Treatment of Kaposi's Sarcoma with Vinblastine in Patients with Disseminated Dermal Disease

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Key words: classic Kaposi's sarcoma, disseminated disease, chemotherapy

Abstract

Background: Classic Kaposi's sarcoma is a rare tumor with an indolent behavior. Local therapy is not applicable in disseminated cutaneous disease. Patients with advanced disease are usually treated with systemic chemotherapy.

Objectives: To assess the effectiveness and toxicity of single-agent vinblastine in the treatment of disseminated and recurrent Kaposi's sarcoma

Methods: Ten patients with wide cutaneous spread of classic Kaposi's sarcoma were treated with single-agent vinblastine, 6 mg/m^2 intravenously once every 2 weeks. Vinblastine was continued for 2 months after achieving a maximal response.

Results: The male:female ratio was 2.3:1, and median age 64 years (range 50–79 years). The median number of involved nodules in the skin was 34. The overall response rate was 90%, 5 with complete response (50%) and 4 with partial response (40%). Complete responders had a longer duration of response than partial responders: 41.2 vs. 14.8 months. The median survival of all patients was 33 months. Side effects were minimal and tolerable.

Conclusions: Vinblastine is very effective in the treatment of extensive classic Kaposi's sarcoma, and results in a high response rate, long survival and disease-free survival with tolerable toxicity.

IMAJ 2001;3:251–253

Kaposi's sarcoma is now the most frequent malignancy associated with acquired immunodeficiency syndrome [1]. The classic form of Kaposi's sarcoma was described in 1872 [2]. Unlike AIDS-associated sarcoma, the classic form is an infrequent and less aggressive disease [3]. It occurs mostly in elderly men of Mediterranean, Eastern European or Jewish heritage [4]. Classic KS is generally indolent and has a chronic course. This form is a multifocal cutaneous angiolymphoproliferative disease that usually appears first in the lower extremities. Local disease is treated mainly by radiotherapy, with complete response rates of 80–90% [5]. Because of serious complications, radiotherapy is not used in patients with widely involved skin areas where large body surfaces could be irradiated. Other treatment modalities include simple excision, cryotherapy, intralesional therapy and laser therapy for very localized tumors [6]. These modalities are limited and cannot be used repeatedly or in recurrent or widespread disease.

Systemic treatment with cytotoxic agents is the treatment of choice for patients with widespread cutaneous or visceral KS or progressive disease. Excellent responses with tolerable side effects have been seen with single-agent and combination chemotherapy regimens. Vinblastine produces response rates of 90% in classic KS [7]. Because this disease is most commonly found in the elderly, a population that often suffers from other concomitant chronic diseases, we chose to use single-agent vinblastine to treat patients with disseminated disease. The present report summarizes the results of vinblastine treatment in 10 patients with disseminated classic Kaposi's sarcoma.

Methods

Between September 1994 and August 1999, 10 patients with histologically proven disseminated classic Kaposi's sarcoma were treated in our center. All had wide skin areas involving more than 30% of their skin surface. Baseline investigations included a complete history and physical examination, and documentation of all lesions. Each patient had a chest radiograph, computed tomography scan of the chest and abdomen, electrocardiogram, serum chemistry, complete blood counts, and serum tests for human immunodeficiency virus and cytomegalovirus. Patient characteristics at entry to the study are shown in Table 1. The male:female ratio was 2.3:1, and the median age 64 years (range 50–79).

All patients had extensive cutaneous disease in multiple areas of the skin. Lesions were found on both legs in five patients, on the legs and feet in three, and legs and trunk in two patients. The number of skin areas involved in each patient was eight or more (range 8–12). The median number of skin lesions was 34 (range 20 to > 50). All had a normal CT scan, normal renal and

KS = Kaposi's sarcoma

Table 1. Patient characteristics

No. of patients	10
Gender	
Male	7
Female	3
Age (yr)	
Median	64
Range	50–79
Ethnicity	
Sephardic Jews	5
Ashkenazic Jews	3
Arabs	2
Site of disease	
Legs	5
Legs and feet	3
Legs and trunk	2
No. of lesions	
Median	34
Range	20–>50
Previous therapy	
Radiotherapy	3
None	7

Table 2. Results of therapy

Response to chemotherapy	
Overall	9 (90%)
Complete	5 (50%)
Partial	4 (40%)
Stable disease	1 (10%)
Progression	0
Duration of response for all patients (mo)	
Median	26.7
Range	6-60
Median duration due to response (mo)	
Complete responders	41.2
Partial responders	14.8
Stable disease	14
Survival time (mo)	
Median	33
Range	13-65

hepatic functions and a performance status 2–3 according to World Health Organization criteria. HIV test was negative and CMV test was positive in all patients. Three patients had recurrence of the disease in previously irradiated skin areas as well as in new areas. No previous systemic chemotherapy had been performed.

Patients were treated with single-agent vinblastine (6 mg/m^2) intravenously every 2 weeks. In the event that the white blood count was less than 3x10^3/L or neutrophil counts <1,000/L, treatment was delayed until the blood count returned to normal levels. Chemotherapy was administered until complete response or maximal partial response was achieved, and then continued for two additional months for consolidation. CR was defined as a complete disappearance of all lesions, and PR as a 50% decrease in the number and/or size of lesions as compared to the baseline. Stable disease indicated a less than 50% reduction in tumor size or number of lesions, but no progression. Patients were clinically evaluated every 2 weeks until the end of treatment.

Results

The overall response rate was 90% [Table 2]. CR was achieved in 5 of 10 patients (50%), PR in 4 patients (40%), and one patient had a minimal response (stabilization of disease). Time to response was 4–10 months (median 5.8 months). The duration of treatment was 6–12 months (median 8.3 months), and median follow-up 31 months (range 6–65). The median duration of response for all patients was 26.7 months, 41.2 months for complete responders and 14.8 months for partial responders. Median survival of all patients was 33 months (range 13–65). One patient who did not achieve an objective response developed extremely large lesions on both legs and extensive abdominal lymphatic involvement, and died at home 16 months after onset of treatment. Autopsy was not performed on any patient. One patient with PR died after disease progression of infectious disease. Another patient with PR had disease progression after 13 months and is currently continuing treatment with interferon-alpha. The other two PR patients are still in response, 3 and 5 months after the cessation of treatment.

Toxicity was tolerable. There were no deaths associated with the treatment. Myelosuppression was mild and only one patient had a neutrophil count of <500/L. Nausea and vomiting occurred in only one patient.

Discussion

Systemic therapy is usually not recommended in patients with early stage cutaneous Kaposi's sarcoma with a small number of lesions. Chemotherapy is generally accepted in patients with rapidly progressive AIDS-related Kaposi's sarcoma or visceral involvement. A number of single agents have shown activity in AIDS-KS and include etoposide and vinca alkaloids (vinblastine, vincristine) [8,9]. Combination chemotherapy, however, produces higher response rates than monotherapies and is particularly effective in patients with disseminated disease [10,11]. An overall response rate of 70% was achieved in patients treated with doxorubicin, bleomycin and vindesine combination [12]. The choice of chemotherapy for patients with disseminated classic KS remains problematic because of its indolent behavior and the higher response rates to chemotherapy compared to AIDS-KS. In this study the overall response rate obtained with vinblastine in 10 patients with disseminated

HIV = human immunodeficiency virus
CMV = cytomegalovirus
CR = complete response
PR = partial response

cutaneous classic KS was 90% (CR 50%), which is similar to the best results published in the literature and is comparable to the response to chemotherapy combinations (11,12). Side effects were tolerable and patients could continue treatment for 6–12 months. Treatment results were unaffected by the patients' age, gender, ethnicity, previous treatment, CMV serum positivity, and the extent of the disease.

Brenner et al. [13] reported a 73% objective response rate in patients with classic KS treated with vinblastine. Other treatment modalities including interferon-alpha, human chorionic gonadotropin and pegylated-liposomal doxorubicin are also highly effective in the treatment of disseminated KS [14–16]. Vinblastine, however, is less costly and yields the same result. There is no contraindication to radiotherapy administered to limited areas of the skin following treatment with vinblastine [17].

In conclusion, vinblastine should be considered a highly active drug for treating disseminated classic Kaposi's sarcoma; the response rates are comparable to multi-agent regimens but vinblastine has less toxicity and assures an improved quality of life.

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Capsule

Secretion from the endoplasmic reticulum

Newly synthesized integral membrane and secretory proteins must traverse the endoplasmic reticulum (ER) and then the Golgi complex en route to the cell surface. Transport from the ER to the Golgi complex has been the subject of much scrutiny. Muniz et al. have used a cell free system that reconstitutes budding from the ER of yeast cells to examine the export of proteins that, lacking a transmembrane anchor, are linked by a glycolipid (GPI) to the membrane. Such GPI-anchored proteins were found to leave the ER in vesicles distinct from those used by integral membrane proteins. The sorting and packaging mechanism that recognizes this class of proteins remains unidentified, but these findings require some adjustment to the idea that all proteins leave the ER together to be sorted later in the pathway.

Cell 2001;104:313