AIDS-related Kaposi’s Sarcoma: A Phase II Study of Liposomal Doxorubicin

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ABSTRACT
TLC d-99 is a unique liposomal formulation of doxorubicin that consists of phosphatidyl choline/cholesterol. The objectives of the study were to evaluate safety and efficacy of two doses of TLC d-99 in the treatment of patients with AIDS-related Kaposi’s Sarcoma (KS). Forty HIV-infected persons with biopsy-proven KS were randomized to receive TLC d-99 at doses of either 10 (low) or 20 (high) mg/m² every 2 weeks. Patients assigned to the low-dose arm could be escalated to the high-dose arm if their KS progressed after 3 cycles of therapy. Median age was 35 years (range, 26–47) and median CD4 count was 13 (range, 0–440). Nineteen patients were assigned to receive the low dose, and 21 patients were assigned to the high dose. Partial response occurred in 15% (6 of 40) of the patients or in 5% (1 of 19) and 24% (5 of 21) in the low- and high-dose arms, respectively; stable disease was observed in 65% (26 of 40) or in 68% (13 of 19) and 62% (13 of 21) in the low and high doses, respectively. Neutropenia was the major toxicity and was observed in 68% and 81% of patients with the low- and high-dose arms, respectively; grade 4 neutropenia was observed in 16 and 14%, respectively. Mild alopecia was noted in only 8%. Therefore, TLC d-99 is active against AIDS-related KS, and the response is dose-dependent.

INTRODUCTION
KS⁴ is the most common neoplastic complication associated with AIDS. Early in the earlier epidemic, it affected more than one-third of the patients with HIV infection (1). Its treatment depends on the extent and the severity of the disease (2). For many patients, local therapies will be appropriate, but in certain subgroups—namely, those with aggressive, rapidly progressive cutaneous disease, extensive symptomatic cutaneous lesions, or visceral diseases—systemic chemotherapy will be required.

Doxorubicin is active in treating AIDS-KS; however, as a single agent, it has an overall response rate of only 10–30% (3). A combination of chemotherapy agents involving doxorubicin, bleomycin, and vincristine was a frequently administered regimen at the time of this study. For most patients with KS, this regimen was associated with a response rate up to 80%. Toxicity associated with this regimen included progressive neutropenia, alopecia, nausea and vomiting, and neuropathy. While these regimens were active, they were toxic and increased the morbidity of HIV disease. They were known to have cumulative end-organ toxicities that prohibit long-term use (4, 5). In some patients, the KS disease would often eventually progress, despite ongoing therapy. In addition, some patients could not tolerate these regimens for a variety of reasons, including myelosuppression, neuropathies, nausea, and vomiting.

Liposomes, microscopic phospholipid spheres, have been shown in animal models and earlier trials in human to improve the pharmacokinetic and therapeutic indices when compared with free (conventional) formulation of the drug (6). Recent clinical studies have demonstrated the effectiveness of liposomal doxorubicin (Doxil) and daunorubicin (DaunoXome) in AIDS-related KS (7–9). However, the former may be associated often with palmer-plantar erythrodyesthesia (7), and the latter may be considered less potent on a mg-per-mg basis.

TLC d-99 is a unique formulation of doxorubicin and consists of egg phosphatidyl choline–cholesterol liposomes, less than 1 μm in size. This formulation is manufactured by a remote loading technique, which ensures its stability and reproducibility (10). Recently, a Phase I study showed this compound was well tolerated (11). We, therefore, investigated this compound as an alternative liposomal anthracycline agent and evaluated the safety and effectiveness at two dose levels in the treatment of patients with AIDS-related KS.

The abbreviations used are: KS, Kaposi’s sarcoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CI, confidence interval.
Patients and Methods

Clinical Protocol. Forty patients were enrolled at five sites (Mount Sinai Medical Center, New York, NY; Beth Israel Deaconess Medical Center, Boston, MA; Albany Medical Center, Albany, NY; New York University Medical Center, New York, NY; and Alta Bates Comprehensive Cancer Center, Berkeley, CA) from January 1995 to September 1996. Patients were required to have biopsy-proven AIDS-KS with at least 10 mucocutaneous lesions or with development of 6 or more new cutaneous lesions within the prior month or with documented visceral disease; five lesions had to be measurable. In addition, patients needed to have serological evidence of HIV infection, a Karnofsky performance score of ≥ 60%, left ventricular ejection fraction within normal limits on echocardiographic or radionuclide measurement (≥ 50%), hemoglobin level ≥ 9 g/dl, neutrophil count ≥ 1,200 cells/μl, and platelet count ≥ 75,000 cells/μl. Patients were excluded if they had received prior anthracycline therapy of more than 60 mg/m², prior liposomal anthracycline therapy, radiation therapy within 30 days before entry, or chemotherapy within 4 weeks of entry, or if they had an active opportunistic infection or a history of allergic reaction to anthracyclines or eggs. Pregnant or lactating women were excluded. Patients were also excluded for any history of significant cardiac, renal, or hepatic diseases. Informed consent was obtained from all of the patients, and institutional review boards of the participating centers approved the protocol.

The number of mucocutaneous lesions was recorded at baseline and at each subsequent visit. Five cutaneous indicator lesions were prospectively identified by investigators and were assessed for thickness, nodularity, color, size, pain, and edema at entry into the study and every 2 weeks thereafter; the Karnofsky performance status was assessed on the same schedule. Endoscopic evaluation for visceral (pulmonary or gastrointestinal) AIDS-KS was routinely performed as indicated.

Response Criteria. The first major objective of the study was to determine responses to the study drug TLC-99, which were assessed using the criteria established by the ACTG (12). Patients receiving more than two doses were considered assessable for response. The definitions and criteria for each response are as follows:

CR was defined as the absence of any detectable residual disease, including tumor-associated edema. For patients with pigmented (brown or tan) macular skin lesions that persisted after an apparent CR, a biopsy was performed on one representative lesion to document the absence of malignant cells. Patients known to have visceral disease were evaluated with appropriate endoscopic or radiographic procedures, and no evidence of AIDS-KS was found. The response was required to persist for at least 4 weeks.

PR was defined as the absence of new cutaneous or oral lesions, of new visceral sites of involvement, or of the appearance or worsening of tumor-associated edema or effusions. In addition, at least one of the following applied: (a) a 50% or greater decrease in the number of all of the previously existing skin lesions lasting for at least 4 weeks; (b) a complete flattening of ≥ 50% of all of the previously raised skin lesions; and/or (c) a 50% decrease in the sum of the products of the largest perpendicular diameters of prospectively selected indicator skin lesions. The response was required to persist for at least 4 weeks.

SD was defined as any response not meeting the criteria for CR, PR, or PD.

PD was defined as any one or more of the following: (a) new visceral sites of involvement, or progression of visceral disease, i.e., an increase in lesions or effusion on chest radiograph, or increase in size or number of gastrointestinal lesions seen on endoscopy; (b) the development of new or increasing tumor-associated edema or effusion that lasted at least 1 week and interfered with the patient’s normal activities; (c) a 25% increase in the number of skin lesions; (d) a change in the character of > 25% of all of the previously “flat” skin lesions to “raised” skin lesions, i.e., > 25% of previously macular skin lesions becoming nodular or plaque-like; and (e) a 25% increase in the sum of the products of the largest perpendicular diameters of the indicator skin lesions.

The second major objective of the study was to determine the toxicities of the study therapy. Modified ACTG criteria were used to assess toxicities.

Treatment Regimen. Eligible patients were randomly assigned to receive TLC-99 at doses of either 10 or 20 mg/m² every 2 weeks. TLC-99 was administered as a continuous i.v. infusion over a period of 1 h into a free-flowing line. Therapy could be delayed for up to 14 days for grade 3 toxicity other than granulocytopenia. Objective tumor response and clinical benefits were assessed every 2 weeks within the 48 h before drug administration. Colony stimulating factors were prescribed at the discretion of the investigators. Those patients assigned to the 10-g/m² treatment group were permitted to be escalated to the 20-g/m² group if their KS progressed after 3 cycles of treatment. TLC-D99 was supplied by Liposome Company Inc. (Princeton, NJ).

Participants were assessed for response to treatment and treatment-related toxicity before each dose of study therapy. Medical history (especially that related to potential adverse events), complete blood cell counts, and serum chemistry analyses were obtained at each treatment visit. Other clinical or laboratory evaluations were performed as deemed necessary by the investigators. Follow-up left ventricular ejection fraction studies (either by radionuclide scanning or by echocardiogram) were required prior to the next cycle after receiving lifetime cumulative doxorubicin doses of 300 mg/m² and of 400 mg/m² and at the end of the study.

Results

Patient Characteristics. Forty patients with extensive KS were enrolled; the clinical characteristics at entry are listed in Table 1. They were all either homosexual or bisexual men. Median age was 35 (range, 26–47 years old). The majority had poor immune function with 65% of the patients with CD4 lymphocyte count less than 50 cells/μl and a median CD4 count of 13 cells/μl (range, 0–440). Visceral KS was documented by endoscopic examination in 28 patients (70%); sites of involvement included the lung in 15, the gastrointestinal tract in 7, and...
both sites in 6 patients. Twenty patients (50%) had received prior systemic chemotherapy. No patient, except one, had received protease inhibitors during the conduct of this study.

All forty of the patients were evaluable. Nineteen patients were randomized to receive 10 mg/m², and 21 were randomized to receive 20 mg/m². There were no differences between these two groups with respect to the median age, CD4 counts, Karnofsky performance score, and baseline laboratory tests.

The median cumulative doses of TLC d-99 during the study were 110 mg/m² (20–340 mg/m²), 93 mg/m² (20–260 mg/m²), and 126 mg/m² (40–340 mg/m²) for the whole group, for the lower-dose arm, and for the higher-dose arm, respectively. Ten patients (53%), randomized to receive 10 mg/m², had their doses increased to 20 mg/m² after their KS progressed after three cycles of treatment with the lower dose.

PR occurred in 15% (6 of 40; 95% CI, 6–30%), or in 5% (1 of 19) and 24% (5 of 21) in the low- and high-doses arms, respectively. SD was observed in 65% (26 of 40; 95% CI, 48–79%), or in 68% (13 of 19) and 62% (13 of 21) in the low- and high-doses arms, respectively. Ten patients (53%), randomized to receive 10 mg/m², had their doses increased to 20 mg/m² after their KS progressed after three cycles of treatment with the lower dose.

Hematological toxicity is shown in Table 4. Overall, neutropenia was the most common adverse event (75%). Six patients (15%) were noted to have neutrophil counts of less than 500 cells/µl with three on each arm. Anemia was noted in 30% of patients. However, only one patient each from the low- (5%) and high-dose (5%) arm was noted to have hemoglobin of less than 7 g/dl. Only mild thrombocytopenia was reported in 20% of the patients.

Decreases of cardiac ejection fraction from 58% to 44% and from 65% to 46% were noted in two patients who received the study drug at lifetime cumulative doses of 80 mg/m² and 180 mg/m², respectively. None of these patients developed clinical or radiological evidence of loss of cardiac function. However, no significant cardiac ejection fraction changes were noted at other cumulative doses nor at cumulative doses of more than 201 mg/m². None of our patients had received a total cumulative dose of more than 400 mg/m² of TLC d-99.

DISCUSSION

The findings of this open-label randomized comparative trial demonstrate that TLC d-99 is effective in patients with advanced AIDS-KS. This study also suggests that there may be a dose-response relationship, with 20 mg/m² more effective than 10 mg/m². Because half of our patients had received prior chemotherapy, our findings imply that this new agent is active in both chemotherapy-naïve and chemotherapy-experienced patients.

Response rates are difficult to compare across published studies because of different study populations, and different criteria for assessing response are either not described in detail or vary between studies. It is important to point out that close to 40% of our study population were either Afro-American or Hispanic, compared with only 10% in most of the other liposomal anthracycline studies. These ethnic groups traditionally have difficulty in accessing HIV care and do worse with HIV infection (13, 14). In addition, they generally do less well with neoplastic diseases (15, 16).

However, responses were seen in both cutaneous and visceral diseases. Cutaneous lesion had to have either flattened or disappeared. Responses in visceral diseases had to be documented by endoscopy. Endoscopic evaluation for visceral AIDS-KS was not routinely performed in the reported studies with pegylated-liposomal doxorubicin (Doxil; Ref. 17–21). It is possible that their studies may overestimate tropic fever was reported among 15% of the group; however, it occurred on only the higher-dose arm. Minimal alopecia, thought to be drug-related, was noted in only three patients (8%).

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Treatment</th>
<th>10 mg/m²</th>
<th>20 mg/m²</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>19</td>
<td>21</td>
<td>40</td>
</tr>
<tr>
<td>Age: median (range)</td>
<td>36 (29–45)</td>
<td>34 (26–47)</td>
<td>35 (26–47)</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>10 (53%)</td>
<td>15 (71%)</td>
<td>25 (63%)</td>
</tr>
<tr>
<td>Black</td>
<td>8 (42%)</td>
<td>4 (21%)</td>
<td>12 (30%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (5%)</td>
<td>2 (10%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Sex: male</td>
<td></td>
<td></td>
<td>40 (100%)</td>
</tr>
<tr>
<td>Median CD4 count, cells/µl (range)</td>
<td>13 (0–271)</td>
<td>23 (0–440)</td>
<td>13 (0–440)</td>
</tr>
<tr>
<td>Prior treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>5 (13%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>20 (50%)</td>
<td></td>
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</tr>
<tr>
<td>IFN</td>
<td>7 (18%)</td>
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</tbody>
</table>

Table 2 Responses by treatment group

<table>
<thead>
<tr>
<th>Treatment</th>
<th>10 mg/m²</th>
<th>20 mg/m²</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>5</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>Response to treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>1 (5)</td>
<td>5 (24)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>SD</td>
<td>13 (68)</td>
<td>13 (62)</td>
<td>26 (65)</td>
</tr>
<tr>
<td>PD</td>
<td>2 (11)</td>
<td>0 (0)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>3 (16)</td>
<td>3 (14)</td>
<td>6 (15)</td>
</tr>
</tbody>
</table>
the reported response. On a weight basis, this product appears to be as active as pegylated-liposomal doxorubicin and more potent than liposomal daunorubicin (DaunoXome), which requires 40 mg/m² to achieve comparable response (9). It is worth noting that our compound was also active in 10 patients at the lower dose of 10 mg/m² of doxorubicin.

The toxicity is acceptable and easily manageable. Our toxicity profile is consistent with the result of the earlier Phase I study reported by Cowens et al. (11). All hematological toxicity can be managed easily with growth factors, e.g., filgrastim (granulocyte colony stimulating factor, G-CSF) for leukopenia, and erythropoietin for anemia. Toxicities that often accompany doxorubicin-containing combination chemotherapy for AIDS-KS are alopecia, nausea, and vomiting. Although usually not of serious medical consequences, these toxicities are important to the individual’s quality of life. The incidence of alopecia was 8% in our study cohort. Nausea and vomiting occurred in 13% of patients and was not severe in any patient.

Overall, TLC d-99 appeared to be well tolerated. Of note, acute infusion-related reactions, which were characterized by flushing, chest pain, dyspnea, difficulty in swallowing, hypotension, and/or back pain, as well as rashes and palmar-plantar erythrodyesthesia have been reported with pegylated-liposomal doxorubicin (17–21). However, these reactions have not been reported with TLC d-99.

A long-term potential toxicity of doxorubicin is the development of anthracycline-induced cardiomyopathy. Although no cardiac toxicities were noted in our patients, no firm conclusions can be drawn from this study given the relatively low cumulative doses.

A preliminary randomized study of this drug versus doxorubicin for metastatic breast cancer showed none of 69 patients on the TLC d-99 arm (mean cumulative dose, 394

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Fig. 1 Progression-free survival time.

![Graph showing progression-free survival time](image1)

Fig. 2 Duration of response.

![Graph showing duration of response](image2)
remained active throughout the study as indicated by a lack of advanced immunodeficiency and AIDS-KS. In addition, patients on the doxorubicin arm (mean cumulative dose, 366 mg/m²) developed congestive heart failure, whereas 3 of 75 patients (mean cumulative dose, 366 mg/m²) developed congestive heart failure (P < 0.004; Ref. 22).

The median duration of response of 7.2 months suggests that this liposomal doxorubicin can provide benefit during a significant portion of the remaining life of patients with advanced immunodeficiency and AIDS-KS. In addition, patients remained active throughout the study as indicated by a lack of decline in Karnofsky performance scores.

In conclusion, the response rates of TLC d-99 in this group of patients with other multiple chronic medical problems are encouraging and comparable with those of other liposomal anthracyclines (7, 9, 17–21). However, our present report involved only a limited number of subjects. Further study is needed to expand our experience with this drug. Comparative studies of TLC d-99 versus other liposomal formulations of anthracyclines are also needed.

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