24. Breitz HB, Sullivan K, Nelp WB. Imaging lung cancer with radiolabeled antibodies. *Semin Nucl Med* 1993, **23**, 127–132.
25. Vanhagen PM, Krenning EP, Reubi JC, Oei Y, Lowemberg B, Lambert SWJ. Somatostatin receptor scintigraphy of malignant lymphomas. *Brit J Haemat* 1993, **83**, 75–79.
26. Weinstock JV, Blum AM, Malloy T. Macrophages within the granulomas of murine schistosoma mansoni are a source of a somatostatin 1–14-like molecule. *Cell Immunol* 1990, **131**, 381–390.
27. Weinstock JV. Neuropeptides and the regulation of granulomatous inflammation. *Clin Immunol Immunopath* 1992, **64**, 17–22.
28. Crippa F, Bombardieri E, Chiti A, Soresi E, Boffi R, Buraggi GL. ^{111}In-Octreotide uptake in granulomatous lesion and tumor in a patient with small-cell lung cancer. *J Nucl Biol Med* 1994, **37**, in press.

Pergamon

European Journal of Cancer Vol. 31A, No. 2, pp. 188–192, 1995
Elsevier Science Ltd
Printed in Great Britain
0959–8049/95 $9.50+0.00

0959-8049(94)00432-3

Treatment of Poor Prognosis Epidemic Kaposi's Sarcoma with Doxorubicin, Bleomycin, Vindesine and Recombinant Human Granulocyte–Monocyte Colony Stimulating Factor (rh GM-CSF)

P.J.M. Bakker, S.A. Danner, C.H.H. ten Napel, F.P. Kroon, H.G. Sprenger, R. van Leusen, P.L. Meenhorst, A. Muusers and C.H.N. Veenhof

The efficacy and toxicity of doxorubicin, bleomycin and vindesine in epidemic Kaposi's sarcoma, and the role of rh GM-CSF in chemotherapy-induced neutropenia were evaluated in this Phase II study. Patients with progressive Kaposi's sarcoma were eligible, and were staged according to ACTG criteria. Treatment consisted of 20 mg/m^2 doxorubicin, and a fixed dose of 15 mg bleomycin and 4 mg vindesine every 2 weeks. All patients continued antiretroviral medication with severe myelosuppression, patients received subcutaneous 5 μg/kg rh GM-CSF (Leucomax) from days 2–12. Response and toxicity were measured according to ACTG and WHO criteria. 27 patients were evaluable, 25 patients classified as having a poor prognosis. The response rate was 70% (3 CR, 16 PR), the duration of response was 18 weeks (range 8–25) and the median survival 30 weeks (range 4–63+). The cause of death was mostly opportunistic infection. 4 patients died of pulmonary Kaposi's sarcoma. The toxicity of this regimen was mainly myelosuppression and 13 patients were treated with rh GM-CSF. Complete recovery of the white blood cells occurred in seven of the 27 courses of rh GM-CSF (26%). No bacterial infections were recorded, but 5 patients (19%) developed an opportunistic infection during treatment. Peripheral neuropathy occurred in 16% of patients.

Combination chemotherapy is effective in poor prognosis Kaposi's sarcoma but has a shortlasting effect. The main toxicity of this treatment is severe myelosuppression which can be ameliorated by rh GM-CSF. It remains to be established whether rh GM-CSF is also able to reduce the incidence of opportunistic infections.

Key words: Kaposi's sarcoma, chemotherapy, hematopoietic growth factors, AIDS
Eur J Cancer, Vol. 31A, No. 2, pp. 188–192, 1995

INTRODUCTION

KAPOSI'S SARCOMA (KS) was one of the first recognised manifestations of human immunodeficiency virus (HIV) infection. It is the most common malignancy associated with AIDS and occurs almost exclusively in homosexual men [1–3]. AIDS-associated Kaposi's sarcoma of the skin can be easily recognised and generally presents as a multifocal tumour, with lymph node, gastrointestinal tract and pulmonary localisations as common manifestations. It appears that HIV-associated KS differs in many ways from a primary tumour with metastatic lesions.

Experimental data support the hypothesis that HIV *tat* gene expression, enhanced cytokine production including tumour necrosis factor (TNF), interleukin-1 (IL-1), IL-6 and underlying immunodeficiency are of crucial importance in the development of KS [4]. Although indolent behaviour and even spontaneous regression of KS has been reported in non-immunocompromised hosts, the AIDS-associated form of KS frequently behaves as an aggressive tumour. Treatment is frequently necessary because of painful lesions, severe oedema, or because of the stigmatic and disfiguring features of Kaposi's sarcoma. Local treatment is only indicated in those cases with severe localised complaints or in the case of minimal disease. Most patients will, however, need some form of systemic treatment during the course of their illness, because of extensive cutaneous disease or potential life-threatening visceral involvement. The interferons alpha and beta have shown their value only in the subset of patients with a relatively preserved immune functional status, no history of prior opportunistic infections and the absence of B-symptoms [5–7]. Other biological agents, such as TNF and the interleukins, have been tested to a lesser extent than interferon. So far, their clinical usefulness appears limited. Chemotherapy, especially multiagent chemotherapy, has resulted in high response rates [8–13]. The major drawback of combination chemotherapy is the frequently associated severe neutropenia.

Several studies have shown that rh GM-CSF can be safely applied to HIV-infected patients without upregulation of HIV replication [14–18]. Doses up to 250 $\mu g/m^2$ of rh GM-CSF have been associated with acceptable toxicity and were able to reduce treatment induced neutropenia. The number of studies with rh GM-CSF in patients receiving neutropenia inducing chemotherapy are limited and were mainly performed in patients with non-Hodgkin lymphomas. The objectives of our study were to evaluate the response rate, response duration and survival in patients with poor prognosis Kaposi's sarcoma, after treatment with a myelosuppressive multiagent regimen including doxorubicin, bleomycin and vindesine (ABV). Furthermore, we investigated the toxicity and efficacy of rh GM-CSF in reducing the risk of chemotherapy induced neutropenia and the incidence of infections. In contrast to the study of Gill and colleagues [18], our patients continued their antiretroviral therapy. In addition, we investigated whether the substitution of vincristine for vindesine could reduce the incidence of peripheral neuropathy.

PATIENTS AND METHODS

The trial design was a prospective phase II multicentre study. 32 patients entered this study. All, except 1 IVDU, were homosexual males who fulfilled the Centres for Disease Control surveillance criteria for AIDS. All patients has a histologically proven Kaposi's sarcoma. Patients were included in this study if they had extensive cutaneous disease or visceral involvement and progressive measurable or evaluable disease. Baseline investigations included a complete history and physical examination with the measurement of five indicator lesions.

Endoscopy (gastroscopy, proctosigmoidoscopy) was performed in all patients. Bronchoscopy was undertaken for patients with pulmonary complaints or in the presence of asymptomatic chest radiograph abnormalities. All patients had a chest radiograph, electrocardiogram, CD4 cell counts, serum chemistry and complete blood counts. Patients were eligible if they had a white blood cell count of $\geq 2 \times 10^9/l$, neutrophils $\geq 1.0 \times 10^9/l$ and platelets $\geq 75 \times 10^9/l$. Adequate renal and hepatic functions (less than twice the upper limit) were also required.

Antiretroviral therapy was continued during treatment. No previous systemic chemotherapy was allowed. Patients were considered ineligible for the study if they had an active uncontrolled infection or a performance status 3 or 4 according to WHO criteria. Treatment consisted of 20 mg/m^2 doxorubicin, and a fixed dose of 15 mg bleomycin and 4 mg vindesine. All drugs were given intravenously. Treatment was repeated every 2 weeks and continued until objective evidence of disease progression, unacceptable toxicity or patient refusal. Patients continued treatment, preferably at full doses. In case of severe neutropenia with neutrophil counts between 500 and 1000/μl, only the dose of doxorubicin was reduced to 50%.

Recombinant human GM-CSF (Leucomax, Schering-Plough, Amstelveen, the Netherlands), 5 μg/kg, was administered subcutaneously (s.c.) in one dose on days 2–12 if the neutrophil count was less than <500/μl or when dose modification (50% doxorubicin) was necessary for a second consecutive time due to neutrophil counts between 500 and 1000/μl.

The indicator Kaposi's sarcoma lesions were evaluated before initiating therapy and every other treatment cycle to assess tumour response. Patients were monitored for toxicity before each treatment. Haematological toxicity was monitored weekly with complete blood counts. All other laboratory studies were repeated monthly. Toxicity was assessed according to the WHO toxicity scale [19].

Complete response (CR) was defined as disappearance of all lesions for a minimum of 4 weeks. Residual pigmented lesions were biopsied to confirm a complete response. Partial remission (PR) was defined as a ≥50% decrease in the total number of lesions and/or ≥50% decrease in the sums of the products of two perpendicular diameters of the measured indicator lesions for a period of at least 4 weeks. Stable disease was defined as a decrease in tumour number of size of <50% or an increase of <25% for 4 weeks. Progressive disease was defined as any new lesion or an increase in size of old lesions of >25%.

Overall and partial response duration was calculated from the date of first treatment until the date of progression. Complete response duration was calculated from the first date of complete response until the date of progression. Survival was calculated from the date of the start of treatment until death.

RESULTS

32 patients were eligible for this study. Of these 32 patients, 5 had had no prior treatment. 11 had previous local radiotherapy for symptomatic lesions, 6 had been previously treated with alpha interferon and 10 had been treated previously with intralesional vinblastin. All treatments were stopped at least 6 weeks before the patients received systemic chemotherapy. 27 out of 32 were evaluable for response and toxicity. 4 patients were not included because of early death due to other AIDS-related disease (2 cases), refusal of treatment (1), and insufficient follow-up data (1). One patient was excluded from the final analysis because of major protocol violation.

Correspondence to P.J.M. Bakker.
P.J.M. Bakker and C.H.N Veenhof are at the Division of Medical Oncology, F4-224, Academic Medical Centre, Meibergdreef 9, 1005 AZ Amsterdam; S.A. Danner, C.H.H. ten Napel, H.G. Sprenger, F.P. Kroon and R. van Leusen are at the National Aids Therapy Evaluation Centre (NATEC), Academic Medical Centre; A. Muusers is at the Comprehensive Cancer Centre, Amsterdam, The Netherlands.
Revised 26 Aug. 1994; accepted 4 Oct. 1994.

Table 1. Patient characteristics

Patients entered (*n*)	32	
Patients evaluable (*n*)	27	(84%)
Male	27	
Age (years)		
Median	39	
Range	26–54	
Antiretroviral therapy	24	(89%)
Previous opportunistic infections (*n*)	20	(74%)
Site of disease		
Cutaneous	27	(100%)
Lymphoedema/ulceration	20	(74.2%)
Symptomatic visceral	18	(67%)
CD4 cell count (× 10^6/l) *n*		
≤ 200	25	(93%)
>200	2	(7%)
Prognosis (*n*)		
Good	2	(7%)
Poor	25	(93%)

The characteristics of the 27 evaluable patients are shown in Table 1. All patients were homosexual males with a WHO performance status of 0–2. The median age was 39 years (range 26–54). The majority of these patients (24/27) were on antiretroviral therapy at the start of treatment. All patients were staged according to the staging system recommended by the ACTG [20].

Only 2 patients were considered to be in the good risk group (TO, IO, SO), the majority were poor risk KS. 20 of 27 patients experienced previous opportunistic infections and 25 patients had pretreatment CD4 cell counts of <200 × 10^6/l. All patients showed extensive cutaneous lesions, including tumour-associated oedema or ulceration in 20 of 27 patients and pulmonary involvement in 18. These 27 patients received 103 treatments with a median of 4 cycles (range 2–10). Three patients (11%) had a histologically proven complete remission of their KS, partial remission was obtained in 16 patients (59%). The overall response rate was 70% (95% CI 49–86). 4 patients had stable disease and 4 patients progressed (Table 2). The time to treatment failure in complete responders was 8 weeks, and median duration of partial response was 18 weeks (range 8–25 weeks).

Table 2. Results

Response to chemotherapy		
Overall	19	(70%)
Complete	3	(11%)
Partial	16	(59%)
Stable disease	4	(15%)
Progression	4	(15%)
Duration of response (weeks)		
Complete	8	
Partial median	18	
range	8–25	
Survival time (weeks)		
Median	30	
Range	4–63+	

Table 3. Laboratory parameters at baseline

Parameters	Mean	SD	Range
Haemoglobin mmol/l	6.99	0.84	5.5–8.7
White blood cells (× 10^9/l)	3.44	1.54	1.2–9.2
Neutrophils (× 10^9/l)	2.00	1.12	0.54–5.9
Platelets (× 10^6/l)	200	94	86–405
CD4 cells (× 10^6/l)	91.0	166.8	10–760

Median survival time for all patients was 30 weeks (range 4–63+ weeks). In the subset of patients with pulmonary Kaposi's sarcoma, the overall response rate was 73% including the 3 complete responders (17%) and 10 partial responders (56%). The duration of response in this group was not notably different from that of the whole group of patients, with a median of 17 weeks (range 8–25 weeks). The median survival time of this subset of patients was identical to that of the whole group of patients, that is, 30 weeks (range 4–63+ weeks).

The mortality rate was 85%. Death due to Kaposi's sarcoma occurred in 4 patients (15%), all with pulmonary involvement. The causes of death in the other patients were opportunistic infections (59%) or a combination of infectious complications and a general wasting syndrome (11%).

The major toxicity of the ABV regimen is severe myelosuppression. Table 3 shows the pretreatment haematological parameters. 13 patients required rh GM-CSF during treatment. The effect of rh GM-CSF on white blood cell and neutrophil counts is shown in Table 4. Recovery of white blood cell counts to 2–3 × 10^9/l occurred in 10 of the 27 courses (37%), recovery to values between 3–4 × 10^9/l in nine courses (33%) and complete recovery in seven courses (26%). rh GM-CSF was well tolerated with only minimal toxicity, 2 patients developed one episode of eosinophilia and another one episode of fever. No bacterial infections were recorded during therapy. Opportunistic infections during chemotherapy occurred in 5 patients (19%). *Mycobacterium avium* and candida infections were documented in 3 patients, 1 patient developed a herpes simplex infection and another a CMV infection. 2 of these patients received rh GM-CSF. Nausea and vomiting occurred in only 8% of the 103 courses of chemotherapy and were usually grade I, with only 1 patient developing grade III nausea and vomiting. Alopecia grade I and II occurred in 50% of the patients, and complete

*Table 4. Efficacy of rh GM-CSF first four courses of chemotherapy**

		WBC × 10^9/l			Neutrophils × 10^6/l		
Course	*n*	Mean	SD	Range	Mean	SD	Range
1	0						
2	8/27 (30%)	2.40	2.02	0.50–6.50	1.17	0.92	0.25–2.60
3	6/18 (33%)	3.87	1.58	1.40–5.50	2.11	1.09	0.78–3.63
4	6/14 (43%)	3.52	2.04	2.20–7.60	2.14	1.69	0.31–4.71

* All values were determined at day 8 after the start of chemotherapy. The number of patients treated with rh GM-CSF after four courses were too small for the calculation of mean values and standard deviation.

alopecia in 5%. Peripheral neuropathy (grade I, II) was seen in 16% of patients.

DISCUSSION

Our patients belonged to a poor prognosis group in which the main determinant of survival is the incidence of previous opportunistic infections. The median survival in this group of patients is roughly in the order of 8 months. Treatment of Kaposi's sarcoma has not been shown to have an effect on survival, but may produce worthwhile palliation. Therefore, non-toxic treatments are preferable. However, patients with extensive cutaneous disease and/or life threatening visceral involvement often need potential toxic, systemic treatment. Since it has been shown that the α-interferons are less effective in patients with low CD4-counts and prior opportunistic infections, chemotherapy is often the only option.

Although single agent chemotherapy has substantial activity in AIDS-associated Kaposi's sarcoma, combination chemotherapy results in higher overall response rates and includes more complete remissions [21, 22]. The most frequently used combination regimens are bleomycin and vincristine (BV) or the combination of doxorubicin, bleomycin and vincristine (ABV). Regimens containing anthracyclines probably have a higher response rate, but are considerably more toxic.

Currently, no randomised trials have been performed comparing BV with ABV with regard to their relative efficacies and toxicities, as well as quality of life issues. The most frequent and serious toxicity of anthracycline containing regimens is myelosuppression, with an increased risk of bacterial infections. Recently, it has been reported that the risk of opportunistic infections is also increased during chemotherapy [23, 24]. Particularly in patients with an already compromised bone marrow function, as in HIV infected patients on antiretroviral therapy as were ours, it seems necessary to decrease the risk of infectious complications. Recombinant granulocyte–macrophage colony stimulating factor can be safely applied to HIV-infected patients on antiretroviral therapy without up regulation of HIV.

rh GM-CSF exerts its effect by proliferation of myeloid precursor cells and so enhances not only the number but also the function of neutrophils and mononuclear phagocytes. Treatment of Kaposi's sarcoma with rh GM-CSF has been reported by Gill and associates [18]. In their study, 6 patients were treated with rh GM-CSF. All antiretroviral or myelosuppressive agents were discontinued in this study at least 2 weeks before study entry. Treatment with rh GM-CSF appeared to be safe, with no upregulation of P-24 antigen observed, and efficacious in those patients who required myelotoxic therapy with poor bone marrow function. None of their patients experienced bacterial infections, and only 1 patient developed a CMV retinitis during treatment.

In this study, we used a very effective multiagent chemotherapy regimen in a group of patients with poor prognosis Kaposi's sarcoma, the majority of whom already had a compromised bone marrow function due to the concomitant use of myelosuppressive antiretroviral medication. The overall response rate of 70% with three complete responders and 16 partial responders is similar to that of other reports of multiagent regimens. No notable difference response rate was observed in patients who used rh GM-CSF. The partial response duration was short, with a median duration of 18 weeks. The median survival time of 7.0 months in our study is also short and reflects the poor immune status of these patients. While the majority of the patients died because of opportunistic infections after treatment was stopped, only 4 patients died of their Kaposi's sarcoma. Our results in the subset of patients with pulmonary Kaposi's sarcoma are in accordance with the results of several small series of patients with pulmonary Kaposi's sarcoma. Gill and associates [11] treated 20 patients with pulmonary Kaposi's sarcoma and cytotoxic chemotherapy consisting of either doxorubicin alone, a combination of doxorubicin, bleomycin and vincristine (ABV) or bleomycin and vincristine (BV). They reported a response rate of 60% with a median survival in the responders of 10 months and in the non-responders of 6 months.

Garay and colleagues [25] have reported on 11 patients with pulmonary Kaposi's sarcomas treated with chemotherapy whose median survival was only 6 months.

Medurin and colleagues [26] reported a median survival of only 3.8 months in 11 patients with pulmonary Kaposi's sarcoma. However, in this study, only a small proportion of the patients received chemotherapy. This may have contributed to the reported short survival of this group of patients. Furthermore, from these studies and the study by Gill and associates [18], it can be concluded that treatment improves the survival of the subset of patients with pulmonary Kaposi's sarcoma.

The clinical profile of the Kaposi's sarcoma patient is, however, gradually changing. The majority of the patients will not only be severely immunocompromised, but will also present themselves with more extensive visceral disease. This is shown in our study where 18 patients had extensive pulmonary Kaposi's sarcoma. Therefore, it can be expected that, in parallel with the prolongation of life due to other therapeutic measures, the Kaposi's sarcoma related mortality of these patients will increase eventually.

The necessity of effective, relative non-toxic maintenance treatments in these patients will therefore increase. In the meantime, patients receiving treatment will need support with haematopoietic growth factors in case of severe treatment induced neutropenia. In our study, treatment with rh GM-CSF 5 μg/kg was associated with minimal toxicity. P-24 antigen was determined monthly in 9 of 13 patients who received rh GM-CSF. No upregulation of HIV was noted, P-24 antigen expression was unaltered during treatment with rh GM-CSF. It was shown that rh GM-CSF was able to reduce treatment induced neutropenia. Complete recovery to normal values occurred, however, only in seven of the 27 courses. Despite the severe neutropenia and partial recovery under rh GM-CSF, no bacterial infections were recorded. 5 patients (19%) developed opportunistic infections during treatment. The number of infections observed in this study is lower than could be expected since the recent literature showed an incidence of 23–45% [23, 24]. Whether rh GM-CSF was responsible for the low incidence of opportunistic infections in this study remains to be established. Randomised studies should address this issue in the future. Peripheral neuropathy with vindesine was less severe than that reported for vincristine. Neuropathy in 16% of our study patients is low when considering a reported background neuropathy of 15–50% in these patients [27, 28]. The disadvantage of vindesine is the eventual contribution to myelosuppression, and so its use may have added to the severe myelosuppression of the ABV regimen.

Because of the toxicity of this regimen (nearly half of the patients needed bone marrow support), the need for maintenance treatment and the general poor condition of these patients, ABV cannot be considered standard treatment. Currently, however, ABV or BV remain the most effective treatment modalities, especially in patients with potentially life threatening localis-

ations of their Kaposi's sarcoma. The effect of chemotherapy in patients with a pulmonary localisation of their Kaposi's sarcoma is often dramatic and does rapidly result in a symptomatic improvement in these patients. For the future, research has to be directed to less toxic but as effective treatments as ABV. A promising new development is the application of the liposomal encapsulated daunorubicin and doxorubicin.

Response rates comparable to multiagent regimens with minimal toxicity have been reported for these drugs [29, 30]. Randomised trials are now ongoing comparing multiagent chemotherapy regimens (ABV, BV) with these liposomal encapsulated drugs. These studies also include quality of life issues.

1. Odajnyk C, Muggia FM. Treatment of Kaposi's sarcoma: overview and analysis by clinical setting. *J Clin Oncol* 1985, **3**, 1277–1285.
2. Groopman JE. Biology and therapy of epidemic Kaposi's sarcoma. *Cancer* 1987, **59**, 633–637.
3. Beral V, Peterman TA, Berkelman RL, Jaffe HW. Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? *Lancet* 1990, **335**, 123–128.
4. Roth KW, Brandstetter H, Stürzl M. Cellular and molecular features of HIV-associated Kaposi's sarcoma. *AIDS* 1992, **6**, 895–913.
5. Krown SE. AIDS-associated Kaposi's sarcoma: pathogenesis, clinical course and treatment. *AIDS* 1988, **2**, 71–80.
6. Wit de R, Schattenkerk JKML, Boucher CAB, Bakker PJM, Veenhof CHN, Danner SA. Clinical and virological effects of high-dose recombinant interferon-alpha in disseminated AIDS-related Kaposi's sarcoma. *Lancet* 1988, **ii**, 1214–1217.
7. Groopman JE, Scadden DT. Interferon therapy for Kaposi's sarcoma associated with the acquired immunodeficiency syndrome (AIDS). *Ann Int Med* 1989, **110**, 335–337.
8. Volberding PA. The role of chemotherapy for epidemic Kaposi's sarcoma. *Semin Oncol* 1987, **14**, 23–26.
9. Laubenstein LJ, Krigel RL, Odajnyk CM. Treatment of epidemic Kaposi's sarcoma with etoposide or a combination of doxorubicin, bleomycin and vinblastine. *J Clin Oncol* 1984, **2**, 1115–1120.
10. Gelman E, Longo D, Lane HC, *et al.* Combination chemotherapy of disseminated Kaposi's sarcoma in patients with the acquired immune deficiency syndrome. *Am J Med* 1987, **82**, 456–462.
11. Gill PS, Akh B, Colletti P, *et al.* Pulmonary Kaposi's sarcoma: clinical findings and results of therapy. *Am J Med* 1989, **87**, 57–61.
12. Gill PS, Rarick MU, Espina B, *et al.* Advanced acquired immune deficiency syndrome-related Kaposi's sarcoma: results of pilot studies using combination chemotherapy. *Cancer* 1990, **65**, 1074–1078.
13. Gompels MM, Hill A, Jenkins P, *et al.* Kaposi's sarcoma in HIV infection treated with vincristine and bleomycin. *AIDS* 1992, **6**, 1175–1180.
14. Groopman JE, Mitsuyasu RT, DeLeo BJ, *et al.* Effect of recombinant human granulocyte-macrophage colony stimulating factor on myelopoiesis in the acquired immunodeficiency syndrome. *New Engl J Med* 1987, **317**, 593–598.
15. Levine JD, Allan JD, Tessitore JH, *et al.* Recombinant human granulocyte-macrophage colony-stimulating factor ameliorates zidovudine-induced neutropenia in patients with acquired immunodeficiency sydrome (AIDS)/AIDS-related complex. *Blood* 1991, **78**, 3148–3154.
16. Davey RT, Davey VJ, Metcalf JA, *et al.* A phase I/II trial of zidovudine and granulocyte-macrophage colony-stimulating factor in the treatment of human immunodeficiency virus type I infection. *J Infect Dis* 1991, **64**, 43–52.
17. Kaplan LD, Kahn JO, Crowe S, *et al.* Clinical and virologic effects of recombinant human granulocyte-macrophage colony stimulating factor in patients receiving chemotherapy for human immunodeficiency virus-associated non-Hodgkin's lymphoma: results of a randomized trial. *J Clin Oncol* 1991, **9**, 925–940.
18. Gill PS, Bernstein-Singer M, Espina BM, *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**, 1477–1481.
19. *WHO Handbook for Reporting Results of Cancer Treatment.* Geneva 1975.
20. Krown SE, Metroka C, Wernz JC. Kaposi's sarcoma in the acquired immunodeficiency syndrome: a proposal for uniform evaluation, response and staging criteria. *J Clin Oncol* 1989, **7**, 1201–1207.
21. Gaumes E, Guermonprez G, Katlama C, Gentilini I. AIDS-associated mucocutaneous Kaposi's sarcoma treated with bleomycin. *AIDS* 1992, **6**, 1483–1487.
22. Gill PS, Rarick M, McCutchan JA, Albrecht H, Stellbrink HJ, Meiger W. Systemic treatment of AIDS-related Kaposi's sarcoma: results of a randomized trial. *Am J Med* 1991, **90**, 427–433.
23. Flettenberg A, Stoehr A, Dijk v U, *et al.* Increasing risk for opportunistic infections (CDC IV C1) during chemotherapy in patients with Kaposi's sarcoma. IX International Conference on AIDS, Berlin, June 1993 [Abstr. 1557].
24. Tavio M, Antinori A, Cusini M, Andreoni M, Fasan M, Tirelli U. Adriamycin, Bleomycin, Vindesine (ABV) in 40 HIV infected patients with advanced Kaposi's sarcoma. IX International Conference on AIDS, Berlin, June 1993 [Abstr. 1559].
25. Garay SM, Belenke M, Fazzini R, Schinella R. Pulmonary manifestations of Kaposi's sarcoma. *Chest* 1987, **91**, 39–43.
26. Medurin GU, Stoven DE, Lee M, *et al.* Pulmonary Kaposi's sarcoma in the acquired immunodeficiency syndrome: clinical, radiographic, and pathologic manifestations. *Am J Med* 1986, **81**, 11–18.
27. De la Monte SM, Gabuzda DH, Ho OD, *et al.* Peripheral neuropathy in the acquired immunodeficiency syndrome. *Ann Neurol* 1988, **23**, 485–492.
28. Winer JB, Bang B, Clarke JR, *et al.* A study of neuropathy in HIV infection. *Am J Med* 1992, **83**, 473–488.
29. Presant CA, Scolaro M, Kennedy P, *et al.* Liposomal daunorubicin treatment of HIV-associated Kaposi's sarcoma. *Lancet* 1993, **341**, 1242–1243.
30. Jablonowski H, Szelényi H, Ambrecht C, Mauss S, Niederau C, Stromhmeyer G. Liposomal doxorubicin. A new formulation for the treatment of Kaposi's Sarcoma: a study of safety and efficacy in AIDS patients. IX International Conference on AIDS, Berlin, June 1993 [Abstr. 1573].