REVIEW ARTICLE

Drug Safety 1999 May; 20 (5): 403-425
0114-5916/99/0005-0403/$11.50/0



# A Risk and Benefit Assessment of Treatment for AIDS-Related Kaposi's Sarcoma

*Guglielmo Nasti, Domenico Errante, Sandra Santarossa, Emmanuela Vaccher* and *Umberto Tirelli*

Division of Medical Oncology and AIDS, Centro di Riferimento Oncologico, Aviano, Pordenone, Italy

## Contents



## Abstract

Kaposi's sarcoma is the most common malignancy observed in patients with HIV-1 infection, and causes considerable morbidity and, when the lungs are involved, mortality. Therapy should be based on an evaluation of prognostic factors, in particular the extent and rate of tumour growth, patient symptoms, immune system condition and concurrent complications of AIDS. Nevertheless, considering the palliative role of Kaposi's sarcoma therapy, the potential benefits of therapy must be weighed against the high risk of adverse effects. Therefore, quality of life assessment is an integral component of therapeutic decisions.

Localised Kaposi's sarcoma cutaneous tumours have been successfully treated with surgical excision, laser therapy, liquid nitrogen cryotherapy and radiotherapy. In patients with moderately extensive cutaneous or mucosal disease and

CD4+ cell counts of ≥200/ml, immunotherapy and antiretroviral drugs are indicated. Preliminary results indicate that antiretroviral therapy might be effective and well tolerated in the treatment of less advanced Kaposi's sarcoma.

In patients with aggressive and extensive mucocutaneous disease or with visceral manifestations of Kaposi's sarcoma, systemic cytotoxic therapy is indicated. However, the optimal treatment has yet to be found. The combination of doxorubicin, bleomycin and vincristine (ABV) has produced high overall response rates and is indicated as first-line treatment for patients with life-threatening or visceral disease. In patients who are leucopenic and require chemotherapy, single or dual agents associated with lower myelotoxicity [i.e. bleomycin, vincristine/vinblastine or a combination of bleomycin and vincristine/vinblastine (BV)] are most widely used. Other effective cytotoxic regimens are liposomal anthracyclines, paclitaxel and vinorelbine. To date, 3 randomised trials have compared these drugs to ABV and BV. In a large phase III study, the efficacy of liposomal daunorubicin was comparable with that of ABV. In 2 phase III studies, liposomal doxorubicin was compared with ABV and BV regimens and was found to be significantly more effective in producing objective responses. Therefore, liposomal doxorubicin, although more myelosuppressive than the BV regimen, is now considered by many physicians as the first-line therapy in patients with advanced stage Kaposi's sarcoma.

Paclitaxel and vinorelbine have potential in Kaposi's sarcoma, but additional studies are needed to evaluate different schedules and to compare their activity with that of the reference regimens.

Institution or continuation of both effective antiretroviral therapy and prophylaxis of opportunistic infections should be recommended to all patients receiving systemic cytotoxic therapies. However, attention must be paid to the cross-toxicity and possible pharmacokinetic interactions between antiretrovirals and antineoplastics.

Kaposi's sarcoma is the most common malignancy observed in patients with HIV-1 infection.[1] It is the source of considerable morbidity and, when lung is involved, can be life-threatening.[2] In Western countries, Kaposi's sarcoma is over 2000 times more common in HIV-infected individuals than in the general population. Among people with newly diagnosed AIDS in the US and in Europe, the prevalence of Kaposi's sarcoma ranges from 1% in men with haemophilia to 21% in homosexual men.[3,4] The 5- to 10-fold higher risk of Kaposi's sarcoma in homosexual men in comparison with other groups is probably related to one or more environmental factors to which homosexual men are more frequently exposed. The percentage of patients with Kaposi's sarcoma as the index diagnosis for AIDS has been declining since 1996, when potent antiretroviral combination regimens became available. In particular, within 1 year (1996 compared with 1995) after protease inhibitors became available, there was a 50% reduction in newly acquired Kaposi's sarcoma within a subcohort of 1003 homosexual men with HIV infection from the Frankfurt AIDS Cohort Study.[5] However, considering the Kaposi's sarcoma occurrence after AIDS diagnosis for other causes, the overall incidence of Kaposi's sarcoma seems unchanged, although this data should be confirmed soon.

Recently, a significant improvement has been made in our understanding of the pathogenesis of Kaposi's sarcoma. New epidemiological data suggest that a novel human herpesvirus, provisionally termed Kaposi's sarcoma–associated herpesvirus or human herpesvirus-8, a member of the transforming γ herpesviruses, may be aetiologically linked to Kaposi's sarcoma. Chang et al.[6] recently

found herpesvirus-like DNA sequences in Kaposi's sarcoma tissue from patients with HIV infection. Many groups have now confirmed and extended these findings, consistently demonstrating the presence of these sequences in all forms of Kaposi's sarcoma (i.e. classical, HIV-associated, African endemic and post-transplantation Kaposi's sarcoma).[7,8]

There is still uncertainty about the histological nature of Kaposi's sarcoma cells. Endothelial cells were first considered the cells of origin of Kaposi's sarcoma[9] because of the presence of factor VIII–related antigen in spindle cells. Recently, the identification of smooth muscle–specific α-actin,[10] both in cultures of cells derived from Kaposi's sarcoma lesions and in the lesions themselves, favours the hypothesis that the cells may originate from a smooth muscle cell progenitor. Another area of active research is the definition of interactions between cytokines and HIV infection in facilitating the development of Kaposi's sarcoma. The activation of cytokines such as interleukin (IL)-1, tumour necrosis factor-α and IL-6, in addition to HIV-related immune function irregularities, could result in the proliferation of mesenchymal progenitor cells and affect the rate of growth of Kaposi's sarcoma lesions as well.[11,12] HIV itself, through the expression of the tat protein, could directly increase the growth of Kaposi's sarcoma cells. The role of cytokines in the modulation of Kaposi's sarcoma cells has important clinical implications in that several drugs which modulate cytokine activity could potentially be of benefit to patients with Kaposi's sarcoma.

Although several staging systems for Kaposi's sarcoma have been proposed, none of them has been universally accepted. The Oncology Committee of the US National Institute of Allergy and Infectious Diseases–sponsored AIDS Clinical Trials Group (ACTG) has proposed a system of response and staging criteria. The new staging system includes the description of tumour extent, the status of the immune system and the presence or absence of other HIV-related disease manifestations.[13]

## 1. Treatment – General Considerations

Treatment of AIDS-related Kaposi's sarcoma presents several problems and treatment decisions should be based on an accurate evaluation of prognostic factors. For this reason there is consensus that Kaposi's sarcoma therapy in patients with AIDS should be individualised. Treatment decisions must take into consideration the extent and the rate of tumour growth, patient symptoms, immune system condition and concurrent complications of AIDS. Since no current therapies have been found to be curative, both delivery of effective anti–Kaposi's sarcoma treatment and maintenance of adequate control of HIV and other infections remain the current goal in the treatment of AIDS-related Kaposi's sarcoma. Nevertheless, considering the palliative role of Kaposi's sarcoma therapy, the potential benefits of therapy must be weighed against the high risk of adverse effects. As such, quality of life assessments should be considered an integral component of therapeutic decisions. Current recommendations for Kaposi's sarcoma treatment are as follows:[14]

- Localised disease: surgical excision; cryotherapy with liquid nitrogen; laser therapy; radiotherapy; local injection with vinblastine, vincristine, bleomycin; interferon-α (IFNα)
- Indolent disseminated cutaneous and/or lymphadenopathic disease: immunotherapy ± zidovudine single-agent chemotherapy; highly active antiretroviral therapy (HAART)
- Aggressive, disseminated disease: dual or multiagent chemotherapy.

## 2. Local Therapy

Localised Kaposi's sarcoma cutaneous tumours have been successfully treated with surgical excision, laser therapy, liquid nitrogen cryotherapy and radiotherapy.[15,16] With any local modality, there is generally residual evidence of the disease process, whether it be a scar associated with laser therapy or cryotherapy, or residual pigmentation after irradiation or intralesional injections. The modal-

ity chosen depends mainly upon the expected adverse effects of the intervention.

Radiotherapy, which has been frequently employed in the treatment of classical Kaposi's sarcoma, has become the most important therapy in the local treatment of AIDS-related Kaposi's sarcoma. Whole body electron beam therapy, fractionated focal x-ray therapy in doses up to 4500 cGy, and single dose treatments of 800 cGy produced complete remissions in 50 to 80% of patients. However, postradiation hyperpigmentation remained in 20% of lesions and 10% of patients had a local recurrence. In addition, patients with HIV infection tend to have more radiation-related complications for any given dose than non–HIV-infected patients. Treatment of the oral cavity and pharynx has resulted in unexpectedly severe mucositis in some patients with HIV and treatment of large volumes of skin has led to the development of lymphoedema.[15-18]

Late complications of radiotherapy include fibrosis, ulceration, and superinfections. Large-field irradiation must be used cautiously, especially in the lower extremities when treating an oedematous leg or groin region. Even with low doses, considerable browny induration may develop within months in the treatment fields. This phenomenon occurs at a much lower dose then would be expected in the HIV-negative patients. Furthermore, because these patients may continue to receive multiple courses of medications such as doxorubicin prolonged follow-up after radiation therapy is essential. Complications of radiotherapy may take many months to appear, and they may be aggravated by subsequent therapies, such as doxorubicin-containing regimens.[19]

In order to find the best dosage regimen, Stelzer and Griffin[20] in a prospective randomised trial treated patients with Kaposi's sarcoma lesions with 1 of 3 regimens: 800 cGy in a single fraction, 20Gy in 10 fractions, or 40Gy in 20 fractions. Complete response rate and duration of disease control were superior in the 2 higher dose arms than in the single fraction arm. Lesions treated with 20 to 40Gy had a 79 to 83% complete remission rate (regardless of residual pigmentation), whereas the single fraction complete remission rate was only 50%. No differences were noted in the acute toxicity of the 3 regimens, but late toxicity was reported only in the high dose arm. In general, a single dose of 800 cGy has been effective in reducing symptoms associated with Kaposi's sarcoma in patients with advanced HIV disease, while a fractionated course is more suitable in patients with more extensive disease and a longer life expectancy.

Intralesional injections of vinblastine, vincristine, bleomycin and IFNα have also been reported to be effective treatments.[21-23] The only adverse effect was local pain and skin irritation. Recently, intralesional injection of β–human chorionic gonadotropin has been shown to be useful in small lesions[24] (see section 4.1). However, these approaches serve mainly as cosmetic therapies, being reserved for small, thin tumours.[15]

## 3. Systemic Therapy

### 3.1 Immune Response-Modifiers

IFNs are proteins and glycoproteins with antiviral, immunomodulatory and antiproliferative activities. IFNα is the only immunomodulating agent known to play a role in the treatment of AIDS-related Kaposi's sarcoma.[15,16,25] Clinical trials using high doses (≥20MU) of IFNα have given response rates of 18 to 46%. The first sign of tumour regression is usually noted within 4 to 8 weeks, but maximal responses generally require 6 or more months of treatment. The optimal duration of IFNα treatment is unknown. The rate of response and the time to response have been found to be dose-related. Factors associated with a poor response to IFN therapy include prior or present opportunistic infections, systemic symptoms and CD4+ counts <200 cells/$mm^3$.

Adverse effects generally consist of myelosuppression, hepatic abnormalities, influenza-like symptoms (fever, chills, myalgias, anorexia) and occasionally hypotension. These adverse effects can be avoided to some degree by initiating treat-

ment with low doses of IFN and gradually escalating to full dose.

Although the strong association noted between immune status and response suggests that IFNα activity should be optimal in the setting of a good immune system, no improvements in the immunological parameters have been reported in patients who received the drug. Its precise mechanism of antitumour action remains unclear and controversial.[25]

### 3.2 Combination Therapy with Interferon-α

*In vitro* studies have shown that zidovudine and IFNα act synergistically to inhibit the replication of HIV in peripheral mononuclear cells at concentrations achievable in patients.[25] Three studies have been conducted to evaluate this drug in AIDS-related Kaposi's sarcoma (table I).

In 1989, Kovacs et al.[26] reported the results of the first phase I–II clinical trial involving 39 patients with AIDS-related Kaposi's sarcoma. These patients received zidovudine 250, 100 or 50mg every 4 hours, 6 weeks after therapy with IFNα had been initiated at a dosage of 5 MU/day. The dosage of IFNα was then increased every 2 weeks until a maximum tolerated dose was determined. Dose-limiting adverse effects included neutropenia (57%), fatigue (16%), thrombocytopenia (14%) and hepatic dysfunction (11%). The optimal regimen for long term administration that maximised the dosage of each drug was: zidovudine 100mg every 4 hours and IFNα 5 to 10 MU/day. Of the 22 patients evaluable for response, 11 (50%) had a complete or partial remission, and 8 (36%) showed an anti-HIV effect.

In a phase I trial, Krown et al.[27] administered IFNα 4.5, 9 or 18 MU/day and zidovudine 100 or 200mg every 4 hours to 41 patients with AIDS-related Kaposi's sarcoma. Neutropenia (45%) was the major dose-limiting adverse effect. The maximum tolerated dose for IFNα and zidovudine, respectively, were 18 MU/day and 100mg every 4 hours. Of the 37 evaluable patients, 17 (46%) showed complete or partial tumour regression. Anti-tumour effects occurred more frequently in patients with baseline CD4+ counts ≥200 cells/mm$^3$ (65%) than in patients with lower baseline counts (30%). Given the small number of patients with elevated serum levels of HIV-p24 antigen before the treatment, no conclusion about potential antiviral synergy were drawn.

Fischl et al.[28] reported the treatment of 56 patients with IFNα at a dosage of 9, 18 or 27 MU/day and zidovudine at a dosage of 100 or 200mg every 4 hours for 8 weeks followed by a 8-week maintenance period. In all treatment groups major adverse effects were anaemia (overall occurrence 18%), neutropenia (40%), and hepatotoxicity (42%). Neutropenia limited the dosages to zidovudine 1200 mg/day and the lowest dose of IFNα (9 MU/day). Hepatotoxicity was dose limiting with IFN 27 MU/day and zidovudine 600 mg/day. Cumulative dose-related anaemia or neutropenia were not seen during long term follow-up. The

**Table I.** Combination interferon-α (IFNα) and zidovudine (AZT) trials for AIDS-related Kaposi's sarcoma

| Maximum tolerated dose of IFNα and AZT | Evaluable patients (n) | Overall response[a] (%) | Adverse effects (%) | Reference |
|---|---|---|---|---|
| IFNα 5-10 MU/day; AZT 600 mg/day | 22 | 50 | Neutropenia (57); fatigue (16); thrombocytopenia (14); hepatotoxicity (11) | 26 |
| IFNα 18 MU/day; AZT 600 mg/day | 37 | 46 (65 if CD4+ cell count ≥200/mm$^3$; 30 if CD4+ cell count <200/mm$^3$) | Neutropenia[b] (45) | 27 |
| IFNα 18 MU/day; AZT 600 mg/day | 43 | 47 | Neutropenia[b] (40); hepatotoxicity (42); anaemia (18) | 28 |
| IFNα 18 MU/day; AZT 600 mg/day | 63 | 40 | Neutropenia[b] (27); anaemia (16); hepatotoxicity (16) | 29 |

a Complete and partial response.

b Grade 3 (according to the WHO).

maximum tolerated dosage for the combination was defined as IFNα 18 MU/day and zidovudine 600 mg/day. The overall antitumour response rate was 47%. Tumour regression was associated with better survival and pretreatment CD4+ counts ≥ 200 cells/mm$^3$. In patients with detectable HIV-p24 antigen, progressive antigen suppression was seen with increasing doses of the combination therapy.

Fischl et al.[29] in a phase II multicentre study evaluated 63 patients with IFNα (18 MU/day) and zidovudine (600 mg/day). Although this trial included patients with low CD4+ counts, therapy resulted in tumour regression in 40% of patients and the median duration of response was 22.4 weeks. The major adverse effects included anaemia (16%), neutropenia (27%) and elevated serum transaminase levels (16%).

The conclusions drawn from these studies were that combination therapy with IFNα and zidovudine can be safely administered to patients with Kaposi's sarcoma, with overall response rates higher than those achieved with IFNα alone.

The addition of granulocyte-macrophage colony-stimulating factor (GM-CSF) to the combination regimen of zidovudine and IFNα has been studied in an attempt to ameliorate the myelosuppression seen with coadministration of these agents. In 2 studies,[30,31] patients who developed neutropenia while receiving zidovudine and IFNα were given GM-CSF without any alterations in the dosages of the drugs. The tumour response rates were 41 and 50% for the two studies. No adverse effects on immune function or HIV activity were reported. The addition of GM-CSF ameliorated the neutropenia in all patients. However, nonhaematological adverse effects precluded a major increase in the maximum tolerated dose of IFNα and zidovudine.

No data with the combination of IFNα and other antiretroviral drugs are available. Some studies have been performed using IFNα in combination with conventional antineoplastic chemotherapy. No positive synergistic effect was found and the haematological and subjective adverse effects were more severe.[15,25]

### 3.3 Highly Active Antiretroviral Therapy

Trials are in progress with the aim of determining the anti–Kaposi's sarcoma activity of antiretroviral regimens containing protease inhibitors, based on some evidence that zidovudine alone may have some utility in the management of Kaposi's sarcoma.[32,33] Protease inhibitors are highly selective and potent inhibitors of HIV replication. Clinical studies have demonstrated a marked reduction in plasma viral load, sustained improvement in immune function and prevention of AIDS-related complications in HIV-infected patients.

The first observation has been reported by Murphy et al.,[34] who reported a case of complete regression of cutaneous Kaposi's sarcoma in a patient with AIDS after beginning treatment with the protease inhibitor indinavir. Conant et al.[35] described preliminary findings from 5 patients with Kaposi's sarcoma treated with ritonavir 600mg twice daily, who experienced improvement or resolution of Kaposi's sarcoma lesions. All patients had cutaneous lesions at multiple sites without visceral involvement and CD4+ lymphocyte counts were $<100 \times 10^6$/L. Tavio et al.[36] have recently reported preliminary data of a prospective study, confirming the clinical feasibility and antineoplastic activity of HAART in patients with AIDS-related Kaposi's sarcoma. To date, 9 patients have been enrolled and the median time of treatment was 12 weeks. Partial responses occurred in 3 patients, and all of them were given indinavir as the protease inhibitor. Treatment was well tolerated and no interruption of therapy for adverse effects was observed. Partial restoration of immune function and control of HIV viral load were not always accompanied by an objective response of sarcoma. In 2 patients Kaposi's sarcoma progressed while receiving HAART, despite the underlying HIV infection being controlled. Recently, Volm and Wernz[37] studied a cohort of 13 patients who had previously required long term systemic therapy for AIDS-related Kaposi's sarcoma (IFN alone in 4 patients and a variety of cytotoxic drugs in 9 patients). Systemic therapy was withdrawn before the study. Following the institution of effective antiretroviral therapy with a

variety of regimens (all patients eventually received a protease inhibitor) viral load decreased dramatically and none of the 13 patients experienced Kaposi's sarcoma progression during the absence of systemic therapy for a median of 10 weeks.

Speculatively, protease inhibitors may inhibit Kaposi's sarcoma–associated herpesvirus proteins. It is more likely, however, that Kaposi's sarcoma regression is linked to decreased HIV replication with an associated decrease of cytokine levels and to the restoration of immune function.

HAART might be a useful alternative both to immune response-modifiers during less aggressive stages of Kaposi's sarcoma disease and to systemic cytotoxic drugs in the long term maintenance therapy of advanced Kaposi's sarcoma. The management of Kaposi's sarcoma with HAART is very interesting as it targets both tumour cells and the underlying HIV infection. The likelihood of long term treatment with agents with low adverse effect profiles makes this approach very attractive.

### 3.4 Cytotoxic Chemotherapy

In general, systemic chemotherapy is reserved for patients with widespread, symptomatic disease, in particular when visceral disease is present, and who are unlikely to respond to or have failed IFN treatment. There are many difficulties in comparing different chemotherapeutic trials in patients with AIDS-related Kaposi's sarcoma. No uniform staging system has been used to group patients in many of the clinical trials. Therefore, it must be kept in mind that the high partial remission rate seen in some trials employing a single drug may reflect patients who are in a better prognostic group or have limited disease. Moreover, response criteria have varied considerably from study to study.

#### *3.4.1 Single Agent Chemotherapy*

Several single agent therapies have been reported to be active in AIDS-related Kaposi's sarcoma and include the vinca alkaloids (vincristine and vinblastine), anthracyclines (doxorubicin, epirubicin), epipodophyllotoxins (etoposide, teniposide) and bleomycin.[38-48] Although clinical trials with single agent chemotherapy showed significant overall response rates, responses were short lived and the occurrence of opportunistic infections was a major problem. Overall response rate ranges from 10 to 76%, although most have been partial responses. In general, for patients who are leucopenic and require chemotherapy, vincristine and bleomycin are the single agents used most widely.

Rieber et al.[39] first reported data on vincristine (1.4 mg/m$^2$/week) as single agent in patients with Kaposi's sarcoma. Of the 5 patients treated, 4 achieved a partial response and 1 progressed while on therapy. The duration of response was short, with a median of 10 weeks. Treatment was well tolerated and none of the patients developed myelosuppression, neurotoxicity or gastrointestinal toxicity.

Lassoued et al.,[40] in a nonrandomised trial, evaluated the efficacy and safety of bleomycin as a single agent in treatment of non–life-threatening Kaposi's sarcoma. Thirty patients were treated with intramuscular bleomycin (5 mg/day for 3 days every 2 or 3 weeks) and 30 others with a slow continuous intravenous infusion of bleomycin (6 mg/m$^2$/day for 4 days every 4 weeks). A partial response was observed in 29 patients (48.3%). There was no difference in response rate between intramuscular or intravenous route. The adverse effects (fever and skin rash; 12 and 3%, respectively) were minimal and led to discontinuation of the treatment in only 2 (3.3%) patients. Nonsymptomatic pulmonary toxicity was observed.

Remick et al.[41] evaluated a continuous infusion schedule of higher dosages of bleomycin (20 mg/m$^2$/day for 3 days every 3 weeks) in 17 patients with advanced stage AIDS-related Kaposi's sarcoma. There were 11 partial remissions (65%) with a median survival duration of 7 months. Only 1 cycle (2%) was complicated by an absolute neutrophil count less than 500, and there were no episodes of febrile neutropenia. There were no other clinically significant (>grade 3) adverse effects. A major limitation of this schedule is the 3-day continuous infusion, which reduces patients' quality of

life compared with other regimens. These studies have shown that bleomycin as a single agent is a good alternative in the treatment of patients with non–life-threatening Kaposi's sarcoma and that the intramuscular route should be preferred for convenience and cost reasons.

Another attractive single agent regimen, which allows outpatient treatment, has been reported by Laubenstein et al.[42] They treated 41 patients with etoposide (150 mg/m$^2$ three times daily every 28 days). Complete remission was achieved in 30% of patients and partial remission in 46%. The median response duration was 9 months. The particularly high rate of overall response (76%) observed in this study is due mostly to the early stage disease of patients. In general, therapy was subjectively well tolerated by the patients. Dosage reduction of 25 to 50% was required because of haematological adverse effects (grade 3 to 4) in 11 patients (26%), with 3 patients requiring hospitalisation for neutropenia and fevers.

Schwartsmann et al.[43] in a phase II pharmacokinetic study evaluated long term, low dose, oral etoposide in 25 patients. Etoposide was administered orally at 25 mg/m$^2$ twice a day for 7 days every 2 weeks. All patients had advanced stage Kaposi's sarcoma. The overall response rate was 32% and the median progression-free survival was 8 weeks. The regimen was well tolerated. The main effects consisted of mild to moderate nausea and vomiting in approximately half of the patients, and grade 3 to 4 leucopenia and thrombocytopenia in 8 of 25 (36%) and 5 of 25 (20%) of patients, respectively. However, only 2 patients had to discontinue the treatment because of prolonged and severe neutropenia, and no instances of drug-induced neutropenia lead to septic shock death. This apparent efficacy of the regimen could be a result of the prolonged maintenance of cytotoxic plasma concentrations of etoposide during each treatment course, and the absence of toxic peak concentrations of the drug. The major benefit of this schedule, together with the low toxicity, is the feasibility of outpatient management of the therapy, which avoids discomfort and costs of hospitalisation.

A phase II trial of teniposide (360 mg/m$^2$ every 3 weeks was conducted by Schwartsmann et al.[44]). Teniposide is a podophyllotoxin derivative similar to etoposide but with a longer elimination half-life and superior antitumour activity. Of the 25 patients treated 40% had an objective response. Results were comparable to those observed with etoposide, but responses were of short duration (median 9 weeks). In addition, occurrence of bone

**Table II.** Single agent chemotherapy for AIDS-related Kaposi's sarcoma

| Chemotherapy | Evaluable patients (n) | Overall response (CR only) [%] | Adverse effects (%) | Reference |
|---|---|---|---|---|
| Etoposide | 41 | 76 (30) | Neutropenia[a] (26) | 42 |
| | 25[b] | 32 (8) | Neutropenia[a] (36) | 43 |
| Vincristine | 18 | 61 (0) | Peripheral neuropathy (44) | 38 |
| | 5 | 80 (0) | | 39 |
| Vinblastine | 38 | 26 (3) | Leucopenia[c] | 45 |
| Bleomycin | 60 | 48 (0) | Fever (12) | 40 |
| | 17[d] | 65 (0) | Fever[e] (54); rash[e] (8) | 41 |
| Doxorubucin | 29 | 48 (3) | Alopecia (55); neutropenia[a] (37) | 45 |
| Tenoposide | 25 | 40 (0) | Leucopenia[e] (100); thrombocytopenia[e] (47) | 44 |

a Grade 3-4 (according to the WHO).
b 25 mg/m$^2$ orally.
c Only grade 1-2 (according to the WHO).
d Continuous infusion.
e Percentage of cycles.
**CR** = complete remission.

**Table III.** Dual agent chemotherapy for AIDS-related Kaposi's sarcoma

| Chemotherapy | Evaluable patients (n) | Overall response (CR only) [%] | Adverse effects (%) | Reference |
|---|---|---|---|---|
| VCR/BLM[a,b] | 46 | 57 (0) | Peripheral neuropathy (28) | 50 |
| VCR/BLM[c] | 18 | 72 (11) | Peripheral neuropathy (55) | 52 |
| VCR/BLM + AZT[d] | 19 | 74 (5) | Neutropenia (21); peripheral neuropathy (5) | 51 |

a Vinblastine instead of vincristine if peripheral neuropathy developed.

b VCR = 2mg; BLM = 30mg, 18-hour infusion.

c VCR = 1.4 mg/m$^2$ (maximum 2mg); BLM = 10 mg/m$^2$.

d VCR = 2mg; BLM = 30mg infusion; AZT = 400 to 1000 mg/day.

**AZT** = zidovudine; **BLM** = bleomycin; **CR** = complete remission; **VCR** = vincristine.

marrow toxicity in all patients has limited further studies of this agent.

Objective responses and adverse effects of single agent regimens are summarised in table II.

#### 3.4.2 Dual Agent Chemotherapy

With the aim of improving objective responses and duration of clinical benefits without increasing adverse events, especially myelosuppression, small studies using a combination of vincristine-bleomycin, vinblastine-methotrexate, vinblastine alternating weekly with vincristine or bleomycin have also been conducted.[49-53] Response rates ranged from 43 to 77%. Interestingly, in 2 studies bleomycin-vincristine chemotherapy was relatively well tolerated and resulted in a high response rate (57 to 72%) in patients presenting with disseminated Kaposi's sarcoma and severe peripheral blood cytopenias. The major adverse effect was peripheral sensory neuropathy in both studies. About 30% of patients required either vincristine dose-reduction or withdrawal. Bleomycin-induced pulmonary toxicity was not observed[50-52] Unfortunately, responses were short lived and the occurrence of opportunistic infections was a major problem.

Clinical results observed in trials employing dual agents are summarised in table III.

#### 3.4.3 Multiagent Chemotherapy

Multiagent chemotherapy employs various combinations of drugs that have been found to be effective as single agents, and they are generally administered to patients with advanced disease and visceral involvement. First multichemotherapeutic regimens specifically devised for AIDS-related Kaposi's sarcoma were a combination of doxorubicin, bleomycin, and vincristine (or vinblastine). Initial studies used doxorubicin administered either 40 mg/m$^2$ every 4 weeks or 20 mg/m$^2$ every 3 weeks.[42,46] Impressive clinical responses were observed in these studies, but neutropenia was a dose-limiting adverse effect in most cases.

Laubenstein et al.[42] treated 31 patients with doxorubicin (40 mg/m$^2$) bleomycin (15IU) and vinblastine (6 mg/m$^2$). Objective response was reported in 84% of patients (23% complete remissions). However, a significant number of these patients developed opportunistic infections (61%) and dose-limiting neutropenia (44%).

Gill et al.[46] reported a multicentre, randomised clinical trial comparing low dosage doxorubicin 20 mg/m$^2$ alone (n = 31) or doxorubicin 20 mg/m$^2$, bleomycin 10 mg/m$^2$ and vincristine 1.4 mg/m$^2$ (ABV) [n = 30] every 2 weeks. Complete and partial tumour remissions were significantly higher with ABV (88%) than with doxorubicin alone (48%) [p = 0.004]. The median survival was 9 months in both groups. Adverse effects were similar in both groups and the regimens were well tolerated.

Treatment-related adverse effects consisted of nausea and vomiting, hair loss, mucositis, peripheral sensory neuropathy and granulocytopenia. Grade 3 to 4 neutropenia occurred in 34% of pa-

tients receiving doxorubicin alone and in 52% of patients receiving ABV. Neutropenia was progressive in successive courses of chemotherapy in both treatment groups. The only significant difference in adverse effects between the two treatment regimens was a more frequent occurrence of peripheral neuropathy in patients receiving ABV. However, only 1 patient (4%) experienced neurotoxicity more than grade 2, and a dose modification for vincristine was required in only 4 patients. 21% of patients receiving doxorubicin and 29% of those taking ABV, developed opportunistic infections during treatment. Notably, the development of *Pneumocystis carinii* pneumonia (PCP) was relatively infrequent in the ABV group, possibly as a result of the prophylactic use of sulpha-containing antibacterials. Bacterial infections occurred almost equally in both groups and the majority of them were associated with severe neutropenia.

The majority of patients with advanced Kaposi's sarcoma are severely immunocompromised and eventually die from opportunistic infections rather than Kaposi's sarcoma. Therefore, a major concern was whether the use of chemotherapy would aggravate the immune dysfunction and predispose patients with AIDS to more opportunistic infections. It is also of interest whether concurrent use of antiretroviral therapies would prevent the occurrence of opportunistic infections.

In an ACTG phase I trial (ACTG 075) Gill et al.[53] determined toxicity and maximum tolerated dose of doxorubicin in combination with fixed doses of bleomycin, vincristine and zidovudine in patients with advanced AIDS-related Kaposi's sarcoma. Of the patients, 26 were treated with zidovudine 100 mg/day orally every 4 hours, along with combination chemotherapy using bleomycin 10 U/$m^2$ and vincristine 1.4 mg/$m^2$ given intravenously in 2-week cycles. In addition, 3 cohorts of 8 patients received escalating doses of doxorubicin each beginning with no doxorubicin and increasing to 15 mg/$m^2$.

The maximum tolerated dose of doxorubicin was 10 mg/$m^2$ when given in combination with zidovudine and bleomycin and vincristine/vinblastine (BV) chemotherapy. Response rate observed with a combined antiretroviral and chemotherapy regimen were similar to those previously reported with ABV chemotherapy alone.

As expected, severe neutropenia was the major dose-limiting adverse effect of the combination therapy. In the cohort receiving doxorubicin 10 mg/$m^2$, only 1 out of 8 patients developed grade 3 and none developed grade 4 neutropenia. One patient experienced neutropenic fever and none experienced neutropenic sepsis. Neurotoxicity occurred frequently at all 3 dosage levels; 11 out of 24 (46%) patients experienced some degree of paraesthesia, and 1 experienced paralytic ileus, which resolved after cessation of therapy. Vincristine dose reductions were required in 6 patients after receiving between 2 and 8 cycles of therapy. Of interest, only 2 patients (8%) developed opportunistic infections while receiving ABV with zidovudine. Previous studies of combination chemotherapy without antiretrovirals in patients with AIDS-related Kaposi's sarcoma have documented opportunistic infections in about 60% of such patients, even with the use of prophylactic therapy for PCP.

The use of recombinant haematopoietic growth factors to support Kaposi's sarcoma patients undergoing chemotherapy has been evaluated in some studies as a means of preventing bacterial infectious complications. In a phase I clinical trial Gill et al.[54] investigated the maximum tolerated dosage of GM-CSF in combination with the ABV regimen. In this dosage escalation trial, GM-CSF 250 μg/$m^2$/day was well tolerated, whereas the next dose escalation to 500 μg/$m^2$/day was associated with dose-limiting adverse effects, including grade 3 fever, fatigue and diarrhoea. GM-CSF prevented the occurrence of severe neutropenia in these patients. Other studies confirmed these data and the use of haematopoietic growth factors to support AIDS patients receiving chemotherapy is now standard practice.[55,56]

High doses of doxorubicin can be utilised with relative safety when less myelosuppressive anti-HIV therapy is administered. ACTG163 evaluated the combination of didanosine or zalcitabine with

ABV in patients with advanced stage Kaposi's sarcoma. Doxorubicin was administered at the dose of 20 mg/m$^2$ along with bleomycin 10 U/m$^2$ and vincristine 1mg every 2 weeks. Tolerance was good in both treatment groups, with no increased incidence of peripheral neuropathy.[57] The incidence of opportunistic infections was low when compared with studies in similar populations in the pre-antiretroviral period.

## 3.5 New Agents Chemotherapy

### *3.5.1 Liposomal Anthracyclines*

The use of liposomal anthracyclines is a novel and attractive approach for the treatment of advanced Kaposi's sarcoma. In the liposomal preparation of daunorubicin the anthracycline has been entrapped into small unilammelar vesicles and it has been formulated to maximise the selectivity of daunorubicin for solid tumours *in situ*. The tumour uptake of liposomal daunorubicin is 10-fold greater than for free daunorubicin. This selective increased drug delivery to the tumour was shown to translate into a significant improvement in therapeutic efficacy with no increase in adverse effects. A number of phase I and II studies showed liposomal daunorubicin to be effective in advanced stage Kaposi's sarcoma and well tolerated. There was minimal myelosuppression, no evidence of cardiac adverse effects and a decrease in the frequency and severity of chemotherapy-related adverse effects compared with historical data.[58-60]

Based on these encouraging results, a randomised phase III trial was conducted to compare the safety and efficacy of liposomal daunorubicin with that of the reference regimen of ABV as primary therapy in advanced AIDS-related Kaposi's sarcoma. 232 patients were randomised to receive liposomal daunorubicin 40 mg/m$^2$ or a combination regimen of doxorubicin 10 mg/m$^2$, bleomycin 15U, and vincristine 1mg, administered intravenously every 2 weeks. The doses of the reference regimen used were chosen to permit concomitant antiretroviral therapy. Overall response rates (25% for liposomal daunorubicin and 28% for ABV), time to treatment failure, and overall survival were similar in both treatment groups. Neutropenia was the predominant haematological adverse effects in both treatment arms. Patients treated with liposomal daunorubicin experienced grade 4 neutropenia significantly more frequently than ABV patients (15% for liposomal daunorubicin and 5% for ABV; $p = 0.02$). The frequencies of grade 3 neutropenia and grade 3 + grade 4 leucopenia were similar between the 2 treatment arms.

Thrombocytopenia of ≥grade 2 and anaemia were rare for both arms. Of the patients receiving liposomal daunorubicin, 37 (32%) compared with 20 ABV patients (18%) received granulocyte colony-stimulating factor (G-CSF) during the course of the clinical trial. Nonhaematological adverse effects consisted mostly of nausea, fever, fatigue, diarrhoea, and cough among liposomal daunorubicin patients, and fever, fatigue, nausea, neuropathy, and alopecia among ABV patients. Alopecia was observed in 36% of ABV patients, as compared with 8% of liposomal daunorubicin patients ($p < 0.0001$). The alopecia was mostly mild to moderate in severity. Similarly, neuropathy was seen in 41% of ABV patients, but only in 13% of liposomal daunorubicin patients ($p < 0.0001$). In 3% of ABV patients and in 1% of liposomal daunorubicin patients, the neuropathy was severe or life-threatening (grade 3 or grade 4). All other toxicity differences were not significant.

Cardiac function remained stable, with no instances of congestive heart failure in either treatment group. During the course of the clinical trial, 42 patients receiving liposomal daunorubicin (36%) developed an opportunistic infection and 20 additional patients (17%) developed neutropenic fevers, without documented infections. Among ABV patients, 29 (26%) developed an opportunistic infection during the course of the clinical trial and 12 additional patients (11%) developed neutropenic fevers, without documented infections.[61]

These data confirm that liposomal daunorubicin is effective in the treatment of patients with advanced AIDS-related Kaposi's sarcoma. Liposomal daunorubicin had comparable efficacy to ABV, was associated with significantly less alope-

cia and neuropathy, and produced no evidence of cardiac adverse effects. Patients on liposomal daunorubicin experienced more grade 4 neutropenia and had a higher incidence of opportunistic infections. The authors concluded that liposomal daunorubicin can though be recommended as well tolerated and effective primary therapy for advanced AIDS-related Kaposi's sarcoma.

Doxorubicin incorporated in the polyethylene glycol (PEG)-coated (pegylated) liposomal formulation has also been demonstrated to be effective in advanced stage Kaposi's sarcoma. Administration of PEG-coated liposomal doxorubicin achieved 5-fold to 11-fold increases in doxorubicin concentration in Kaposi's sarcoma lesions compared with equal doses of standard doxorubicin. In patients with AIDS-related Kaposi's sarcoma liposomal encapsulation has also been shown to result in the delivery of more doxorubicin to Kaposi's sarcoma lesions than to adjacent healthy skin.[62] Whereas liposomal daunorubicin has a half-life of approximately 8 hours, liposomal doxorubicin has an additional modification of the liposome with the addition of PEG, which reduces the update by the reticuloendothelial system with the resultant half-life of approximately 30 hours.[63]

To date, many clinical studies have been performed to assess the safety and efficacy of PEG-coated liposomal doxorubicin in patients with advanced stage Kaposi's sarcoma. In these trials PEG-coated liposomal doxorubicin was highly active.[64-66] The best benefit-risk ratio was achieved with a dosage of 20 mg/m$^2$ administered at 2- or 3-week intervals. At this schedule PEG-coated liposomal doxorubicin was generally well tolerated. The most frequent dose-limiting adverse effect was myelosuppression, with about 60% of patients experiencing significant neutropenia (grade 3 to 4). Other adverse events included: palmar-plantar erythrodysaesthia (hand-foot syndrome), usually mild and not requiring a dose reduction; anaemia; thrombocytopenia and nausea. The distinct adverse effect of hand and foot syndrome is similar to that seen with fluorouracil given by infusion, and is secondary to its long half-life.[63] Few data are available on the cardiac tolerability, but it seems to be associated with a lower incidence of cardiac adverse effects than standard doxorubicin. However, cardiomyopathy has occurred in a small number of patients receiving high cumulative doses of PEG-coated liposomal doxorubicin (>550/m$^2$).

Recently, using cardiac biopsy, Berry et al.[67] evaluated anthracycline-induced cardiac damage in AIDS-related Kaposi's sarcoma patients treated with pegylated liposomal doxorubicin (cumulative doses 440 to 840 mg/m$^2$) relative to historical control patients given comparable cumulative doses of standard doxorubicin.

In light of these results randomised comparative trails of PEG-coated liposomal doxorubicin versus standard ABV or BV regimens have been conducted. Northfelt et al.[68] compared PEG-coated liposomal doxorubicin with standard ABV in patients with advanced stage Kaposi's sarcoma. Of the patients, 258 were randomised to PEG-coated liposomal doxorubicin (20 mg/m$^2$) or ABV (A = 20 mg/m$^2$, B = 10 U/m$^2$, V = 1mg), every 2 weeks. PEG-coated liposomal doxorubicin was significantly more effective than ABV in producing objective responses (45.9% versus 24.8%; $p < 0.001$) with a comparable adverse effect profile. The occurrence of adverse effects for PEG-coated liposomal doxorubicin compared with ABV, respectively, were: leucopenia 36 versus 42%; nausea and/or vomiting 15 versus 34%; peripheral neuropathy 6 versus 14%; alopecia 1 versus 19%; and any severe (grade 3 or 4) adverse event 92 versus 94%. The most common adverse event in both groups was leucopenia and 44% of patients who received liposomal doxorubicin and 53% of patients who received ABV were given either G-CSF or GM-CSF. Eight patients who received liposomal doxorubicin and 3 patients who received ABV experienced episodes of sepsis. Opportunistic infections occurred in 37 and 30% of patients treated with liposomal doxorubicin and ABV, respectively. Although, opportunistic infections and sepsis were more common in patients who received liposomal doxorubicin, this agent appeared to be better toler-

ated than ABV. In particular subjective adverse effects such as alopecia, neuropathy, nausea and vomiting occurred less frequently in patients who received liposomal doxorubicin.

In another study Northfelt et al.[69] evaluated PEG-coated liposomal doxorubicin (20 mg/m$^2$ IV every 3 weeks) in 53 patients who had experienced disease progression or intolerable adverse effects while receiving standard ABV or BV chemotherapy. Of the 53 patients, 19 (36%) had a partial response and 1 patient had a clinical complete response. Of the 28 patients who were in progression while receiving standard doxorubicin, 32% had a partial remission.

Overall, 76% of patients reported at least 1 adverse event that was possibly or probably related to PEG-coated liposomal doxorubicin and 30% reported at least 1 severe adverse event thought to be related to PEG-coated liposomal doxorubicin. Leucopenia was the most common adverse event and occurred in 40% of patients. Five patients experienced an episode of sepsis while in the study. Of the patients, 33 (62%) received colony-stimulating factors during the course of therapy. Thrombocytopenia occurred in 5.7% of patients. Nausea and vomiting occurred in 15% and alopecia occurred in 9%; none of these events were severe. Palmar-plantar erythrodysaesthia occurred in 1 patient. Opportunistic infections occurred in 23 patients (43%).

Recently, Stewart et al.[70] conducted a randomised study that compared PEG-coated liposomal doxorubicin 20 mg/m$^2$ with a combination of bleomycin 15 IU/m$^2$ and vincristine 2mg in 241 patients with advanced stage Kaposi's sarcoma. Both regimens were administered by intravenous infusion every 3 weeks for 6 cycles. Half the patients in each treatment group were taking 1 or more antiretroviral drugs and the majority of them were on regular antimicrobial prophylaxis. Results were comparable with the previous studies by Northfelt.[68,69] The response to PEG-coated liposomal doxorubicin was superior to BV: 58.7% *vs* 23.3% ($p < 0.001$).

Differences in the adverse effect profile between the 2 regimens were evident. In particular, the incidence of paraesthesia (14 versus 3%) and constipation (13 versus 2%) was significantly higher in patients who received BV, whereas leucopenia (72 versus 51%) and oral candidiasis (35 versus 21%) were more commonly seen in patients who received PEG-coated liposomal doxorubicin. Grade 3 leucopenia was recorded in 28.9% of patients who received PEG-coated liposomal doxorubicin and 12.5% of those who received BV. Significantly more patients on PEG-coated liposomal doxorubicin experienced an opportunistic infection: 49.6 versus 30% who received BV ($p < 0.002$).

From these studies it is clear that PEG-coated liposomal doxorubicin is an effective regimen in advanced stage Kaposi's sarcoma for both naive and pretreated patients. Although better tolerated by patients, PEG-coated liposomal doxorubicin is significantly more myelotoxic compared with the BV regimen, and this is associated with an increased incidence of infections. Concomitant use of both antiretroviral therapy and haematological growth factors is needed, with the aim of reducing opportunistic infections and myelotoxicity.

#### *3.5.2 Paclitaxel*

Paclitaxel is a novel cytotoxic agent with preliminary evidence of anti-tumour efficacy in patients with Kaposi's sarcoma. Neutropenia has been the primary dose-limiting adverse effect of paclitaxel in phase I and II trials. Reduction in neutrophil counts are usually observed by day 8, with the nadir occurring on days 8 to 11. Neutropenia has not been cumulative in most patients. Neutrophil count nadirs generally remain unchanged during subsequent courses of therapy, suggesting that paclitaxel did not produce irreversible haematopoietic stem cell toxicity. Recovery usually occurs by day 15 to 21. Peripheral neuropathy may also be severe, and occasionally dose-limiting. Hypersensitivity reactions, dyspnoea, hypotension and angioedema have also occurred, and patients should receive premedication with corticosteroids and antihistamines.

Other adverse effects include alopecia, arthralgia, myalgia, gastrointestinal disturbances, mucositis, bradycardia and cardiac conduction irregularities, rashes and elevated liver enzyme levels.[71-73] Concomitant use of ritonavir (a protease inhibitor) and paclitaxel may increase the area under the concentration-time curve of paclitaxel by as much as 3-fold.[73] Ritonavir is thought to be metabolised by several cytochrome P450 (CYP) isoenzymes, with CYP3A prominent among them. The CYP3A enzymes may also be significantly involved in paclitaxel metabolism. As a result, ritonavir may competitively inhibit paclitaxel metabolism thereby producing paclitaxel toxicity.

Saville et al.[74] first investigated paclitaxel activity in AIDS-associated Kaposi's sarcoma. Initially, they reported interesting data on 20 patients. The initial dosage was 135 mg/m$^2$ IV over 3 hours every 21 days, without filgrastim support. The dose was increased as tolerated to a maximum of 175 mg/m$^2$. On the evidence of the encouraging results, the study was modified to permit filgrastim support and then to assess a 96-hour infusion schedule for those patients who progressed. A full description of this casuistic has been recently reported by the authors.[75] All patients (n = 29) had advanced Kaposi's sarcoma and severe immunodeficiency. Of 28 assessable patients, 20 had major responses (71.4%) to the 3 hour infusion schedule and all 4 patients who had previously received anthracycline therapy for Kaposi's sarcoma responded. In all, 10 patients were escalated up to a maximum dose of 175 mg/m$^2$ and 3 patients to a pick of 155 mg/m$^2$. Ten patients went on to receive paclitaxel by 3-hour infusion with filgrastim because they developed progressive disease on doses of paclitaxel that had been reduced to less than 135 mg/m$^2$ because of neutropenia. Of 6 patients who went on to receive a 96-hour infusion of paclitaxel, 5 had major responses.

Adverse effects were, in general, similar to those seen with paclitaxel in other settings. The most frequent dose-limiting adverse effects was neutropenia. Although grade 4 neutropenia was observed in patients who received filgrastim (4 out of 10 patients; 40%), it was relatively less frequent than in patients who did not receive this agent (22 out of 29; 75%). Grade 4 anaemia and thrombocytopenia were also observed with reasonable frequency [5 out of 29 patients (17%) and 6 out of 29 patients (20%); respectively). Other adverse effects included delayed rash, fevers and eosinophilia. Two African-American patients developed acute renal failure, 1 with accompanying cardiomyopathy, and both patients were subsequently withdrawn from the study. The adverse effect profile in the 6 patients who received the 96-hour infusion regimen was similar to that of the patients receiving the 3-hour infusion regimen. This study has shown that paclitaxel as a single agent has significant activity in advanced stage Kaposi's sarcoma both in naive and pretreated patients. It is noteworthy that the 96-hour infusion schedule appears to give even higher response rates without additional adverse effects than the short infusion. However, as the authors pointed out, the potential usefulness of the long infusion schedule should be weighed against the additional treatment complexities and the increased costs.

With the aim of reducing the toxic effects of paclitaxel, Gill et al.[76] employed a low dose regimen. They studied 56 patients with advanced AIDS-related Kaposi's sarcoma. Patients were stratified for prior systemic therapy (chemotherapy or biological response-modifiers; n = 40) versus no prior systemic therapy (n = 16). Paclitaxel was administered at a dose of 100 mg/m$^2$ IV over 3 hours every 2 weeks. Visceral disease was present in 35% of patients and median CD4+ count was 20/μl. There was 1 complete response and 32 partial responses (complete remission + partial responses = 59%). Major response was not different between the treatment subgroups (55% for patients receiving prior systemic therapy versus 69% in all others). Grade 3 or 4 neutropenia was the most common adverse event occurring in 62% of patients. Anaemia or thrombocytopenia was less common, occurring in 25 and 27% of patients respectively. Severe nonhaematological adverse effects were uncommon, occurring in less than 15% of patients.

Overall, the results of these trials compared favourably with those of other single agents or combination regimens for advanced Kaposi's sarcoma. However, additional studies will be needed to evaluate different dosage schedules of paclitaxel and to compare its activity with that of the reference regimens.

#### *3.5.3 Vinorelbine*

Vinorelbine is a cytotoxic agent with preliminary evidence of anti-tumour activity in patients with Kaposi's sarcoma. It has been shown to be active against various tumour types and is relatively safe and well tolerated.[77]

Errante et al.,[78] within the Italian Cooperative Group on AIDS and Tumours, treated 22 patients with vinorelbine 30 mg/m$^2$ given intravenously every 2 weeks. Complete remission occurred in 3 of 22 evaluable patients (14%) and partial remission in 8 patients (38%). Other patients had stable (n = 5) or progressive (n = 5) disease. The toxic effects of vinorelbine consisted predominantly of myelosuppression. In particular, leucopenia (grades 3 and 4) was observed in 7 and 5 patients, respectively. Fourteen patients received G-CSF for secondary prophylaxis. Grade 3 thrombocytopenia occurred in 1 patient and grade 3 anaemia in 1 patient. Neurotoxicity was not observed and no patient discontinued treatment because of adverse effects. Because of its favourable adverse effect profile, this agent may be an excellent choice for palliative treatment of patients who may be unable to tolerate more toxic therapies. Furthermore, the low toxicity of vinorelbine makes it an attractive addition for combination regimens.

Within the Italian Cooperative Group on AIDS and tumours an ongoing pilot study is under way on vinorelbine in combination with paclitaxel plus G-CSF. Preliminary results are not yet available.

## 4. Other Agents

### 4.1 Human Chorionic Gonadotropin

There are many studies that support the hypothesis that sex hormones play a role in the pathogenesis of Kaposi's sarcoma.[79] Furthermore, some authors have suggested that clinical progression of Kaposi's sarcoma is closely associated with the hormonal status of patients.[80] Recently, Lunardi-Iskandar et al.[81] described the positive activity of the β-chain of human chorionic gonadotropin on tumorigenesis and metastasis of the neoplastic Kaposi's sarcoma cell line in immunodeficient mice. Since that finding only a few small clinical trials[24,82,83] have been conducted to test the antitumour activity of human chorionic gonadotropin. The results of these trials have been conflicting.

Harris,[82] first obtained a 'marked tumour regression' by treating 6 patients with escalating doses of human chorionic gonadotropin (between 150 000IU and 700 000IU IM for each dose) thrice weekly. There was no information on the commercial preparations of human chorionic gonadotropin used, the type and duration of response, or on the period of treatment. No dose-limiting adverse effects were reported. Conversely, Tirelli et al.[83] did not show any evidence of activity of human chorionic gonadotropin by treating 13 patients with human chorionic gonadotropin in dosages ranging from 4000IU to 32 000IU thrice weekly for 4 months (trial 1), and 100 000IU to 300 000IU thrice weekly for 3 months (trial 2). It is noteworthy that the dose of human chorionic gonadotropin administered in trial 2 was higher than that found by Harris[82] in her trial as the minimal effective dose, i.e. 100 000IU. In trial 1 non–dose-limiting adverse effect was observed, while in trial 2, one patient developed malaise, fatigue, ascites, impaired renal function and anaemia requiring human chorionic gonadotropin withdrawal. Similar symptoms had been previously described as possibly related to the systemic treatment with low dose human chorionic gonadotropin.[84]

More recently, Gill et al.[24] showed that intralesional injection of human chorionic gonadotropin induces the regression of AIDS-related Kaposi's sarcoma lesions in a dose-dependent manner. In a phase I to II trial, 24 patients received intralesional injection of human chorionic gonadotropin 3 times a week for 2 weeks at doses of 250, 500, 1000 and 2000IU (6 patients each). There was

complete resolution of Kaposi's sarcoma lesions in 10 out of 12 patients using the higher dosages of human chorionic gonadotropin. Treatment was well tolerated at all doses.

It is noteworthy that Gill et al.[24] used the most active product after *in vitro* evaluation of 4 commercial available human chorionic gonadotropin preparations. They found that they did not all have the same antitumour activity and different lots of the same preparation varied in their activity. We suspect that the antitumour activity of human chorionic gonadotropin, if any, might not be related to the β-subunit of human chorionic gonadotropin, but rather to some unidentified and co-purified components present in the different commercial human chorionic gonadotropin, thereby explaining the conflicting results of the various trials.

At present, human chorionic gonadotropin has shown very limited activity against Kaposi's sarcoma. In addition, possible dose-limiting toxicity means that human chorionic gonadotropin should not be recommended outside investigational trials.

### 4.2 Anti-Herpesvirus Agents

The identification of a new herpesvirus as a possible causal factor in the development of Kaposi's sarcoma has led to a great deal of enthusiasm in finding agents active against human herpesvirus-8 replication. So far, however, studies on the activity of anti-herpesvirus drugs have produced conflicting results.

Jones et al.,[85] in a large US retrospective study, found a significantly reduced risk of developing Kaposi's sarcoma associated with the use of foscarnet but not with aciclovir or ganciclovir. Conversely, a similar study from France did not find a reduced risk with any of the 3 drugs.[86] Finally, UK researchers have published a report suggesting that foscarnet and ganciclovir, but not aciclovir treatment may offer protection against Kaposi's sarcoma.[87] These differences may lay, in part, in the way in which the analysis was performed.

There are also anecdotal reports of remissions of early Kaposi's sarcoma following treatment with foscarnet.[88] At the same time, many other Kaposi's sarcoma patients have received foscarnet or other anti-herpesvirus drugs without any apparent improvement of their Kaposi's sarcoma.

Little is known about the response of human herpesvirus-8 to the administration of these agents. An interesting study has evaluated human herpesvirus-8-DNA sequences in peripheral blood mononuclear cells and demonstrated its persistence in patients receiving anti-herpesvirus drugs.[89] Recently, Humphrey et al.[90] measured the effects of different anti-herpesvirus drugs on human herpesvirus-8 release *in vitro*, using a cell line derived from peripheral effusion (body cavity based) lymphoma latently infected with human herpesvirus-8. The results showed that human herpesvirus-8 replication is insensitive to aciclovir [50% inhibitory concentration ($IC_{50}$) = 60.80 μmol/L], but sensitive to ganciclovir ($IC_{50}$ = 2.7 to 4 μmol/L), foscarnet ($IC_{50}$ = 80 to 100 μmol/L) and cidofovir ($IC_{50}$ = 0.5 to 1 μmol/L).

All the 4 clinically available agents (aciclovir, ganciclovir, cidofovir and foscarnet) are only effective during active viral replication, acting by inhibition of the viral DNA polymerase during lytic viral replication. It is possible that human herpesvirus-8, like Ebstein-Barr virus, persists in peripheral blood mononuclear cells and in spindle cells in a latent form that is not dependent on viral replication enzymes. This consideration could be at the basis of the low therapeutic value of anti-herpesvirus drugs observed so far. On the other hand, human herpesvirus-8 infection precedes the development of clinical Kaposi's sarcoma and presumably, during this interval, virus produced by lytic replication spreads to spindle cells where a latent infection is set up. For these reasons, a more likely role for anti–human herpesvirus-8 drugs should be in the prevention or retardation of Kaposi's sarcoma development, rather than in the treatment of Kaposi's sarcoma.

To date, anti–human herpesvirus-8 drugs have neither therapeutic nor prophylactic indications for Kaposi's sarcoma.

## 5. Risks and Benefits

Knowledge of drug-associated adverse effects, especially the benefit-risk ratio, is critical to the evaluation of any agent and/or combination regimens. In a disease like AIDS-related Kaposi's sarcoma, where only palliative treatments are available, information on the adverse effects of the drugs and their impact on the quality of life is particularly important in assessing their role in the disease management.

The treatment of AIDS-related Kaposi's sarcoma presents several problems. First, the majority of patients have aggressive, widespread and visceral disease. Secondly, the immunodeficiency and the history of previous opportunistic infections complicate the administration of immunosuppressive chemotherapy. Thirdly, leucopenia commonly seen in patients infected with HIV makes the use of conventional multiagent chemotherapy regimens difficult. The bone marrow of HIV-infected patients shows changes similar to a myelodysplastic syndrome. Anaemia and neutropenia are of major clinical importance as both are accentuated by drugs that interfere with haematopoiesis, such as zidovudine, ganciclovir and sulfa-containing antibacterials that are frequently used in HIV patients. In light of the above considerations, therapy of AIDS-related Kaposi's sarcoma produces several majors clinical problems: short response time in spite of response rate obtained; the occurrence of opportunistic infections; the drop in the immunological parameters; and bone-marrow toxicity. Therefore, one of the present challenges in the therapy of AIDS-related Kaposi's sarcoma is the integration of antiretroviral therapy with antineoplastic chemotherapy and haematopoietic growth factors.

In order to obtain the highest benefit-risk ratio, Kaposi's sarcoma treatment needs to be individualised on the basis of the patient's overall clinical and immunological status and of the toxic profile of concomitant therapies for HIV infection.

Immediate therapeutic intervention is thought unnecessary if a patient is found to have a stable or slowly progressive cutaneous disease and no cosmetic complications. Local therapy is suitable for patients with few lesions, particularly those that can cause either emotional or physical distress. There are many local therapeutic options. The modality chosen depends mainly on the expected adverse effects of the intervention. Whereas intralesional vinblastine or cryotherapy may be ideal for small lesions on the skin or oral cavity, such treatments can be quite painful on the sole of feet, eyelids, or penis, or for larger lesions in any site.

Radiation therapy is an effective therapy both as a local modality in patients with minimal disease and for relief of local symptoms unresponsive to systemic therapy. No single dosage schedule is appropriate for all patients. Doses and schedule of radiation depends on life expectancies and extent of lesions. Prolonged follow-up after radiation therapy is essential, because complications of radiation may take many months to appear, and they may be aggravated by subsequent therapies, such as doxorubicin-containing regimens.

In patients with moderately extensive cutaneous or mucosal disease and CD4+ cell counts of ≥200/ml, immunotherapy and antiretroviral drugs are indicated. Combination therapy with low dosages (<18 MU/day) of IFNα and zidovudine (600 mg/day) showed the best benefit-risk ratio.[27-28] This schedule is associated with overall response rates higher than those achieved with high dosages (>6 MU/day) of IFNα alone, and with lesser adverse effects. Neutropenia (grade 3 to 4) remains a significant dose-limiting adverse effect, occurring in about 45% of patients. Poor prognostic factors for response include constitutional symptoms (fever, night sweats and bodyweight loss), prior or concurrent opportunistic infections, and endogenous IFN levels. Major benefits of this treatment regimen are the long-standing responses, the usually mild adverse effects and the concomitant effect on the underlying HIV infection.

Preliminary results indicated that HAART (including protease inhibitors) might be an effective and well tolerated anti–Kaposi's sarcoma therapy in less advanced Kaposi's sarcoma,[34-36] while in patients with advanced Kaposi's sarcoma appears

to prolong periods of disease control after conventional systemic treatments.[37] HAART has had a dramatic impact in the prevention rather than in the treatment of Kaposi's sarcoma. The extensive use of HAART in patients with HIV infection has significantly reduced new cases of Kaposi's sarcoma.

Furthermore, many cases of Kaposi's sarcoma now develop in patients already receiving HAART and therefore alterative treatments are usually necessary. However, the use of HAART in combination with other therapies is crucial in the management of advanced stage Kaposi's sarcoma, since suppression of HIV replication is essential for a long-lasting regression of Kaposi's sarcoma. All patients not receiving HAART who developed mild or asymptomatic Kaposi's sarcoma, should be treated as a first option with HAART.

Systemic cytotoxic therapy is indicated in patients with aggressive and extensive mucocutaneous disease or with visceral Kaposi's sarcoma localisations. In this setting the optimal treatment regimen has yet to be found. Since there is no single best regimen, physicians should choose the most suitable treatment for each patient on the basis of the individual's need, an accurate benefit-risk ratio assessment and also considering the importance of including patients in prospective comparative studies. Furthermore, because there are only few randomised clinical trials the choice of chemotherapy regimens is based on the results of phase II studies. Since the definition and application of response criteria may differ between studies, few conclusions can be drawn in absence of direct comparisons.

Doxorubicin-based regimens (ABV) are associated with high overall response rates, and in general, are indicated as first-line treatment for patients with life-threatening or visceral disease. The best benefit-risk ratio is obtained with the following schedule: doxorubicin 10 mg/m$^2$, bleomycin 15U, and vincristine 1mg, every 2 weeks.[53] Overall responses are similar to those achieved with higher doses of doxorubicin, while the incidence of opportunistic infections is significantly lower. Support of GM-CSF decreased the duration of neutropenia but did not prevent the occurrence of severe neutropenia.[55] In patients who are leucopenic and require chemotherapy, single or dual agents associated with lower myelotoxicity [i.e. bleomycin, vincristine/vinblastine or a combination of bleomycin and vincristine/vinblastine] are the antineoplastic treatments most widely used.[41,43,50,52] Other cytotoxic regimens that have been shown to be effective with similar ranges of response rate and response duration to ABV are liposomal anthracyclines, paclitaxel and vinorelbine.

To date, few randomised trials have compared these new drugs to the reference regimens ABV and BV. Liposomal daunorubicin showed the best benefit-risk ratio at a dosage of 40 mg/m$^2$ every 2 weeks in noncomparative dose-ranging studies. In a large phase III study, the efficacy of liposomal daunorubicin was comparable to that of ABV. Response rates, time to treatment failure, and overall survival were similar in both arms.[61] Liposomal doxorubicin showed the best benefit-risk ratio at dosage of 20 mg/m$^2$ every 2 to 3 weeks in many noncomparative and dose-ranging trials. In 2 phase III studies, liposomal doxorubicin has been compared with the ABV and BV regimen. In both studies liposomal doxorubicin was significantly more effective in producing objective responses.[68-70] In light of these results, liposomal doxorubicin, although more myelosuppressive than the BV regimen, is now considered by many physicians as the first-line therapy in patients with advanced stage Kaposi's sarcoma. Furthermore, liposomal doxorubicin (20 mg/m$^2$ every 3 weeks) have shown to be an effective alternative for the treatment of patients who have failed to respond to previous chemotherapy regimens, including anthracycline.

Paclitaxel (135 mg/m$^2$ every 3 weeks) and vinorelbine (30 mg/m$^2$ every 2 weeks) have shown substantial activity against advanced stage Kaposi's sarcoma as single agents.[75-78] In particular, paclitaxel is highly active in pretreated patients and, to date, it is considered an optimal choice for the treatment of patients with anthracycline-resistant Kaposi's sarcoma. A comparison of clinical responses and major toxicities among the most ef-

fective cytotoxic regimens for advanced stage Kaposi's sarcoma is shown in table IV.

In light of the results observed among the different regimens, some guidelines for the management of advanced Kaposi's sarcoma treatment should be developed.

The BV regimen or low myelosuppressive single agents (bleomycin, oral etoposide) should be the treatment of choice in patients with HIV-related myelodysplastic disease who are receiving myelosuppressive therapies (i.e. zidovudine, sulfa-containing antibacterials, ganciclovir). In this setting liposomal doxorubicin and the ABV regimen, both with the support of haematological growth factors, should be a suitable alternative in patients with life-threatening disease who require rapid tumour regression. Liposomal doxorubicin and liposomal daunorubicin should be preferred in patients with HIV-related neuropathy and/or undergoing therapies with agents that produce peripheral neuropathy, such as didanosine, zalcitabine or stavudine. In this setting, cytotoxic agents that cause neurotoxicity, such as vinca alkaloids (vincristine, vinblastine) should be used cautiously.

Paclitaxel and vinorelbine are effective agents but, to date, they should be considered as second-line regimens. In particular, paclitaxel should be the treatment of choice in patients who have previously received anthracyclines, considering its activity in anthracycline-resistant Kaposi's sarcoma.

Institution or continuation of both effective antiretroviral therapy (reverse transcriptase agents with protease inhibitors) and prophylaxis of opportunistic infections (i.e. PCP) should be recommended to all patients receiving systemic cytotoxic therapies.

Antiretroviral therapy is associated with a decreased incidence of opportunistic infections in patients receiving chemotherapy and may affect survival favourably.[91,92] Ideally, the agents chosen should not have overlapping adverse effects with chemotherapeutic agents. In general, less myelosuppressive antiretrovirals agents such as didanosine, zalcitabine, lamivudine or stavudine, or the

**Table IV.** Major studies on therapy of advanced stage Kaposi's sarcoma: efficacy and toxicity

| Chemotherapy | Dose and schedule | Response rate (%) | Toxicity (%) | Reference |
|---|---|---|---|---|
| Liposomal daunorubicin | 40 mg/m$^2$ q2 wk | 25 | Neutropenia[a] (51); alopecia[c] (8); neuropathy[d] (13) | 61[b] |
| *vs* ABV | A = 10 mg/m$^2$; B = 15 U; V = 1mg | 28 | Neutropenia[a] (40); alopecia[c] (36); neuropathy[d] (41) | 61[b] |
| Liposomal doxorubicin | 20 mg/m$^2$ q3 wk | 46 | Leucopenia (36) | 68[b] |
| *vs* ABV | A = 20 mg/m$^2$; B = 10 mg/m$^2$; V = 1mg | 25 | Leucopenia (42) | 68[b] |
| Liposomal doxorubicin | 20 mg/m$^2$ q3 wk | 58 | Leucopenia[d] (72); neuropathy[d] (3) | 70[b] |
| *vs* BV | B = 15 IU/m$^2$; A = 2mg | 23 | Leucopenia[d] (51); neuropathy[d] (14) | 70[b] |
| Paclitaxel | 135-175 mg/m$^2$ q3 wk | 71 | Neutropenia[a] (75); thrombocytopenia[a] (20) | 75[e] |
| Vinorelbine | 30 mg/m$^2$ q3 wk | 52 | Leucopenia[a] (54) | 78[e] |

a Grade 3-4 [according to the South Western Oncology Group (SWOG)].

b Multicentre, randomised study.

c Grade 1-2 (according to SWOG).

d Overall (according to SWOG).

e Phase II study.

**A** = doxorubicin; **ABV** = a triple combination of doxorubicin, bleomycin and vincristine; **B** = bleomycin; **BV** = a dual combination of bleomycin and vincristine; **V** = vincristine.

combinations of any 2 of these with no overlapping adverse effects may be the best tolerated regimen in patients receiving chemotherapy.

Furthermore, an antiretroviral agent that does not alter the metabolism of cytotoxic agents should be chosen. Since protease inhibitors (especially ritonavir and indinavir) and many cytotoxic drugs (anthracyclines, vinca alkaloids, etoposide and paclitaxel) are metabolised by the liver and have a high affinity for CYP3A family, drug interactions may occur.

To date, clinical studies on the feasibility of concomitant chemotherapy and HAART in Kaposi's sarcoma setting are not available. Preliminary data are available on concomitant cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) chemotherapy and HAART as compared with CHOP alone, in 15 patients with HIV-related non–Hodgkin's lymphoma. The results showed that the combination of chemotherapy and HAART is feasible and may improve the clinical outcome in HIV-related non–Hodgkin's lymphoma patients (Vaccher, personal communication).

In general, however, careful attention must be directed to the cross-toxicity and possible pharmacokinetic interactions between antiretrovirals and antineoplastic drugs.

## 6. Conclusions

The incidence of HIV-related malignancies is expected to increase over time as there is a longer survival due to the improvement of therapy and prophylaxis of HIV-related opportunistic infections. Therapeutic advances for AIDS-related Kaposi's sarcoma are urgently needed, but there are may obstacles to the effective treatment of these tumours. Optimal treatment strategies should integrate antiretroviral therapy and infection prophylaxis into chemotherapy regimens. Future therapeutic strategies may include the use of biological therapies, such as inhibitors of growth factors or cytokines, the use of monoclonal antibodies and the new antineoplastic agents.

In the meantime, physicians should always consider the inclusion of their patients in well designed prospective studies where new therapeutic strategies are carefully evaluated.

## Acknowledgements

The authors want to thank Daniela Furlan and Maddalena Mosconi for their expert technical assistance in the preparation of the manuscript. This manuscript was supported by Associazione Italiana Ricerca Sul Cancro grants.

## References

1. Gill PS, Hamilton A, Naidu Y. Epidemic (AIDS-related) Kaposi's sarcoma: epidemiology, pathogenesis and treatment. AIDS Updates 1994; 7: 1-11
2. Tirelli U, Vaccher E, Lazzarin A, et al. Epidemic Kaposi's sarcoma in Italy, a country with intravenous drug users as the main group affected by HIV infection. Ann Oncol 1991; 2: 373-6
3. Beral V, Peterman TA, Berkelman RL, et al. Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? Lancet 1990; 335: 123-8
4. Serraino D, Salariina G, Franceschi S, et al. The epidemiology of AIDS-associated non-Hodgkin's lymphoma in the World Health Organization European Region. Br Cancer 1992; 66: 912-6
5. Brodt HR, Kamps BS, Gute P. Changing incidence of AIDS-defining illness in the era of antiretroviral combination therapy. AIDS 1997; 11: 1731-8
6. Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science 1994; 266: 1865-9
7. Huang YO, Li JJ, Kaplan MH, et al. Human herpesvirus-like nucleic acid in various forms of Kaposi's sarcoma. Lancet 1995; 345: 759-61
8. Su IJ, Hsu YS, Chang YC, et al. Herpesvirus-like DNA sequences in Kaposi's sarcoma from AIDS and non-AIDS patients in Taiwan. Lancet 1995; 345: 722-3
9. Rutgers JL, Wieczorek R, Bonetti F, et al. The expression of endothelial cell surface antigens by AIDS-associated Kaposi's sarcoma: evidence for a vascular endothelial cell origin. Am J Pathol 1986; 122: 493-9
10. Weich HA, Salahuddin SZ, Gill P, et al. AIDS-associated Kaposi's sarcoma-derived cells origin in long-term culture express and synthetize smooth muscle alpha-actin. Am J Pathol 1991; 139: 1251-8
11. Miles SA, Rezai AR, Salazar-Gonzalezs JF, et al. AIDS-related Kaposi's sarcoma-derived cells produce and respond to interleukin 6. Proc Natl Acad Sci U S A 1990; 87: 4068
12. Molina J-M, Scadden DT, Byrn R, et al. Production of tumor necrosis factor a and interleukin 1b by monocytic cells infected with human immunodeficiency virus. J Clin Invest 1989; 84: 733
13. Krown S, Metroka C, Wernz J. Kaposi's sarcoma in the acquired immune deficiency syndrome: a proposal for uniform evaluation, response, and staging criteria. J Clin Oncol 1989; 7: 1201-7
14. Krigel RL, Friedman-Kien A. Kaposi's sarcoma in AIDS: diagnosis and treatment. 2nd ed. In: De Vita V, Hellman S, Rosenberg SA, editors. AIDS – etiology, diagnosis, treatment and prevention. Philadelphia: JB Lippincott Company, 1988: 245-61

15. Pluda J, Broder S, Yarchoan R. Therapy of AIDS and AIDS-associated neoplasms. Cancer Chemother Biol Response Modif 1992; 13: 395-439
16. Buchbinder A, Friedman-Kien A. Clinical aspect of Kaposi's sarcoma. Curr Opin Oncol 1992; 4: 867-74
17. Cooper JS, Steinfeld A, Lerch I. Intentions and outcomes in the radiotherapeutic management of epidemic Kaposi's sarcoma. Int J Radiat Oncol Biol Phys 1990; 20: 419-22
18. de Wit R, Smit W, Veenhof K, et al. Palliative radiation therapy for AIDS-associated Kaposi's sarcoma by using a single fraction of 800 cGy. Radiother Oncol 1990; 19: 131-6
19. Swift PS. The role of radiation therapy in the management of HIV-related Kaposi's sarcoma. Hematol Oncol Clin North Am 1996; 10: 1069-80
20. Stelzer KJ, Griffin TW. A randomized prospective trial of radiation therapy for AIDS-associated Kaposi's sarcoma. Int J Radiat Oncol Biol Phys 1993; 27: 1057-61
21. Poignonec S, Lachiver LD, Lamas G, et al. Intralesional bleomycin for acquired immunodeficiency syndrome-associated cutaneous KS. Arch Dermatol 1995; 131: 228
22. Schwartz RA. Kaposi's sarcoma: advances and perspectives. J Am Acad Dermatol 1996; 34: 804-14
23. Lilenbaum RC, Ratner S. Systemic treatment of Kaposi's sarcoma: current status and future directions. AIDS 1994; 8: 141-51
24. Gill PS, Lunardi-Iskandar Y, Louie S, et al. The effects of preparations of human chorionic gonadotropin of AIDS-related Kaposi's sarcoma. N Engl J Med 1996; 335: 1261-9
25. Krown S. Interferon and other biologic agents for the treatment of Kaposi's sarcoma. Hematol Oncol Clin North Am 1991; 5: 311-22
26. Kovacs J, Deyton L, Davey R, et al. Combined zidovudine and Interferon-α therapy in patients with Kaposi sarcoma and the Acquired Immunodeficiency Syndrome (AIDS). Ann Intern Med 1989; 111: 280-7
27. Krown S, Gold J, Niedzwiecki D, et al. Interferon-α with zidovudine: safety, tolerance, and clinical and virologic effects in patients with Kaposi sarcoma associated with the Acquired Immunodeficiency Syndrome (AIDS). Ann Intern Med 1990; 112: 812-21
28. Fischl M, Uttamchandani R, Resnick L, et al. A phase I study of recombinant human interferon-α2a or human lymphoblastoid interferon-αn1 and concomitant zidovudine in patients with AIDS-related Kaposi's sarcoma. J AIDS 1991; 4: 1-10
29. Fischl MA, Finkelstein DH, He W, et al. A phase II study of recombinant human interferon alpha 2a and zidovudine in patients with AIDS-related Kaposi's sarcoma. J Acquir Immune Defic Syndr 1996; 11: 379-84
30. Scadden D, Bering H, Levine J, et al. Granulocyte-macrophage colony stimulating factor mitigates the neutropenia of combined interferon alfa and zidovudine treatment for acquired immunodeficiency-associated Kaposi's sarcoma. J Clin Oncol 1991; 9: 802-8
31. Krown S, Paredes J, Bundow D, et al. Interferon-α, zidovudine and granulocyte-macrophage colony stimulating factor: a phase I AIDS clinical trials group study in patients with Kaposi's sarcoma associated with AIDS. J Clin Oncol 1992; 10: 1344-51
32. Yarchoan R, Broder S. Preliminary results on the use of dideoxynucleosides in the therapy of AIDS. In: Chanock RM, Lerner RA, Brow F, et al., editors. Vaccines 87: modern approaches to new vaccines. Cold Spring Harbor (NY): Cold Spring Harbor Laboratory, 1987
33. Yarchoan R, Klecker RW, Weinhold KJ, et al. Administration of 3'-azido-3'-deoxythymidine, an inhibitor of HTLV-III/LAV replication, to patients with AIDS or AIDS-related complex. Lancet 1986; I: 575
34. Murphy M, Armstrong D, Sepkowitz KA, et al. Regression of AIDS-related Kaposi's sarcoma following treatment with an HIV-1 protease inhibitor. AIDS 1997; 11: 261-2
35. Conant MA, Opp KM, Poretz D, et al. Reduction of Kaposi's sarcoma lesions following treatment of AIDS with ritonavir. AIDS 1997; 11: 1300-1
36. Tavio M, Spina M, Errante D, et al. Feasibility and activity of highly active antiretroviral therapy (HAART) in patients with HIV infection and Kaposi's sarcoma (KS): preliminary results [abstract 226]. Sixth European Conference on Clinical Aspects and Treatment of HIV-infection; 1997 Oct 11-15; Hamburg, Germany
37. Volm MD, Wernz J. Patients with advanced AIDS-related Kaposi's sarcoma (EKS) no longer require systemic therapy after introduction of effective antiretroviral therapy [abstract 162]. American Society of Clinical Oncology; 1997 May 17-20; Denver
38. Mintzer D, Real FX, Jovino L, et al. Treatment of Kaposi's sarcoma and thrombocytopenia with vincristine in patients with the acquired immunodeficiency syndrome. Ann Intern Med 1985; 102: 200-2
39. Rieber E, Mittelman A, Wormser GP, et al. Vincristine and Kaposi's sarcoma in the acquired immunodeficiency syndrome. Ann Intern Med 1984; 101: 876
40. Lassoued K, Clauvel JP, Katlama C, et al. Treatment of the acquired immunodeficiency syndrome-related Kaposi's sarcoma with bleomycin as a single agent. Cancer 1990; 66: 1869-72
41. Remick SC, Reddy M, Herman D, et al. Continuous infusion bleomycin in AIDS-related Kaposi's sarcoma. J Clin Oncol 1994; 12: 1130-6
42. Laubenstein LJ, Krigel RL, Odajnyk CM, et al. Treatment of epidemic Kaposi's sarcoma with etoposide or a combination of doxorubicin, bleomycin and vinblastine. J Clin Oncol 1984; 2: 1114-8
43. Schwartsmann G, Sprinz E, Kromfield M, et al. Clinical and pharmacokinetic study of oral etoposide in patients with AIDS-related Kaposi's sarcoma with no prior exposure to cytotoxic therapy. J Clin Oncol 1997; 15: 2118-24
44. Schwartsmann G, Sprinz E, Kronfeld M, et al. Phase II study of teniposide in patients with AIDS-related Kaposi's sarcoma. Eur J Cancer 1991; 27: 1637-9
45. Volberding P, Abrams D, Conant M, et al. Vinblastine therapy for Kaposi's sarcoma in the acquired immunodeficiency syndrome. Ann Intern Med 1985; 103: 335-8
46. Gill P, Rarick M, McCutchan A, et al. Systemic treatment of AIDS-related Kaposi's sarcoma: results of a randomized trial. Am J Med 1991; 90: 427-33
47. Shepherd FA, Burkes RL, Ke P, et al. A phase II study of 4'-epirubicin in the treatment of poor-risk Kaposi's sarcoma and AIDS. AIDS 1991; 5: 305-9
48. Fischl M, Krown S, O'Boyle K, et al, and the AIDS Clinical Trials Group. Weekly doxorubicin in the treatment of patients with AIDS-related Kaposi's sarcoma. J AIDS 1993; 6: 259-64
49. Kaplan L, Abrams D, Volberding P. Treatment of Kaposi's sarcoma in acquired immunodeficiency syndrome with an alternating vincristine-vinblastine regimen. Cancer Treat Rep 1986; 70: 1121-2

50. Gompels ML, Hill A, Jenkins P, et al. Kaposi's sarcoma in HIV infection treated with vincristine and bleomycin. AIDS 1992; 6: 1175-80
51. Lipman MCI, Swaden LS, Sabin CA, et al. Kaposi's sarcoma in HIV infection treated with vincristine and bleomycin. AIDS 1993; 7: 592-3
52. Gill P, Rarick M, Bernstein-Singer M, et al. Treatment of advanced Kaposi's sarcoma using a combination of bleomycin and vincristine. Am J Clin Oncol 1990; 13: 315-9
53. Gill PS, Miles SA, Mitsuyasu RT, et al. Phase I AIDS Clinical Trials Group (075) study of doxorubicin, bleomycin and vincristine chemotherapy with zidovudine in the treatment of AIDS-related Kaposi's sarcoma. AIDS 1994; 8: 1695-9
54. Gill P, Berstein-Singer M, Espina B, et al. Adriamycin, bleomycin and vincristine chemotherapy with recombinant granulocyte-macrophage colony-stimulating factor in the treatment of AIDS-related Kaposi's sarcoma. AIDS 1992; 6: 1477-81
55. Gill PS, Mitsuyasu RT, Montgomery T, et al. AIDS Clinical Trials Group Study 094: a phase I/II trial of ABV chemotherapy with zidovudine and recombinant human GM-CSF in AIDS-related Kaposi's sarcoma. Cancer J Sci Am 1997; 3: 278-83
56. Tavio M, Vaccher E, Antinori A, et al. Combination chemotherapy with doxorubicin, bleomycin, and vindesine for AIDS-related Kaposi's sarcoma. Cancer 1996; 77: 2117-22
57. Mitsuyasu RT, Gill P, Paredes J, et al. Combination chemotherapy, adriamycin, bleomycin, vincristine (ABV) with dideoxyinosine (ddI) or dideoxycytidine (ddC) in advanced AIDS-related Kaposi's sarcoma (ACTG 163) [abstract 822]. American Society of Clinical Oncology: 1995 May 20-23; Los Angeles
58. Gill PS, Espina BM, Cabriales S, et al. A phase I/II clinical and pharmacokinetic evaluation of liposomal daunorubicin (Daunoxome) in the treatment of advanced AIDS-related Kaposi's sarcoma. J Clin Oncol 1995; 13: 996-1003
59. Presant CA, Scolaro M, Kennedy P, et al. Liposomal daunorubicin treatment of HIV-associated Kaposi's sarcoma. Lancet 1993; 341: 1242-3
60. Girard P-M, Bouchaud O, Goetschel A, et al. Phase II study of liposomal encapsulated daunorubicin in the treatment of AIDS-associated mucocutaneous Kaposi's sarcoma. AIDS 1996; 10: 753-7
61. Gill PS, Wernz J, Scadden DT, et al. Randomized phase III trial of liposomal daunorubicin (DaunoXome) versus doxorubicin, bleomycin, vincristine (ABV) in AIDS-related Kaposi's sarcoma. J Clin Oncol 1996; 14: 2353-4
62. Coukell AJ, Spencer CM. Polyethilene glycol-liposomal doxorubicin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the management of AIDS-related Kaposi's sarcoma. Drugs 1997; 53: 520-38
63. Jie C, Tulpule A, Zheng T, et al. Treatment of epidemic (AIDS-related) Kaposi's sarcoma. Curr Opin Oncol 1997; 9: 433-9
64. Goebel F-D, Goldstein D, Goos M, et al. Efficacy and safety of Stealth® liposomal doxorubicin in AIDS-related Kaposi's sarcoma. Br J Cancer 1996 73: 989-94
65. Harrison M, Tomlinson D, Stewart S. Liposomal-entrapped doxorubicin: an active agent in AIDS-related kaposi's sarcoma. J Clin Oncol 1995; 13: 914-20
66. Bogner JR, Kronawitter U, Rolinski B, et al. Liposomal doxorubicin in the treatment of advanced AIDS-related Kaposi's sarcoma. J AIDS 1994; 7: 463-8
67. Berry G, Billingham M, Alderman E, et al. The use of cardiac biopsy to demonstrate reduced cardiotoxicity in AIDS Kaposi's sarcoma patients treated with pegylated liposomal doxorubicin. Ann Oncol 1998; 9: 711-6
68. Northfelt DW, Dezube BJ, Thommes JA, et al. Pegylated-liposomal doxorubicin, bleomycin and vincristine in the treatment of AIDS-related Kaposi's sarcoma: results of a randomized phase III clinical trial. J Clin Oncol 1998; 7: 2445-51
69. Northfelt DW, Dezube BJ, Thommes JA, et al. Efficacy of PEG-coated liposomal doxorubicin in the treatment of AIDS-related Kaposi's sarcoma after failure of standard chemotherapy. J Clin Oncol 1997; 15: 653-60
70. Stewart S, Jablonowski H, Goebel FD, et al. Randomized comparative trial of PEG-coated liposomal doxorubicin versus bleomycin and vincristine in the treatment of AIDS-related Kaposi's sarcoma. J Clin Oncol 1998; 16: 683-91
71. Spencer CM, Faulds D. Paclitaxel. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the treatment of cancer. Drugs 1994; 48: 794-847
72. Rowinsky EK, Cazenave LA, Donehower RC. Taxol: a novel investigational antimicrotubule agent. J Natl Cancer Inst 1990; 82: 1247-59
73. Ritonavir (Norvir) package insert. Abbot Laboratories, North Chicago (IL), 1996
74. Saville MW, Lietzau J, Pluda JM, et al. Treatment of HIV-associated Kaposi's sarcoma with paclitaxel. Lancet 1995, 346: 26-8
75. Welles L, Saville W, Lietzau J, et al. Phase II trial with dose titration of paclitaxel for the therapy of human immunodeficiency virus-associated Kaposi's sarcoma. J Clin Oncol 1998; 16: 1112-21
76. Gill PS, Scadden DT, Groopman J, et al. Low dose paclitaxel (Taxol®) is highly effective in the treatment of patients with advanced AIDS-related Kaposi's sarcoma [abstract no. 77]. Proceedings of the National AIDS Malignancy Conference; 1997 Apr 28-30: Bethesda (MD)
77. Hohneker JA. A summary of vinorelbine (Navelbine) safety data from North American Clinical Trials. Semin Oncol 1994; 21 Suppl. 10: 42-7
78. Errante D, Fasan M, Rizzardini G, et al. Evidence of activity of vinorelbine in patients with previously treated AIDS-associated Kaposi's sarcoma. AIDS 1996; 10: 1742-3
79. Bouscarat F, Dazza MC, Melchiro JC, et al. Kaposi's sarcoma and sex hormones. AIDS 1997; 11: 687-8
80. Klauke S, Schoefer H, Althoff PH, et al. Sex hormones as a cofactor in the pathogenesis of epidemic KS. AIDS 1995; 9: 1295-6
81. Lunardi-Iskandar Y, Bryant JT, Zeman RA, et al. Tumorigenesis and metastasis of neoplastic Kaposi's sarcoma cell line in immunodeficient mice blocked by a human pregnancy hormone. Nature 1995; 375: 64-9
82. Harris PJ. Treatment of Kaposi's sarcoma and other manifestations of AIDS with human chorionic gonadotropin. Lancet 1995; 346: 118-9
83. Tirelli U, Tavio M, Giacca M, et al. Human chorionic gonadrotopin in the treatment of HIV-related Kaposi's sarcoma. AIDS 1997; 11: 387-8
84. Yamaguchi NH, Varella D, Guerra CVC, et al. A case report with unexpected adverse events in one AIDS-related Kaposi's sarcoma treated with beta human chorionic gonadotropin (beta-HCG) [abstract #867]. American Society of Clinical Oncology; 1996 May 18-21: Philadelphia (PA)

85. Jones JL, Hanson DL, Chu SY, et al. AIDS-associated Kaposi's sarcoma. Science 1995; 267: 1078-9
86. Costagliola D, Mary-Kraus M. Can antiretroviral agents decrease the occurrence of Kaposi's sarcoma? Lancet 1995; 346: 578
87. Mocroft A, Youle M, Gazzard B, et al. Anti-herpes virus treatment and risk of Kaposi's sarcoma in HIV infection. AIDS 1996; 10: 1101-5
88. Morfeldt L, Torssander J. Long term remission of Kaposi's sarcoma following foscarnet treatment in HIV-infected patients. Scand J Infect Dis 1994; 26: 749-52
89. Kedes DH, Ganem D. Sensitivity of Kaposi's sarcoma-associated herpesvirus replication to antiviral drugs. J Clin Invest 1997; 99: 2082-6
90. Humphrey RW, O'Brien TR, Newcomb FM, et al. Kaposi's sarcoma (KS)-associated herpesvirus-like DNA sequences in peripheral blood mononuclear cells: association with KS and persistence in patients receiving anti-herpesvirus drugs. Blood 1996; 88: 297-301
91. Tan B, Ratner L. The use of new antiretroviral therapy in combination with chemotherapy. Curr Opin Oncol 1997; 9: 455-64
92. Sparano JA, Sarta C. Infection prophylaxis and antiretroviral therapy in patients with HIV infection and malignancy. Curr Opin Oncol 1996; 8: 392-9

Correspondence and reprints: Dr *Umberto Tirelli*, Division of Medical Oncology and AIDS, Centro di Riferimento Oncologico, via Pedemontana Occ. le 12, 33081 Aviano (PN), Italy.
E-mail: oma@ets.it