral therapy, and CD4+ cell counts are summarized in Table 2. Twenty-two patients responded by ACTG criteria for index lesions indicating a 50% or more decrease in aggregate index lesion area or height. These included 1 patient with a CCR, 5 patients with a PR based on both area and height criteria, 2 patients with a PR based on area alone, and 14 patients with a PR based on lesion height alone. The intent-to-treat overall response rate based on index lesions was 39% (22/57). Of these responders, 64% (14/22) were tumor in situ stage 1, or at poor risk, by revised ACTG staging.24

Eleven patients (19%) responded to 9-cis-retinoic acid by ACTG criteria applied to overall KS disease severity. This included 1 patient with a CCR and 10 patients with a PR based on at least 50% reduction in the total number of raised lesions. The patients who responded by CCR and PR by overall KS severity criteria responded by index lesions, with 1 exception. This exception was a patient who achieved a PR by overall KS severity but who did not respond by the summed index lesion area because 3 index lesions expanded in area more than other index lesions decreased. Twenty-four patients had stable disease by overall disease severity criteria, and 22 had progressive disease. Ten patients who responded by overall KS disease severity criteria also responded by index lesion criteria, and 1 patient responded only by overall KS disease severity criteria. In total, there were 23 patients who responded by either end point criterion.

The time to response by index lesion response criteria ranged from 4.0 to 21.1 weeks. By a Kaplan-Meier analysis of the time to ACTG-defined index lesion response, 25% of patients were projected to respond within 63 days of treatment, and the median time to response (50% of responding patients) was 135 days of treatment. A similar analysis for response by overall severity criteria indicated that 25% of patients were projected to respond by 145 days, but a median time to response was not reached in this study (Figure 1).

Of the 22 patients who responded by index lesion ACTG criteria, only 3 (14%) later experienced disease progression while undergoing therapy. One patient experienced disease progression following a PR by index lesion height after 274 days. Two patients experienced disease progression by index lesion area criteria after 140 and 288 days, respectively, although both continued to respond by lesion height criteria. Owing to the low rate of relapse, a median duration of response could not be estimated. Thirteen patients withdrew from the study at a time when they were still in response, and 8 patients continued treatment with the study drug for more than 2 years.

Fifty-two patients remained under treatment with 9-cis-retinoic acid for at least 4 weeks. Of these 52 patients, 5 received 60 mg/m² per day without further dose escalation, 26 had their doses increased to 100 mg/m² per day, and 11 patients had their doses increased to 140 mg/m² per day. Fifteen patients did not achieve a stable dose regimen over at least 4 weeks of treatment and had their doses reduced for tolerance. Half (n = 11) of all patient responders reached a maximum dose of 140 mg/m² per day, and the other half reached a maximum of 100 mg/m² per day.

Responses, with photographic documentation shown in Figure 2, occurred during treatment with all dose levels of 9-cis-retinoic acid capsules. Responses based on index lesions were recorded in 7 patients while they took 140 mg/m² per day (1 CCR, 4 PRs by lesion height and lesion area, and 2 PRs by lesion height); 12 patients while taking 100 mg/m² per day (9 PRs by lesion height, 2 PRs

Table 2. Patient Responses to 9-cis-Retinoic Acid Capsules*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (N = 57)</th>
<th>Overall Severity (n = 11)</th>
<th>Index Lesion (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tis-ACTG stage 0 (good risk)‡</td>
<td>19 (33)</td>
<td>5 (26)</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Tis-ACTG stage 1 (poor risk)‡</td>
<td>38 (67)</td>
<td>6 (16)</td>
<td>14 (37)</td>
</tr>
<tr>
<td>Prior KS therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>15 (26)</td>
<td>2 (13)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Local treatment only</td>
<td>10 (18)</td>
<td>2 (20)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Systemic treatment only</td>
<td>17 (30)</td>
<td>5 (29)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Local and systemic treatments</td>
<td>15 (26)</td>
<td>2 (13)</td>
<td>8 (63)</td>
</tr>
<tr>
<td>CD4+ lymphocyte count, cells/µL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>27 (47)</td>
<td>5 (19)</td>
<td>11 (41)</td>
</tr>
<tr>
<td>151-200</td>
<td>6 (11)</td>
<td>2 (33)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>101-150</td>
<td>7 (12)</td>
<td>1 (9)</td>
<td>3 (43)</td>
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<tr>
<td>0-100</td>
<td>13 (23)</td>
<td>2 (15)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (7)</td>
<td>1 (25)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>All patients</td>
<td>57 (100)</td>
<td>11 (19)</td>
<td>22 (39)</td>
</tr>
<tr>
<td>Antiretroviral therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5 (9)</td>
<td>0</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Subset with a protease inhibitor</td>
<td>2 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>51 (89)</td>
<td>11 (22)</td>
<td>20 (39)</td>
</tr>
<tr>
<td>Subset with a protease inhibitor</td>
<td>48 (84)</td>
<td>10 (21)</td>
<td>18 (38)</td>
</tr>
</tbody>
</table>

Abbreviations: ACTG, AIDS Clinical Trials Group; KS, Kaposi sarcoma.
*Data are given as number (percentage).
‡Twelve patients responded by index lesions, 10 patients responded by both index lesions and overall KS disease severity, and 1 patient responded by overall KS disease severity only.¶By criteria of Krown et al.25

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Systemic therapies. Of the 11 patients with KS who had progressive KS despite previous local and systemic therapy, and 8 patients previously treated for KS. Forty-two (74%) of the 57 study participants in this study had been previously treated for KS. Most of the participants in this study had been previously treated for KS. Forty-two (74%) of the 57 study participants had experienced 1 or more previous local or systemic KS treatment (Table 2). Of the 22 patients who responded by index lesion assessment and overall disease severity criteria, 9 (82%) of 33 patients with more than 150 CD4+ cells/µL or fewer responded by overall KS disease severity criteria compared with 7 (21%) of 33 patients with more than 150 CD4+ cells/µL (P = .73, 2-tailed Fisher exact test). Seven (35%) of the 20 patients with fewer than 150 CD4+ cells/µL and 14 (42%) of 33 patients with 150 CD4+ cells/µL or more responded by KS index lesion assessments (P = .77, 2-tailed Fisher exact test).

Effect of CD4+ Lymphocyte Cell Count

The CD4+ counts of patients who responded by index lesion assessment and overall disease severity criteria are listed in Table 2. Three (15%) of 20 patients with 150 CD4+ cells/µL or fewer responded by overall KS disease severity criteria with 7 (21%) of 33 patients with more than 150 CD4+ cells/µL (P = .73, 2-tailed Fisher exact test). Seven (35%) of the 20 patients with fewer than 150 CD4+ cells/µL and 14 (42%) of 33 patients with 150 CD4+ cells/µL or more responded by KS index lesion assessments (P = .77, 2-tailed Fisher exact test).

Effect of Concurrent Antiretroviral Therapy on Response to 9-cis-Retinoic Acid

Of 48 patients who received 3 or more antiretroviral agents that included a protease inhibitor, 10 (21%) responded to 9-cis-retinoic acid treatment by overall severity criteria, and 17 (35%) responded by ACTG index lesion criteria to 9-cis-retinoic acid treatment. Three patients who received antiretroviral agents consisting of at least 2 nucleoside reverse transcriptase inhibitors but no protease inhibitor responded by index lesion criteria to the study medication, and 1 of these also responded by overall severity criteria. Patient tumor response rates did not seem to be related to the number of antiretroviral medications used (P = .52, χ² test [Table 2]).

Measurements of HIV viral load were not part of the study protocol because the importance of viral load to HIV therapy was not clearly established when the study began, and sensitive HIV viral load assays had not yet been validated nor were they routinely available. However, limited viral load data were available for 21 patients who had both screening/baseline and postbaseline HIV viral counts. For the 16 patients whose KS responded by index lesion criteria, the HIV viral load increased for 6 patients. For an additional 7 patients whose KS index lesions responded, the HIV viral load did not change significantly (±10000 copies/mL) from baseline. Three responders by index lesion criteria had a lower HIV viral load postbaseline. Six of 11 patients who responded by overall severity criteria had viral load measurements during treatment. One such patient's viral load was lower, 2 patients' viral loads were slightly higher, and 3 patients had no substantial change in viral load before and during treatment.

Patient Assessment of Treatment

At the last study visit, 47 (82%) of 57 patients indicated on the quality-of-life questionnaire that they experienced a stable or better overall sense of well-being while taking 9-cis-retinoic acid capsules. Furthermore, 39 (68%) of 57 patients indicated that they were “moderately satisfied” or “much more satisfied” with their physical appearance while receiving the study drug.
SAFETY AND TOLERABILITY

The most frequent treatment-related adverse events (ie, those with at least 10% incidence) are listed in Table 3 by COSTART 5 coding. Severity of adverse events was graded per protocol definitions. Symptoms listed as moderate or moderately severe in this table would be moderate by NCI toxicity criteria, and those listed as mild or severe would be the same by NCI criteria. Headache was the most common adverse event. It was alleviated with analgesics and tended to wane after 2 weeks with continued 9-cis-retinoic acid dosing. Some frequently encountered adverse events such as dry skin, rash (erythema), alopecia, exfoliative dermatitis (skin flaking or peeling), cheilitis, and hyperlipemia were similar to toxic effects encountered with other forms of oral retinoid therapy. Of the 57 enrolled patients, 53 (93%) experienced at least 1 adverse event related to study drug. Twenty-one patients (37%) had a primary reason for withdrawal from treatment that was a drug-related adverse event.

Hyperlipemia, the most frequent laboratory abnormality, was reported as an adverse event in 18 cases (32%), of which 3 were classified as severe increases. Elevation in the enzyme aspartate aminotransferase was found in 9 patients (16%), and 5 of these also showed an increase in alanine aminotransferase. These hepatic enzyme changes were mild or moderate except for 1 case where the increase was severe. Five patients (9%) had an increase in serum amylase of which 2 were moderately severe elevations. To what extent antiretroviral therapy or other medications contributed to these findings is uncertain.

Twenty-one (37%) of the 57 patients enrolled experienced a dose-limiting toxic event during the study that resulted in a dose suspension or adjustment. The most common dose-limiting toxic effect consisted of headache in 6 patients (11%) and neutropenia, hypertriglyceridemia, and nausea in 3 patients (5%) each. In 3 patients, dose-limiting toxic events were NCI grade 2, but in 18 patients there were 24 dose-limiting toxic effects of NCI grade 3 and 2 of NCI grade 4. Of these 24 dose-limiting toxic events, 11 (46%) occurred in 8 patients at the 140 mg/m² per day dose, 15 (62%) occurred in 11 patients at the 100 mg/m² per day dose, and 4 (17%) occurred in 3 patients at the 60 mg/m² per day dose. Five patients withdrew from the study because of NCI grade 3 or 4 toxic events.

Seven serious adverse events assessed as being possibly, probably, or definitely related to the study drug were recorded in 5 (9%) of 57 patients. Two patients developed pancreatitis associated with hypertriglyceridemia while receiving 140 mg/m² per day of oral 9-cis-retinoic acid. One patient recovered fully; the other patient eventually died of disseminated aspergillosis, a complication that was not related to the study drug. A third patient developed moderately severe hypercalcemia and mild renal insufficiency while receiving 100 mg/m² per day of the study drug. The 9-cis-retinoic acid treatment was discontinued, and after the patient received intravenous hydration, his electrolyte values quickly returned to normal. He declined to be rechallenged with study drug and withdrew from the protocol. A fourth patient complained of asthenia and shortness of breath and was markedly anemic while receiving 100 mg/m² per day of 9-cis-retinoic acid. A fifth patient had a severe headache while taking 60 mg/m² per day of the study drug and required parenteral narcotics before his headache improved.

Oral candidiasis and herpes simplex were the most common infections recorded during the study, occurring in 11 (19%) of 57 patients and 6 (11%) of 57 patients, respectively. Single instances of bacterial pneumonia, Mycobacterium intracellulare bacteremia, enteramoebiasis, and Clostridium difficile colitis were diagnosed in 4 individuals.
There were 3 deaths during the study, but in no instance was 9-cis-retinoic acid implicated as the cause of death in these events. One patient died from complications of disseminated aspergillosis 64 days after discontinuing treatment with the study medication. A second patient with large bilateral pleural effusions died from respiratory complications 72 days after his last dose of 9-cis-retinoic acid. A third patient, also with large pleural effusions and hypoxia, died 1 day after discontinuing 9-cis-retinoic acid treatment.

The results of this phase 2, open-label trial indicate that 9-cis-retinoic acid capsules have moderate anti-KS activity but with substantial toxic effects at higher doses. The response rate for overall KS disease severity was 19% (11/57), and the objective response rate based on index lesion response criteria was 39% (22/57), with 1 patient with CCR and 21 patients with PR. The projected median time to response according to index lesion response criteria was 135 days, and the median duration of 9-cis-retinoic acid treatment in the study was 15.1 weeks. The response rates observed with 9-cis-retinoic acid also compare favorably with results obtained in other oral retinoid-related KS clinical trials.23-32 Furthermore, in a companion phase 2 trial of 9-cis-retinoic acid capsules nearly identical to the present study, conducted by the AIDS Malignancy Consortium32 and sponsored by the National Institutes of Health, a 37% response rate according to index lesion response criteria was achieved among 62 patients.

The precise mechanisms by which 9-cis-retinoic acid produces its antitumor effects in KS are not well de-

**Table 3. Related Adverse Events Observed With 9-cis-Retinoic Acid Treatment in 57 Male Patients**

<table>
<thead>
<tr>
<th>Adverse Event†</th>
<th>COSTART Terms</th>
<th>Mild</th>
<th>Moderate‡</th>
<th>Moderately Severe‡</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
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<tr>
<td>Headache</td>
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<td>14 (25)</td>
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<td>5 (9)</td>
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<tr>
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<td>10 (18)</td>
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<tr>
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<td>6 (11)</td>
<td>4 (7)</td>
<td>1 (2)</td>
<td>20 (35)</td>
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<td>8 (14)</td>
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<td>3 (5)</td>
<td>18 (32)</td>
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<td>7 (12)</td>
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<td>1 (2)</td>
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<td>0</td>
<td>6 (11)</td>
</tr>
</tbody>
</table>

*Using COSTART (Coding Symbols for the Thesaurus of Adverse Reaction Terms) 5 dictionary preferred terms. Adverse events shown are those occurring with at least a 10% incidence.

†Moderate and moderately severe would be listed as moderate in the National Cancer Institute (NCI) common toxicity criteria.

‡Using NCI common toxicity criteria, these terms would be listed respectively as Dermatol (Scaling), Cardiovasc (Dilation), Dermatol (Dry lips), Neurology (Asthenia), Dermatol (Hair), and Dermatol (Dry mouth). All other terms are the same as in COSTART 5.

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pressive nature of 9-cis-retinoic acid therapy. Other problems that have been occasionally associated with retinoids, including hypercalcemia, depression, thyroid dysfunction, and alopecia occurred rarely with 9-cis-retinoic acid capsules.24,36

For patients with KS, quality-of-life assessments may reflect, among other things, chronic pain control, physical appearance, and functional disability. In the present study, 82% of enrolled patients (47/57) felt that 9-cis-retinoic acid contributed favorably to their quality of life as assessed both by their overall sense of well-being and their level of satisfaction with physical appearance. This response is in contrast to the finding that 93% (33/35) had a drug-related adverse event and 37% of the patients (21/57) had to be removed from the study because of medication-associated toxic effects. This may be explained in part by most of the adverse events being in the mild to moderate range of severity.

A recent analysis of the ACTG KS staging classification suggested that patients with impaired immune response as reflected by a CD4+ count lower than 150 cells/µL had a diminished survival and presumably a lesser capacity to respond to therapeutic interventions.22 However, the results of the present study suggest that the antitumor activity of 9-cis-retinoic acid was independent of the CD4+ cell count. Patients who began the study with a CD4+ count of 150 cells/µL or lower were as likely to respond to 9-cis-retinoic acid as those with more than 150 cells/µL.

Two difficulties with the present study’s findings on the antitumor effects of 9-cis-retinoic acid on KS is that changes in HAART were not adequately controlled for, and HIV viral loads were not uniformly obtained. Importantly, HAART has been associated with a significant decline in the incidence of opportunistic infections and KS in patients with AIDS, and emerging data indicate that this is due in large part to reconstitution of an impaired immune system.35,37 Anecdotal reports suggest that HAART can lead to KS regression,38,39 which may also help explain why the incidence of newly diagnosed KS appears to be on the decline.40,41

A preliminary report involving 13 patients with AIDS-related KS with effective suppression of HIV replication has important clinical implications for KS treatment.41 Before initiation of HAART, these patients received 1 or more systemic therapies for severe KS for a median of 8 months. After the initiation of effective antiretroviral therapy, their median HIV viral load was reduced from about 43,000 copies/mL to nondetectable levels, and their median CD4+ cell count increased from 79 to 180 cells/µL. While undergoing HAART, none of the 13 patients experienced progression of KS despite having discontinued KS therapy for a median of 10 weeks (range, 0-41 weeks).41 By maintaining an adequate immune response in patients, HAART may prevent the recurrence of KS in patients with HIV or may delay or inhibit the progression of KS.

When the present study of 9-cis-retinoic acid was initiated, the importance of HAART was not fully appreciated, HIV viral load monitoring was not routinely available, and a laboratory test for peripheral blood HIV viral quantification was not the standard of care. Consequently, the intermediate and long-term effects of HAART regimens or HIV viral load on KS response to treatment with 9-cis-retinoic acid capsules were not protocol-defined analyses. The number of antiretroviral agents patients were taking and their CD4+ cell counts were not correlated with tumor responsiveness in the present study, but these may be poor surrogates for HIV viral load. Nonetheless, it seems unlikely that the benefits of HAART therapy alone can explain the antitumor responses in the present study because responses were observed in patients with low CD4+ counts, poor risk by tumor in situ stage, 3 or more antiretroviral therapies, and (when limited data were available) elevated HIV viral loads.

Although the advances in HIV management are likely to benefit patients at all stages of HIV infection, including those patients with KS, the prospect of long-term management of KS raises therapeutic challenges. 9-cis-retinoic acid capsules seem nonimmunosuppressive and have moderate antitumor activity in patients with AIDS-related KS. In the present study, responses were durable and were achieved in patients for whom previous topical and systemic therapies had failed. Although limited data suggest that the antitumor effects seen in patients who took 9-cis-retinoic acid capsules occurred independent of baseline CD4+ cell counts and concomitant antiretroviral therapy, these findings should be interpreted with caution in light of recent studies indicating an important effect of HAART in indirectly modulating the growth of KS lesions. Furthermore, therapy-related adverse effects limit this particular formulation and dosing scheme of 9-cis-retinoic acid as a long-term oral strategy for the treatment of AIDS-associated KS.

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19. Food and Drug Administration.


