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Short Communication

Human Chorionic Gonadotropin in the Treatment of HIV-related Kaposi's Sarcoma

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To evaluate the antineoplastic activity of human chorionic gonadotropin (hCG) in the treatment of HIV-related Kaposi's sarcoma (KS), two clinical trials focusing on two different schedules of administration and types of hCG preparation were conducted. In the low-dose group, hCG (Profasi-HP) was administered three times a week intramuscularly at a dose ranging from 4000 to 32 000 IU for 4 months and no objective response was observed among 5 evaluable patients. In the high-dose group, hCG (Gonadotrafon) was given intramuscularly three times a week at a dose ranging from 100 000 to 300 000 IU for 3 months with 1 partial response among 8 evaluable patients. In 6 patients evaluated for HIV viral load, no significant reduction in HIV viraemia was observed. In conclusion, hCG showed very limited activity against KS and no influence on HIV viral load, along with emerging dose-limiting toxicity and high cost of the therapy. © **1998 Published by Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

THE PREVALENCE of Kaposi's sarcoma (KS) as an indicator of acquired immunodeficiency syndrome (AIDS) has been declining since 1987. Nevertheless, KS still remains the most frequent neoplastic manifestation of AIDS in HIV-infected patients, especially in male homosexuals who have up to a 50% probability of presenting with KS in their lifespan [1–3]. Although KS is only rarely the cause of death, it is almost continually a source of major morbidity. As no cure is presently available for KS, the best therapeutic approach is still being debated, and aims mainly for palliation of symptoms. The choice among the therapeutic options (including radiation, intralesional chemotherapy, interferon, systemic cytotoxic agents) mostly depends on the stage of KS and HIV infection, pulmonary KS being a potentially life-threatening disease requiring the most aggressive approach [4].

Human chorionic gonadotropin (hCG) has been primarily investigated as a hypothetical protection factor against intrauterine transmission of HIV [5]. *In vitro* experiments have demonstrated that hCG is able to suppress reverse transcriptase activity in chronically HIV-infected lymphocytes and monocytes and to block viral transmission resulting from cell–cell contact between virus carrying lymphocytes and placental trophoblasts, such activity being mediated by the β-subunit of hCG [5, 6].

More recently, Lunardi-Iskandar and associates [7] described the activity of the β-subunit of hCG on tumorigenesis and metastasis of a neoplastic KS cell line in immunodeficient mice. To test the antitumour activity of hCG, only a few clinical trials have been conducted so far, with a limited number of patients and conflicting results [8–10]. However, recently Gill and colleagues showed that the activity of hCG could be strongly related to the commercial preparation employed [11]. Whether such clinical activity is directly related to hCG or rather to some copurified components of the preparation, remains to be investigated.

With the aim of evaluating the antineoplastic and antiretroviral activity of hCG by the systemic route in patients with KS and HIV infection, we conducted two consecutive phase I–II dose escalating clinical trials focusing on two different schedules of administration and types of commercial hCG preparation.

PATIENTS AND METHODS

Patients with serological evidence of HIV-1 infection and biopsy proven KS in any stage, with the exclusion of life-threatening disease, were enrolled in the study, between June

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1995 and June 1996, at the Division of Medical Oncology and AIDS of Aviano Cancer Centre, in Italy. Other criteria for inclusion were: age over 18 years; performance status 0–2 according to ECOG; life expectancy more than 6 months; no active or uncontrolled infection; adequate hepatic, renal and bone marrow functions (absolute granulocyte count > 750/mm^3, platelet count > 75 000/mm^3, haemoglobin > 8 g/dl; and no therapy, local or systemic, for HIV–KS during the 4 weeks before the entry into the study. The patients' characteristics at study entry are shown in Table 1.

Two consecutive phase I–II clinical trials were carried out with escalating doses of two high purified commercial preparations of hCG, produced by different companies. In trial 1 (low-dose group), hCG (Profasi-HP, Serono, Rome, Italy) was administered intramuscularly three times a week according to the following schedule: 4000 IU weeks 1–4, 8000 IU weeks 5–8, 16 000 IU weeks 9–12, 32 000 IU weeks 13–16. In trial 2 (high-dose group), hCG (Gonadotrafon, AMSA, Florence, Italy) was given intramuscularly three times a week as follows: 100 000 IU weeks 1–4, 200 000 IU weeks 5–8, 300 000 IU weeks 9–12. All concomitant treatments were allowed, with the exception of any antiretroviral therapy within 2 weeks of the start of hCG. Of note, protease inhibitors were not available at our Institution at the time of the study, and all patients had been pretreated with one nucleoside reverse transcriptase inhibitor for at least 18 months before entry into the trial. Moreover, the results of the Delta study and the AIDS Clinical Trial Group (ACTG) 175 with regard to the advantage of a combination antiretroviral regimes versus a monotherapy, were published after the design of the study and the enrolment of patients [12, 13]. Staging of KS was performed according to the ACTG criteria [14] and the New York University (NYU) staging system [15]. Response was evaluated on the basis of ACTG criteria, and toxicity was evaluated according to World Health Organization (WHO) criteria.

Plasma from 6 patients treated with high dosage hCG was collected after 15 min centrifugation of peripheral blood ethylene diamine tetraacetic acid (EDTA) samples and stored in aliquots at − 80 C° until they were analysed. HIV plasma viraemia was evaluated using a reverse transcription-polymerase chain reaction (RT-PCR) competitive approach involving co-reverse transcription and subsequent co-amplification of the sample with *in vitro* transcripted competitor RNA that had the same recognition size of the most common HIV-1 strains and similar length and base pair composition [16].

Table 1. *Patients' characteristics*

	Low-dose trial	High-dose trial
No. of patients	5	8
Median age (years, range)	42 (30–45)	38 (30–63)
Risk group		
Homobisexual	3	3
Heterosexual	1	2
Injecting drug user	1	3
HIV staging previous KS diagnosis*		
A2	–	1
A3	4	4
C3	1	3
Median CD4 count (×10^6/l) at hCG start (range)	38 (16–68)	37 (4–206)
KS staging		
NYU†	1 II, 4 III	8 III
ACTG	5 poor risk	7 poor risk, 1 good risk
Life-threatening disease	None	None
No. of pretreated patients	5	5
Type of pretreatment		
Alpha-interferon	5	4
Chemotherapy	2	1
Radiotherapy	2	2
Median time from KS diagnosis (months, range)	34 (6–60)	20 (4–55)

*Classification according to 1993 CDC classifications. †New York University staging system. ACTG, AIDS Clinical Trial Group. KS, Kaposi's sarcoma; hCG, human chorionic gonadotropin.

RESULTS

The results of the study are shown in Table 2. In the low-dose group, no objective response was observed. 4 patients progressed under treatment and the only patient with stable disease was lost to follow-up after 2 months of therapy. No dose-limiting toxicity was observed. Only one partial response was observed in the high-dose group; the patient progressed 3 months after therapy discontinuation. 5 patients progressed under treatment (after 3, 2, 1, 2, 3 months of therapy, respectively) and the remaining 2 patients with stable disease interrupted the therapy because of compliance decrease in 1 patient and possibly hCG-related toxicity in the other. The latter patient developed malaise, fatigue, ascitis, abnormal renal function and anaemia requiring hCG withdrawal during the second month of therapy. The patient died 1 month later in another institution probably because of an opportunistic infection. Similar symptoms have been previously described by other authors as possibly related to the systemic treatment with hCG [17].

In the high-dose group, 6 patients were scheduled for plasma viral load assessment. No significant changes of HIV plasma viraemia were observed during the treatment. Only 2

Table 2. *Toxicity and results*

	Low-dose trial	High-dose trial
Toxicity		
Local pain in site of injection	1	1
Increased libido	1	1
Depression	–	1
Ascitis	–	1
Median CD4 count (×10^6/l) at hCG end (range)	15 (7–68)	21 (5–110)
No. of patients evaluable for response	5	8
Response		
Complete response	0	0
Partial response	0	1
Stable disease	1	2
Progressive disease	4	5
OI during HCG therapy	None	1
Type of OI	–	1 PCP
No. of dead patients	–	2
Cause of death	–	Unknown
Cost of hCG therapy for a complete course	US$324	US$3738

OI, opportunistic infection; PCP, *Pneumocystis carinii pneumonia*; hCG, human chorionic gonadotropin.

patients showed an occasional viral reduction of 2 and 3 logs after, respectively, 7 and 30 days after the beginning of the therapy. This decline was followed by a resumption of steady state levels in spite of therapy continuation.

The cost of a complete course of hormonal therapy for each patient participating in the trial was US$324 and US$3738 for trials 1 and 2, respectively. The cost of the therapy was established in Italian lira and converted to US dollars at the time of the study.

DISCUSSION

Since Lunardi-Iskandar and associates described the activity of the β-chain of hCG on tumorigenesis and metastasis of a neoplastic KS cell line in immunodeficient mice [7], few data have been available for clinical trials. Harris obtained a 'marked tumor regression' by treating 6 patients with escalating doses of hCG (between 150 000 and 700 000 IU for each dose) intramuscularly three times a week, but neither the commercial preparations of hCG, nor the type and duration of response, nor the treatment period were reported [8]. Conversely, Bower and colleagues and Von Overbeck and associates did not show any evidence of activity of hCG by treating, respectively, 5 and 2 patients with hCG doses ranging, respectively, from 5 000 to 20 000 IU three times a week for 4–12 weeks, and 2 000 to 20 000 IU daily for 2–4 weeks [9, 10]. It has to be stressed that the latter trials were conducted at an hCG dose up to 35-fold lower than that administered by Harris. No dose-limiting side-effects were reported by Harris and Von Overbeck and associates, whereas Bower and colleagues reported various degrees of psychiatric intolerance that contributed to the trial interruption.

More recently, in a preliminary growth inhibition assay, Gill and colleagues found a difference in activity against a tumour producing KS derived cell line (KSY-1 cells), of four commercial preparations of hCG. All these preparations (including the one we administered in the low-dose group, i.e. Profasi) inhibited *in vitro*, growth of KSY-1 cells, although with a variable 50% inhibitory concentration (ranging from 40 to 100 IU/ml of hCG). Using intralesionally the commercial preparation with the most growth inhibitory activity (APL; Wyett, Ayerst) they induced dose-dependent regression and apoptotic cell death in up to 83% of the treated KS lesions [11].

In our study, particularly in the high-dose group, the systemic administration of hCG produced a β-hCG serum level up to 100-fold greater than the concentration of hCG used by Gill and colleagues in their preliminary assay. Nevertheless, in our study, hCG given by a systemic route gave disappointing results. In the low-dose group, patients were given a dose of hCG comparable with the one administered by Bower and colleagues and Von Overbeck and associates with the same negative results. However, in trial 2 (high-dose group), the dose of hCG administered after the second month of therapy (200 000 IU) was higher than the minimal effective dose, i.e. 100 000 IU defined in Harris' trial. However, of 8 evaluable patients, we observed only 1 partial response of 3 month duration, while another patient developed a marked fluid retention and requested interruption of the treatment. In trial 2, the serum level of β-hCG increased up to 10 000 mU/ml, 5-fold higher than the hCG maximum dose administered by Gill and colleagues (2000 IU by intralesional injection). Moreover, this level was remarkably higher than the 50% inhibitory concentration of hCG observed by Gill and colleagues (ranging from 40 to 100 IU of hCG/ml) in their preliminary *in vitro* assay. We suspect, as already suggested [10, 18], that the antitumour activity of hCG, if any, might not be related to the β-subunit of hCG, but rather to some unidentified and copurified components present in the commercial hCG preparation employed by Gill and colleagues, but not in ours. Recently, Albini and associates found the β-core fragment of hCG to be the growth inhibitor factor with the most potent activity on KS immortal and spindle cells [19]. Such a molecule could represent an attractive basis for designing future clinical trials.

In conclusion, hCG showed very limited activity against KS and no activity on HIV viral load in our study, along with emerging dose-limiting toxicity and high cost of therapy. We think that the identification, characterisation and standardisation of purification procedures of the hCG components with the most antitumour activity are needed before beginning other clinical trials.

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