Combination Chemotherapy with Doxorubicin, Bleomycin, and Vindesine for AIDS-Related Kaposi's Sarcoma

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BACKGROUND. Kaposi's sarcoma is the most common neoplasm in patients with human immunodeficiency virus (HIV) infection. Although the best therapeutic approach is still unclear, patients with advanced KS are usually treated with systemic chemotherapy.

METHODS. A prospective multiinstitutional Italian study evaluated the efficacy and toxicity of combination chemotherapy with doxorubicin, bleomycin, and vindesine (ABVi) in patients with progressive and extensive HIV-related KS. Patients were given doxorubicin, 20 mg/m^2 on Day 1; bleomycin, 15 mg on Day 1, and vindesine, 4 mg on Day 1 biweekly ± granulocyte-colony stimulating factor.

RESULTS. Overall, 21 of 38 evaluable patients (55%) achieved an objective response (OR): there was 1 complete response and 20 partial responses. The most important bone marrow toxicity was granulocytopenia in 61% of the evaluable patients; 34% had Grades 3–4 toxicity, according to the World Health Organization Classification. The majority of patients (64%) developed some type of opportunistic infection (OI) during chemotherapy or the follow-up, with cytomegalovirus infection being the most frequent OI observed. The median duration of survival from KS diagnosis and from the start of ABVi therapy was 19 months (range, 3.4–88.5 months) and 9.9 months (range, 0.1–42.4 months), respectively.

CONCLUSIONS. The high rate of OI during ABVi chemotherapy and the follow-up is of concern, although these infections possibly could be due to our patients' low CD4+ lymphocyte counts. However, no toxic death was observed in our patients, suggesting that ABVi could be used in patients with aggressive disease, especially those who were previously untreated. ***Cancer* 1996; 77:2117–22.**
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Although Kaposi's sarcoma (KS) is the most common malignancy in patients with human immunodeficiency virus (HIV) infection, the proportion of patients with KS as their initial manifestation of the acquired immune deficiency syndrome (AIDS) has been declining both in the United States and in Europe.[1,2] In Italy, the main group affected by the HIV epidemic are intravenous drug users; however, homosexual men as in other Western countries, remain at high risk for developing KS.[3] Although the management of KS includes a number of therapeutic options, there is no consensus on the best approach to the different stages of the disease. In fact, it has to be stressed that no curative therapies are presently available; the natural course of the disease may be variable, and a large number of systemic approaches have an immunosuppressive effect. Consequently, many factors have to be carefully evaluated in devel-

oping a treatment strategy: the extent and location of lesions, the presence of tumor-associated symptoms, the presence of HIV-related diseases, and the status of the patient's immune system. Systemic chemotherapy is generally employed in patients with rapidly progressive disease, visceral involvement, and widespread symptomatic disease. When tumor compromises the functions of vital organs, such an approach may result in a rapid tumor regression and may be life-saving.

Among the cytostatic drugs tested so far, vincristine, vinblastine, etoposide, doxorubicin, and bleomycin are reported to be the most effective.[4-7] Such agents, as well as combination chemotherapy regimens such as vincristine and vinblastine[8] or vincristine and bleomycin,[9,10] are more commonly used for less advanced symptomatic disease than the doxorubicin-containing regimens.[11] However, little data exist on comparative studies with various chemotherapy regimens. Nonetheless, there are some indications of a better response rate of doxorubicin, bleomycin, and vincristine (ABV) when compared with doxorubicin alone, with an objective response of 88% and 48%, respectively.[12]

Conversely, chemotherapy, with the induction of bone marrow toxicity, could increase the risk of developing further opportunistic infections (OI). This aspect should be taken into consideration when deciding on treatments to be employed. More aggressive chemotherapy is strongly limited by the patient's hematologic tolerance and alternative therapeutic modalities are currently being investigated, such as liposomal anthracyclines (doxorubicin and daunorubicin).

The study reports the multiinstitutional experience of the Italian Cooperative Study Group on AIDS and Tumors (GICAT) in the treatment of patients with advanced KS with a combination of doxorubicin, bleomycin, and vindesine (ABVi). Vindesine was used instead of vincristine because of its lower neurotoxicity, as suggested by Dr. R. De Wit (Academic Medical Center, Amsterdam, The Netherlands, personal communication).

PATIENTS AND METHODS

Eligibility Criteria

Patients enrolled in this study were affected by HIV infection and biopsy-proven KS with extensive and/or progressive disease. In particular, patients with visceral involvement and/or complications such as edema or effusion were entered into this study. Patients who underwent treatments that included drugs other than doxorubicin, bleomycin, and vindesine or vincristine, as well as those previously treated with immunotherapy and/or radiotherapy, were considered eligible. Patients with prior exposure to alpha-interferon (α-IFN) within 4 weeks, previous local treatment to indicator lesions (i.e., vinblastine, radiotherapy), active uncontrolled infections, and a performance status of 3 or 4 according to the Eastern Cooperative Oncology Group (ECOG)[13] were not elegible. Moreover, the minimum hematologic values for entry into the study included a granulocyte count of greater than 1000/mm^3, platelet count of greater than 75/mm^3, hemoglobin greater than 8 g/dL, a serum creatinine level of less than 150 μmol/L, and a serum bilirubin of less than 30 μmol/L. Previous or concurrent zidovudine treatment was allowed. All patients received prophylaxis against *Pneumocystis carinii* pneumonia when CD4+ lymphocytes were less than 200/mm^3. The New York University (NYU) staging system[14] and AIDS Clinical Trial Group (ACTG) classification[15] were used for KS staging. Patients were treated in several institutions belonging to the GICAT.

Treatment Plan

Patients were treated with doxorubicin (20 mg/m^2), bleomycin (15 mg), and vindesine (4 mg) intravenously (i.v.) every 2 weeks. However, when the granulocyte count was between 500 and 1000/μL and/or the platelet count was between 50 and 75 $\times$ 10^9/L, doxorubicin was reduced by 50%; when granulocytes were less than 500/μL and/or platelets were less than 50 $\times$ 10^9/L, treatment was postponed for 1 week. In cases of an active uncontrolled infection, treatment was postponed until disappearance of the infection. Chemotherapy was administered until complete remission (CR), or two cycles beyond maximum response. Because the hematopoietic growth factor (granulocyte-colony stimulating factor, [G-CSF]) became available, it was given to some patients as a prophylactic therapy for iatrogenic neutropenia at a dosage of 5 μg/kg on Days 2–13 regardless of the leukocyte count at baseline. At that time, G-CSF was not available to all the institutions participating in the study and therefore its employment was not part of the protocol. Patients were not considered evaluable for response if they had not received at least two courses of chemotherapy. Patients showing progressive disease during these two courses of chemotherapy were considered as having failure to treatment.

Assessment of Response

CR was defined as absence of any detectable residual disease, including tumor-associated edema and/or effusion, for at least 4 weeks. A negative skin biopsy for representative remaining pigmented sites was needed to document CR.

Partial response (PR) was defined as the absence of new lesions (skin or oral) or of new visceral sites of involvement or the appearance or worsening of tumor-associated edema or effusion and at least a 50% decrease in the number of all previously documented lesions, or complete flattening of at least 50% of all previously raised

TABLE 1
Patients Characteristics at Study Entry

No. of patients in study	40
Median age (range)	38 (22–61)
Sex ratio (M/F)	39/1
Risk group	
Homobisexual	30 (75%)
Heterosexual	4 (10%)
IVDU	4 (10%)
Homosexual IVDU	2 (5%)
Hematologic status[a]	
Median leucocytes/mm^3 (range)	4000 (1880–8700)
No. of patients with leucocytes < 4000/mm^3	19 (47%)
Median platelets/mm^3 (range)	169.000 (83,000–351,000)
Hemoglobin g/dL (range)	11 (8–15)
Median CD4 lymphocyte count (range)[b]	88 (1–630)
< 100 (no of patients)	21
< 200 > 100 (no. of patients)	9
KS staging	
NYU: II	5
III	20
IV	15
ACTG[c]: Good risk	0
Poor risk	27

IVDU: intravenous drug user KS: Kaposi's sarcoma; NYU: New York University staging system; ACTG: AIDS Clinical Trial Group.
[a] On 40 evaluable patients.
[b] On 36 evaluable patients.
[c] On 27 evaluable patients.

TABLE 2
Treatment and Outcome

No. of pretreated patients	23/40 (57%)
Type of treatment	
Chemotherapy (Patients/OR)	8/2 (25%)
Alpha-interferon (Patients/OR)	15/5 (33%)
Radiotherapy (Patients/OR)	6/4 (66%)
Concomitant AZT therapy (No. of patients)	29 (72%)
Number of patients treated with G-CSF	17/40 (42%)
Number of cycles of chemotherapy	
Patients	40
Median	5
Range	1–12
Evaluable patients for response	38[a]
Overall response rates	21 (55%)
Complete response	1 (2.5%)
Partial response	20 (52.5%)
No change	11 (29%)
Progressive disease	6 (15.5%)
Objective response in pretreated/nonpretreated subsets	
(No. of OR/No. of patients)	
Pretreated	10/21 (48%)
Not pretreated	11/17 (65%)

Patients: no. of patients treated; OR: number of objective responses and percentage; AZT; zidovudine; G-CSF: granulocyte-colony stimulating factor.
[a] Two patients died after first cycle.

lesions (i.e., 50% of all previously nodular or plaque-like lesions become macules), or a 50% decrease in the sum of the products of the largest perpendicular diameters of the macular lesions, or patients with residual tumor-associated edema or effusion who otherwise meet the criteria for a CR, or patients in clinical CR but with residual pathologic disease.

Progressive disease (PD) was defined on the basis of any of the following criteria: an increase of 25% or more in the size of previously existing lesions, the occurrence of new lesions or sites of disease; a change in the features of 25% or more of existing skin or oral lesions from macular to plaque-like or nodular, and the development of new or increasing tumor-associated edema or effusion. Any response not meeting the criteria for PD or PR was defined as no change.

Toxicity Evaluation

Patients were evaluated for toxicity according to the World Health Organization (WHO) criteria.[16]

Dose Intensity

Relative dose intensity was computed as the percentage of total dose actually received by the patients compared with the scheduled dose, according to the method reported by Hrynick.[17]

Statistical Methods

Overall survival was analyzed from the beginning of treatment to the date of death or last follow-up. Survival analysis was carried out by means of the Kaplan–Meyer method.[18] The log rank test was used to test differences across the groups.

RESULTS

Clinical Characteristics

Forty patients were enrolled in the present study between January 1991 and December 1992. Patients characteristics at study entry are shown in Table 1. All patients except one were males (homobisexuals in 75% of the cases) between the ages of 22 and 61 years. Eight patients were already classified as being affected by AIDS before KS diagnosis, because of OI in all patients. Leukocyte count at the beginning of ABVi therapy was greater than 4000/mm^3 in 19 patients (47%). Four patients had been previously treated with chemotherapeutic agents. The median CD4+ lymphocyte count before the start of ABVi was 88/mm^3. Visceral involvement was documented in 15 patients (37%).

Treatment and Outcome

As shown in Table 2, 23 of 40 patients had been previously treated with radiation therapy (RT) and/or α-IFN and/or chemotherapy. Overall, ABVi was administered in 8

patients due to relapse, and in 15 patients due to disease progression under previous treatment. In particular, i.v. etoposide (at the dose of 150 mg/m^2 on Days 1–3 every 3 weeks, for a mean number of 4 cycles with 2 objective responses [OR]) had been administered to all patients who were pretreated with chemotherapy. Five OR were achieved in 15 patients who received α-IFN and 4 OR in 6 patients who underwent RT.

Of 40 patients, 17 received G-CSF as a prophylactic therapy for neutropenia from the first cycle of chemotherapy regardless of their baseline hematologic status. Because G-CSF was not available in several institutions at the beginning of the study, it was not administered to the remaining patients. Because patients treated with G-CSF comprised a large proportion of the patients, we carried out a comparison with nontreated patients, although it is worthwhile to note that G-CSF was not randomily assigned to the groups. The two groups of patients, patients treated with G-CSF and untreated patients, were comparable at baseline with regard to CD4+ lymphocyte count, hemoglobin level, leukocytes, neutrophils, platelets, and previous OI. At the end of the treatment, differences in leukocytes and neutrophils were statistically significant (P = 0.01 in both cases). No statistically significant differences were found between the two groups with regard to CD4+ lymphocytes, hemoglobin, platelets, days of hospitalization, OI, and other infections developed during treatment. The percentage of delays in chemotherapy administration and the relative dose intensity were similar between the two groups (with or without G-CSF), as was the frequency of dose reduction (18% vs. 39%, respectively, P = 0.26).

Thirty-eight of 40 patients were evaluable for response because 2 patients died before the second cycle of causes not related to chemotherapy (Table 2). Overall, the OR rate was 55%. The percentage of OR was 65% in the subgroup of previously untreated patients versus 48% in the previously treated patients, but this difference was not statistically significant.

Adverse Effects

The development of treatment-related bone marrow toxicity and other adverse events are summarized in Table 3. The most important type of bone marrow toxicity was granulocytopenia in 61% of evaluable patients, with 34% having a toxicity Grade of G3-G4, according to WHO.[16] No deaths due to toxic effects of the chemotherapy occurred. However, the majority of patients (64%) developed some type of OI during chemotherapy or follow-up. Cytomegalovirus infection (retinitis, colitis, pneumonia) was the most frequent OI observed. Neither neurotoxicity linked to therapy nor worsening of previously existing neuropathy was observed in our patients.

CD4+ lymphocyte count had significantly decreased from the beginning of chemotherapy (median, 88/mm^3, range, 1–630/mm^3) to the end (median, 49/mm^3, range, 1–383/mm^3). The Wilcoxon test[19] was used to compare the mean CD4+ lymphocytes before and after ABVi (P = 0.002).

TABLE 3
Adverse Effects

Hematologic toxicity	
Granulocytopenia	
No. of evaluable patients	35 (87%)
G1-G2[a]	10 (27%)
G3	7 (20%)
G4	5 (14%)
Thrombocytopenia	
No. of evaluable patients	38 (95%)
G1-G2[a]	6 (16%)
G3	1 (3%)
G4	1 (3%)
Median CD4 lymphocyte count at ABVi end (range)[b]	49/mm^3 (1–383)
OI during ABVi and follow-up	
Total OI	21 (64%)
CMV (retinitis, colitis, pneumonia)	9
Toxoplasmosis	4
PCP	3
Others	5
Not evaluable	7
Mortality during ABVi and follow-up	
No. of deaths	39
No. of patients lost to follow-up	1
Median time of follow-up (mo)	9.9
Cause of death	
OI	18 (46%)
KS	8 (21%)
Others	7 (18%)
Unknown	6 (15%)

OI: opportunistic infections; ABVi: doxorubicin, bleomycin, and vindesine; CMV: cytomegalovirus; PCP: *Pneumocystis carinii pneumonia*; KS: Kaposi's sarcoma.
[a] According to World Health Organization.
[b] In 33 evaluable patients.

Survival

The median duration of survival measured from the time when the patients were diagnosed as having KS and from the start of ABVi, were 19 months (range, 3.4–88.5 months) and 9.9 months (range, 0.1–42.4 months), respectively (Figs 1 and 2). Two adverse prognostic factors for survival were significant: previous OI (P = 0.006) and absence of OR (P = 0.001). A number of prognostic factors were not significantly associated with survival. These included age, risk group, KS staging according to NYU, a CD4+ lymphocyte count of less than 100/mm^3 determined at study entry, hematologic abnormalities developed during chemotherapy, use of G-CSF, and type of OI complicating chemotherapy and follow-up. Previously treated patients showed a significantly shorter survival (P = 0.005) from ABVi start than the untreated patients.

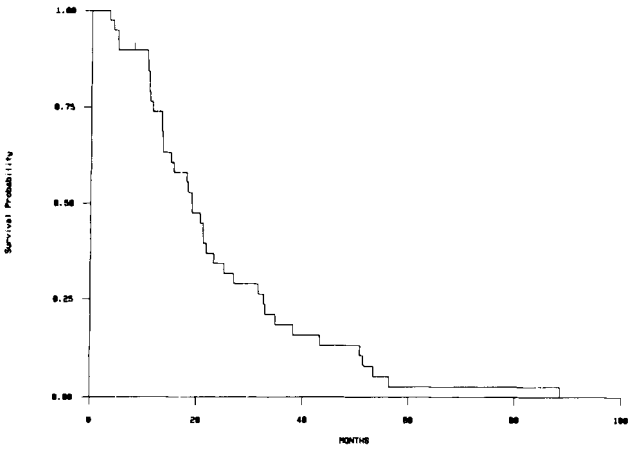

FIGURE 1. Overall survival for Kaposi's sarcoma from diagnosis.

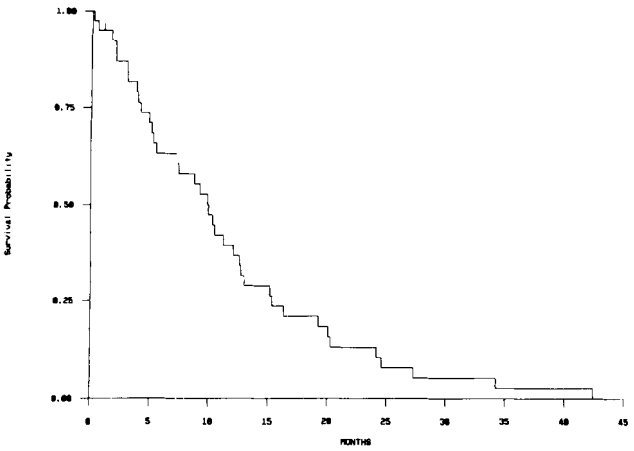

FIGURE 2. Overall survival for Kaposi's sarcoma from beginning of therapy.

However, the mean time elapsed between the first positive diagnosis of KS and the start of ABVi chemotherapy was 14.1 months (standard deviation [SD] ± 11.3) and 8 months (SD ± 17.3) in previously treated and untreated patients, respectively ($P = 0.004$). Until September 1995, 39 patients died and 1 patient was lost to follow-up. The causes of death were the following: 18 patients (46%), HIV-related opportunistic infections; 8 patients (21%), Kaposi's sarcoma; 7 patients (18%), other causes; and 6 patients (15%), unknown causes.

DISCUSSION

Although systemic therapy is not often recommended in patients with early-stage cutaneous KS with a small number of lesions, combination chemotherapy is generally accepted in patients with rapidly progressive disease or visceral involvement. The great variability in the management of KS may be due to the individual experience of the various physicians treating such patients, i.e., specialists in infectious diseases, dermatologists, radiation therapists, or oncologists. Moreover, it has to be stressed that there is no curative therapy for KS and that optimal treatment remains undefined. With the exception of patients with pulmonary involvement who have KS[4] there is no clear evidence that therapy results in an increase in overall survival. Palliation of symptoms, however, remains an important goal in KS, which is associated with high morbidity in more advanced stages.

The OR rate obtained with ABVi in our study was 55% with only 1 CR and was lower than that observed in other studies with ABV (using vincristine instead of vindesine). This difference may be attributed to the higher percentage of previously treated patients (57%) in our series in comparison with the other published studies.[11,12]

A minor difference in OR was observed between patients who did not receive any previous therapy (untreated patients) and pretreated patients (65% OR in untreated vs. 48% OR in pretreated patients). Moreover, untreated patients had a statistically significant increase in the duration of survival ($P = 0.005$) in comparison with pretreated patients. The two groups were then compared in terms of CD4+ lymphocyte count, KS stage, previous OI, neutrophils, and hemoglobin, and no statistically significant difference was found. However, there was a significant difference in the time interval elapsed from the establishment of positive KS diagnosis and ABVi treatment in the 2 groups of patients (mean 8 months in untreated patients vs. 14.1 months in pretreated patients; $P = 0.004$). Therefore, the longer duration of KS in pretreated patients, when compared with untreated patients (before starting therapy), could be an expression of a major severity in the clinical course of KS and HIV infection that cannot be revealed by the CD4+ lymphocyte count and the specific KS stage. This implies that the time elapsed between the establishment of a positive KS diagnosis and the start of therapy seemed to affect the duration of survival more than chemotherapy itself. Alternately, the decreased survival observed in pretreated patients may be explained by the induction of a higher resistance to chemotherapy as a consequence of previous treatments.

Collectively, 61% of the patients developed granulocytopenia during chemotherapy with G3 and G4 toxicity in 20% and 14% of the patients, respectively. However, 47% of patients had a leukocyte count lower than 4000 mm^3 at the beginning of therapy, possibly due to HIV-related myelodysplasia and/or poor bone marrow reserves secondary to previous chemotherapy. Although G-CSF demonstrated efficacy in reducing hematologic toxicity, it was not able to allow for an increase in relative

dose intensity. However G-CSF was selectively administered to certain patients and hence no definitive conclusion on its validity of employment can be drawn in this study.

After chemotherapy, the CD4+ lymphocyte count decreased significantly, possibly explaining the high rate of OI incurring during treatment and follow-up. Conversely, the high percentage of cytomegalovirus infection and other OI observed during ABVi and follow-up may be attributed not only to chemotherapy but also to the natural history of HIV infection.

The overall survival assessed from the start of ABVi was 9.9 months, whereas that from KS diagnosis was 19 months, which is consistent with data reported in other studies.[11,12,20,21] Further studies are necessary to establish whether chemotherapy may actually affect survival in patients with AIDS-related KS. Only OI and OR were significant prognostic factors for survival. The fact that a CD4+ lymphocyte count of less than $100/mm^3$ at the start of ABVi was not associated with a different survival could reflect the low number of patients in our study having a CD4 lymphocyte count greater than $200/mm^3$.

In conclusion, the results obtained with the ABVi regimen were slightly inferior than those reported with ABV (using vincristine instead of vindesine) in the literature, probably due to a less stringent selection of patients. Hematologic tolerance was the major limit, especially when G-CSF was not employed. The high rate of OI during ABVi and follow-up is of concern, although they could be possibly due to the low CD4+ lymphocyte count of our patients. Better control of HIV infection, associated OI, and complications of chemotherapy is clearly needed.

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