Phase I Study of Human Chorionic Gonadotropin Given Subcutaneously to Patients With Acquired Immunodeficiency Syndrome-Related Mucocutaneous Kaposi’s Sarcoma

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Background: In vitro and in vivo clinical studies have shown that certain preparations of human chorionic gonadotropin have antitumor activity against Kaposi’s sarcoma, the most common tumor in patients infected with human immunodeficiency virus type 1 (HIV-1). Methods: A phase I trial was conducted in 18 male patients with acquired immunodeficiency syndrome-related Kaposi’s sarcoma. Successive cohorts of six patients each received human chorionic gonadotropin (A.P.L.; Wyeth-Ayerst, Radnor, PA) subcutaneously at doses of 5000 IU daily (level I), 10,000 IU three times a week (level II), or 10,000 IU daily (level III). Toxic effects, changes in reproductive hormone plasma levels, HIV-1 RNA plasma levels, and response to therapy were evaluated. Results: A.P.L. treatment was well tolerated at all dose levels, and no maximum-tolerated, dose-defined toxic effects were observed at the highest dose tested. The most common side effects were weight gain, increased libido, and increased energy. A persistent increase in testosterone level and a persistent decline in luteinizing hormone and follicle-stimulating hormone levels were seen over time. Major responses were observed in six patients.

Partial remissions (≥50% decrease in lesion numbers, volume, or surface area) were observed at dose level I and dose level II (two patients each); biopsy-confirmed complete remissions (resolution of all lesions) were observed at dose level III (two patients). All but one major response have persisted from 207 to more than 515 days. Nine patients had stable disease lasting 10 weeks or longer. Conclusions: A.P.L. given at daily doses ranging from 5000 to 10,000 IU has antitumor activity in patients with acquired immunodeficiency syndrome-related Kaposi’s sarcoma. A.P.L. can be given for more than 1 year with minimal side effects. Larger efficacy studies are warranted. [J Natl Cancer Inst 1997;89:1797–1802]

Kaposi’s sarcoma (KS) is the most common tumor in patients with the acquired immunodeficiency syndrome (AIDS) (1,2). Current therapeutic options for patients with AIDS-related KS are only palliative and include radiotherapy, treatment with interferon alfa, and systemic chemotherapy (3–9). Toxic side effects limit the usefulness of chemotherapy and interferon alfa, particularly when they are given concurrently with antiretroviral agents (5,9). Therefore, other drugs are needed for the treatment of patients with AIDS-related KS.

AIDS-related KS occurs in more than 30% of homosexual males compared with only 3% of women (10). Lunardi-Iskandar et al. (11) showed that KS malignant cell growth is blocked in pregnant mice during the early stage of pregnancy. In vitro and in vivo studies using sera from pregnant women and commercial preparations of human chorionic gonadotropin (hCG) revealed similar anti-KS effects (11). Highly purified or recombinant hCG heterodimers, however, do not display antitumor effects. The active commercial preparations contain hCG and some factor(s) associated with it, which are not yet completely characterized. In a study of the in vitro effects of various available commercial preparations against a malignant KS cell line, the most active preparation found was A.P.L. (Wyeth-Ayerst Laboratories, Radnor, PA) (12). A.P.L. was then evaluated in 36 patients with AIDS-related KS (12). IntraleSIONAL injections of A.P.L. were shown to be active in a dose-dependent manner (12).

On the basis of the positive findings in preclinical studies and human trials, we hoped to determine if A.P.L. had systemic antitumor activity in patients with AIDS-related KS. We also wished to determine the association between HIV viral load and antitumor activity. We thus performed this phase I study of A.P.L. given subcutaneously to patients who generally had early stage AIDS-related KS that was limited to cutaneous and mucocutaneous lesions. hCG is known to induce high testosterone levels and to inhibit levels of follicle-stimulating hormone and luteinizing hormone. These hormones were monitored during the administration of A.P.L. at different dosages and scheduling during this trial to compare dose-related effects.

Subjects and Methods

Patients

Patients with serologic evidence of human immunodeficiency virus type-1 (HIV-1) infection and biopsy-proven KS with at least three nodular cutaneous lesions were accrued. The study was approved by the Institutional Review Board of the Los Angeles County–University of Southern California Medi-
cal Center. All patients gave written informed consent prior to entry in the study. Eligibility criteria included the following: age greater than 18 years; adequate hepatic, renal, and bone marrow function (absolute granulocyte count >750/mm³ and platelet count >75 000/mm³); Karnofsky performance status score of 50% or above; no acute infection; no previous cancer other than KS; no prior treatment with radiotherapy, systemic cytotoxic chemotherapy, interferon alfa, or other immune response modifiers for AIDS-related KS within 2 weeks of entry into the study; and evidence of active or progressive KS after the immediately preceding therapy before entry into this study. Lesions that were previously treated by radiation or other local therapies and that were considered to be equivocal were not included in these assessments.

**Study Design**

Our previous study (12) tested only intraliesional (direct injection into the lesion) activity of hCG. The hCG preparations were injected in only two lesions, and only six injections were given during a period of 2 weeks. This controlled study compared effects of hCG and placebo in early disease. The current study differs considerably from the previous study (12) in dose, duration, and route of administration of hCG.

In this phase I dose-escalation trial, six consecutive patients each were treated with A.P.L. at 5000 IU daily (level I), 10 000 IU three times a week (level II), or 10 000 IU daily (level III). No further dose escalation was planned because of limitations in the volume of diluent needed to dissolve higher doses of the drug. The manufacturer of A.P.L. suggested preparation of hCG at concentrations of 1000 IU/mL. We could, however, prepare hCG solutions at concentrations as high as 10 000 IU/mL. More concentrated preparations could not be prepared because of the limited solubility of hCG. This situation prevented administering hCG at higher doses. A.P.L. was freshly reconstituted and administered immediately to avoid potential inactivation of the active substance in the preparation.

The therapy consisted of subcutaneous injections of A.P.L. given daily or three times a week until a cumulative duration of prior KS was 7 months (range, 1–48 months; Table 1). The majority of patients had limited KS; only two patients had more than 50 mucocutaneous lesions at study entry. Two patients (11%) had lymphedema. Six patients (33%) had prior opportunistic infections: Three had Pneumocystis carinii pneumonia, one had cryptococcal meningitis, and two had multiple prior opportunistic infections. Seven (39%) of 18 patients reported tumor-related ‘‘B’’ symptoms (i.e., fever, night sweats, or weight loss) prior to study entry. Eleven patients (61%) had a CD4 T-cell count of fewer than 200 cells/mm³ (Table 2). The median viral load at baseline was 25 364 copies/mL (range, 661–130 040 copies/mL). Four patients (22%) were given a nucleoside analogue alone, 10 patients (56%) were given a nucleoside analogue plus a protease inhibitor, and four patients (22%) were on no anti-HIV medication at baseline. Anti-HIV therapy was continued until tumor response was achieved. Six of 18 patients had changes in their anti-HIV therapy during this trial. Prior to this trial, 11 of 18 patients received different anti-KS therapies, which included cys-totherapy, radiation therapy, chemotheraphy, and immunotherapy. Three of 18 patients received intraliesional (hCG) therapy at dose levels of 2000 IU three times weekly prior to this trial.

**Side Effects**

The subcutaneous injections of A.P.L. were generally well tolerated. Although mild side effects were seen (Table 3), no maximum tolerated dose-defining toxic effects occurred at any dose level studied. Therefore, no maximum tolerated dose could be defined. The most common side effects were positive, consisting of the following: weight gain in 15 patients.

**Results**

**Study Patients**

Eighteen homosexual and bisexual men (median age, 39 years; range, 29–56 years) were enrolled in the study (Table 1). There were 12 Caucasians, four Hispanics, one African-American, and one Asian. No patient had symptomatic visceral KS. The lesions were limited to the skin and/or mucous membranes. The median duration of prior KS was 7 months (range, 1–48 months; Table 1). The majority of patients had limited KS; only two patients had more than 50 mucocutaneous lesions at study entry. Two patients (11%) had lymphedema. Six patients (33%) had prior opportunistic infections: Three had Pneumocystis carinii pneumonia, one had cryptococcal meningitis, and two had multiple prior opportunistic infections. Seven (39%) of 18 patients reported tumor-related ‘‘B’’ symptoms (i.e., fever, night sweats, or weight loss) prior to study entry. Eleven patients (61%) had a CD4 T-cell count of fewer than 200 cells/mm³ (Table 2). The median viral load at baseline was 25 364 copies/mL (range, 661–130 040 copies/mL). Four patients (22%) were given a nucleoside analogue alone, 10 patients (56%) were given a nucleoside analogue plus a protease inhibitor, and four patients (22%) were on no anti-HIV medication at baseline. Anti-HIV therapy was continued until tumor response was achieved. Six of 18 patients had changes in their anti-HIV therapy during this trial. Prior to this trial, 11 of 18 patients received different anti-KS therapies, which included cys-totherapy, radiation therapy, chemotheraphy, and immunotherapy. Three of 18 patients received intraliesional (hCG) therapy at dose levels of 2000 IU three times weekly prior to this trial.
(83%) with more than a 10-pound weight gain in nine of the patients (50%), increased libido in nine patients (50%), increased energy in eight patients (44%), and increased appetite in seven patients (39%). Other side effects, including insomnia, bloating, gynecomastia, and mood swings, were all uncommon and did not appear to be dose related. No hematologic toxicity or biochemical abnormality was seen in any of the 18 patients. A persistent increase in serum testosterone level was observed in 15 patients (94%) of 16 patients. Nine (56%) of 16 patients showed more than a 100% increase in testosterone levels, and four patients (25%) showed more than a 50% increase in testosterone levels compared with baseline measurements. Persistent declines in follicle-stimulating hormone and luteinizing hormone levels were seen in 14 (88%) and 13 (81%) of 16 patients, respectively. These effects are consistent with biologic effects of hCG, but they did not appear to be dose related because they were seen at all dose levels.

**KS Response and Association With HIV Parameters**

At dose level I, a major response was observed in two patients, both of whom achieved partial remission (Table 1). The disease in one responder progressed after 207 days on therapy; the other patient remains on therapy and in partial response for 210+ days after the onset of remission. Both patients remain in complete remission off treatment for 210+ and 310+ days, respectively. Two patients treated at this dose level had stable disease lasting 71 and 77 days. The remaining two patients had disease progression within 60 days.
Overall, the major response rate (complete remission plus partial remission) was 33% (complete remission in two patients; partial remission in four). Nine patients had stable disease lasting 10 weeks or greater. Of these 15 patients, two currently remain on therapy. Only three of the six major responders had a CD4+ T-cell count of more than 200 cells/mm³ at baseline (Table 2), and there was no significant difference between a response to baseline (range, 3673–113 873 copies/mL) at baseline (Table 1). Similarly, there was no relation between response to treatment and protease inhibitor (P = .63). Four of the six responders were on a protease inhibitor (i.e., crixivan or norvir) at baseline (Table 1). Similarly, there was no relation between response to treatment and protease inhibitor (P = .64). The remaining two responders showed a partial remission prior to starting protease inhibitor (at 8 and 29 weeks, respectively). The median HIV plasma level in responders was 7856 copies/mL (range, 3673–113 873 copies/mL) at baseline. Two responders showed a one log decline or higher in viral load while on therapy; both of these responders were on protease inhibitors at baseline.

### Discussion

Commercial preparations of hCG have shown activity in preclinical and early clinical trials in patients with AIDS-related KS (11,12,16). We prospectively studied the most active commercial preparation of A.P.L. to be given systemically as a subcutaneous injection. Long-term use of A.P.L. at doses ranging from 5000 IU to 10 000 IU daily or three times weekly was well tolerated in this patient population. Dose-limiting toxicity was not observed at any of the dose levels studied. No further dose escalations were planned, however, because of limitations in the volume of diluent needed to dissolve higher doses of drug. At the dose levels studied, we observed no hematologic toxic effects and only minimal side effects. Also, the drug could be given for prolonged periods without apparent cumulative toxicity. The most severe side effect observed was the development of gynecomastia, which was observed in only one patient. Gynecomastia, however, is a known side effect of hCG, resulting from binding to luteinizing hormone re-

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### Table 2. CD4+ and CD8+ lymphocyte counts* and HIV RNA by PCR,† at baseline, at week 8, at maximal count, and at last evaluation‡

<table>
<thead>
<tr>
<th>Dose level</th>
<th>CD4+</th>
<th>CD8+</th>
<th>HIV RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I, 5000 IU daily</td>
<td>387</td>
<td>2917</td>
<td>10.327</td>
</tr>
<tr>
<td>Level II, 10 000 IU daily</td>
<td>42</td>
<td>483</td>
<td>45.688</td>
</tr>
<tr>
<td>Level III, 10 000 IU daily</td>
<td>213</td>
<td>1412</td>
<td>51.22</td>
</tr>
<tr>
<td>Week 8</td>
<td>3</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Maximal count</td>
<td>4</td>
<td>23</td>
<td>445</td>
</tr>
<tr>
<td>Last evaluation</td>
<td>7</td>
<td>486</td>
<td>1828</td>
</tr>
</tbody>
</table>

*CD4-positive T-cell counts = numbers/min³ blood; CD8-positive T-cell counts = numbers/mm³ blood.
†HIV RNA was expressed as copies/mL of plasma.
‡Month 3.
§Month 4.

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### Table 3. Side effects of A.P.L. therapy in patients with Kaposi’s sarcoma

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Level I, 5000 IU daily (n = 6)</th>
<th>Level II, 10 000 IU three times weekly (n = 6)</th>
<th>Level III, 10 000 IU daily (n = 6)</th>
<th>Total (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>15 (83)</td>
</tr>
<tr>
<td>Increased libido</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>9 (50)</td>
</tr>
<tr>
<td>Increased energy</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>8 (44)</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Bloating</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Mood swings</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Night sweats</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Cravings</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Headaches</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>
ceptors in Leydig cells and stimulating increased production of estradiol (17).

Another notable effect was the persistent increase in serum testosterone levels. In addition, there were even more dramatic decreases in follicle-stimulating hormone and luteinizing hormone levels, which became persistently low or nondetectable shortly after therapy was started. These data are consistent with those previously reported with both intralesional and intramuscular injections of hCG. The increase in testosterone levels may be responsible for many of the positive side effects, including increased appetite and weight gain, occurring in 39% and 83% of the case patients, respectively. These side effects may be particularly desirable in conditions such as AIDS-related wasting.

Complete or partial tumor regression was seen at all dose levels and occurred in 33% of the case patients overall. Both complete responses occurred at the highest dose level of 10 000 IU per day. Nine additional patients (50%) had stable disease for 2 months or longer. Two patients have had stable disease to beyond 1 year each. Neither patient developed new lesions during the period of stable disease; both had tumor regression that, however, did not fulfill the criteria for a major response. Stable disease of prolonged duration in AIDS-related KS is particularly important. To our knowledge, this is one of the first trials in which a substantial number of patients have achieved a response or their disease has remained stable for prolonged periods without significant drug toxicity.

We have examined various parameters that may influence or confound treatment response. These parameters include baseline CD4+ T-cell count, concurrent use of protease inhibitors, HIV plasma RNA levels, and changes in these parameters over time. Baseline CD4+ T-cell count did not predict for response; three of six responders had a CD4+ T-cell count below 200/mm^3. Moreover, while tumor response occurred more commonly in patients receiving protease inhibitors (four of six in this study), the majority of patients on protease inhibitor (six of 10) did not achieve a major response. More importantly, only two of these four responders on a protease inhibitor had declines in their viral load of one log or more while on A.P.L. Therefore, the effects of protease inhibitors and declines in HIV plasma levels upon regression of KS remain unclear. Lastly, we looked for a relationship between response and decline in viral load of one log or more prior to tumor response. It is interesting that two patients not receiving antiviral therapy showed one log or more decline in HIV plasma viremia. Thus, there may be antiviral effects, although only in a limited percentage of cases; this observation is in support of the previously reported in vitro and animal model antiviral effects of some preparations of hCG [our unpublished data; (18)]. Prospective controlled trials are needed to fully appreciate the antiviral effects of hCG preparations in humans.

We have thus shown that certain commercial preparations containing human chorionic gonadotropin-associated factor, such as A.P.L., have antitumor effects in humans. Treatment is well tolerated in immunodeficient patients receiving several other drugs. These findings support the results of a previous study conducted by Harris (16) and an unpublished study (Hermans P, Clumeck N, Picard O, Van Vooren JP, Duriez P, Zucman D, et al.; unpublished data). Harris reported major responses in six patients treated with 200 000 IU of hCG given intramuscularly, three times a week. The viral parameters were not measured, but positive side effects similar to those seen in our study were noted. Using similar doses of hCG given intramuscularly, Hermans et al. found major responses in four immunodeficient AIDS patients with visceral KS. Hermans et al. observed that viral load became undetectable in one patient while on the study drug, with no changes in antiretroviral therapy.

To our knowledge, this is the first report of subcutaneous A.P.L. being used in the treatment of AIDS-related KS. Subcutaneous injection is a more favorable route than intramuscular injection because it is less painful, is more readily accepted by patients, and is easily self-administered. Furthermore, other studies (19,20) have shown that subcutaneous administration of hCG has a similar or a prolonged serum half-life compared with intramuscular injection. In addition, the subcutaneous injections were better tolerated.

In conclusion, in this phase I study, we found that all dose levels tested were safe and had anti-KS activity. The 10 000 IU dose given daily produced the most effective responses with two complete remissions; therefore, we recommend this as a starting dose. Further monitoring to determine long-term effects of the drug is needed. Randomized studies using A.P.L. in patients with mucocutaneous KS are
warranted to define its role in the treatment of this disease. Most importantly, the identification and clinical studies of the active molecule of these preparations are needed.

References


Notes

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