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Kaposi's sarcoma, once a rare neoplasm, is now a common malignant disorder in persons with the acquired immunodeficiency syndrome (AIDS). Kaposi's sarcoma was originally described in 1872 by Moriz Kaposi, a Hungarian physician. Before the development of AIDS, Kaposi's sarcoma was a rare tumor seen in three distinct populations: 1) elderly men of Italian or eastern European Jewish origin, 2) Africans, and 3) patients with immunologic disorders. In the first group, the tumor (classic Kaposi's sarcoma) runs an indolent course. An endemic form of Kaposi's sarcoma is seen in the African population, where both adults and prepubescent children may be affected. The presentation of the disease in these patients is varied; it may be indolent in some adults, locally invasive and aggressive in young adults, or may present as a lymphadenopathic form seen in prepubescent children with generalized nodal and visceral involvement and a very poor prognosis. The third group includes patients with some type of immunologic disorder: renal transplant recipients on immunosuppressive therapy, patients with primary immunodeficiency disorders, or patients with lymphoproliferative diseases. The tumor may be localized or widely disseminated in these patients (1-4). Together, these three groups of patients have a 10% incidence of organ involvement. The heart is most commonly involved (67%), followed by lymph nodes (53%), and the gastrointestinal tract (45%) (5).

Clinical Aspects of Epidemic Kaposi's Sarcoma

Since the recognition of AIDS in 1981, the once rare Kaposi's sarcoma (< 2% of all sarcomas) is now a commonplace neoplasm. Epidemic Kaposi's sarcoma (EKS), as referred to in AIDS patients, is not seen with equal frequency in all high-risk groups. The overall incidence of EKS in association with AIDS is approximately 30% (4), but ranges from 46% to 48% in homosexual men, 4% in heterosexual intravenous drug abusers, and 12% in Haitian AIDS patients (1,3,4).

The increased incidence of EKS in homosexual men, as opposed to other high-risk groups, suggests that these patients may be exposed to additional factors which enhance the development of the neoplasm. One such factor is the cytomegalovirus (CMV). Studies have shown serologic evidence of CMV infections in endemic African Kaposi's sarcoma (2) and in classic Kaposi's sarcoma (6). However, due to the ubiquity of CMV in homosexual men (1), the actual significance of the virus in the etiology of the neoplasm is not yet clear.

The histologic characteristics of Kaposi's sarcoma are identical in all population groups (1). The two essential features necessary for diagnosis include: 1) vascular proliferation, and 2) spindle-shaped neoplastic cells embedded in reticulin fibers (5). The neoplastic cell appears to be of vascular endothelial origin, based on immunohistochemical studies (7) and electron microscopy (8,9). The tumor also appears to be multifocal and systemic at the onset, without the usual characteristics of a metastasizing neoplasm, ie, locally advancing, lymphatic, or hematogenous spread (1,2,4). A hypothesis is that profound cell-mediated immune depression in AIDS patients, which virtually destroys T-cell mediated immune surveillance, may be combined with a specific tumor growth factor which allows for rapid, uninhibited neoplastic vascular proliferation locally or in distant foci. Hence, EKS may be regarded as an opportunistic neoplasm (10).

Four clinical subtypes have been described in the endemic African Kaposi's sarcoma. The nodular subtype is characterized by the presence of skin nodules and a relatively indolent course. The florid and infiltrative forms are associated with locally aggressive tumors and bone involvement. The lymphadenopathic form is usually disseminated, involving lymph nodes and visceral organs (11). EKS resembles both the nodular and lymphadenopathic subtypes (2).

EKS lesions are generally asymptomatic. They may appear initially as pink, red, or violet, flat macules distributed in localized clusters or with wide dissemination (1,4,10). As the lesions progress, they become elevated (plaque stage) and finally may coalesce and become nodules (nodular stage).

A staging system for EKS, initially proposed by Krigel et al (12), is summarized in Table 1. This staging system includes all the variants of Kaposi's sarcoma. Each stage is further subdivided into "A" or "B" subtypes, depending on the presence or absence of fever (unrelated to an infectious source) or weight loss (greater than 10%).

Several important observations may be drawn from the initial longitudinal analysis of the patient population. First, sites of disease are variable. In 61% of patients, lymphadenopathy was generalized at initial presentation. The skin lesion manifestations

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Table 1
Clinical Staging of Kaposi's Sarcoma

Stage I	Cutaneous, locally indolent
Stage II	Cutaneous, locally aggressive with or without regional lymph nodes
Stage III*	Generalized mucocutaneous and/or lymph node involvement
Stage IV	Visceral
Subtype A	No systemic signs or symptoms
Subtype B	Systemic signs: 10% weight loss or fever greater than 100°F orally and unrelated to an identifiable source of infection lasting more than two weeks

*Generalized: more than upper or lower extremities alone; includes minimal gastrointestinal disease defined as more than five lesions and greater than 2 cm in combined diameters.

Table 2
Chemotherapy Trials in Epidemic Kaposi's Sarcoma

Drug	No. of Patients	Percent of Objective Response	Percent of CR*	Percent of PR†
VP-16 (19)‖	41	76	30	46
Vinblastine (20)	38	26	2	23
Vincristine (21)	18	61	0	61
ABV (19)‡	31	84	23	61
ABV (22)‡	9	77	11	66
Bleo-VP-16 (23)	7	100	57	43
Vinblastine/MTX (24)§	9	77	33	44
Vinblastine/Bleo (25)	31	62	0	62
Vinblastine/Vincristine (26)	20	45	5	40

*CR = complete response: total regression of all signs of tumor.
†PR = partial response: greater than 50% regression of each tumor lesion.
‡Adriamycin, bleomycin, and vinblastine.
§Methotrexate.
‖Etoposide.

ranged from none in 8% to generalized in 63%, while only one patient had a locally exophytic lesion. Survival is definitely related to the presence or absence of opportunistic infection (13). Patients who present with EKS but without an opportunistic infection have a better survival rate than those with an opportunistic infection (80% versus 15% alive at 30 months). Patients with "B" symptoms or opportunistic infections do poorly regardless of the stage of infection.

The New York University (NYU) staging system has definite prognostic value (14-16). All patients are subdivided into three groups: 1) the good prognosis group (stage I), with 100% survival at 18 months; 2) the intermediate prognosis group (stages III-A and IV-A), with 85% survival at 18 months; and 3) the poor prognosis group (stages III-B, IV-B, and coexistent opportunistic infections), with 24% survival at 18 months.

While clinical parameters appear to be prognostically useful, laboratory data are also important. The leukocyte and absolute lymphocyte counts in AIDS patients with EKS are closely associated with survival (4). The T-helper/T-suppressor cell ratio and the absolute level of T4 positive T-cells are also excellent predictors of survival (5). Patients with 30% or more T4 (helper) cells survived longer than those with less than 30% T4 cells (68% versus 44% were alive two years after diagnosis). Patients with T4/T8 (suppressor) ratios of at least 1.7 survived longer than those with either a ratio between 1.0 and 1.6 or less than 1.0. Specifically, the proportion of patients alive two years after diagnosis are 93%, 64%, and 43%, respectively (4). In general, as epidemic Kaposi's sarcoma progresses, a progressive decrease occurs in the T4/T8 ratio and the absolute T4 number. A recent analysis of prognostic variables in EKS showed laboratory parameters to be more important in predicting survival than clinical parameters (17). The presence or absence of endogenous interferon coupled with the hematocrit correlated with survival. The best risk group (group I) had absent endogenous interferon with a hematocrit greater than 38.8 and a median survival of 41.34 ± 6.36 months. In contrast, the poorest risk group (group IV) had endogenous interferon present with a hematocrit less than 38.8 and a median survival of 10.55 ± 0.96 months.

Therapy

The treatment of epidemic Kaposi's sarcoma was initially guided by recommendations given at a 1981 National Cancer Institute workshop, where it was suggested that 1) patients with limited disease receive local treatment, ie, radiation; 2) patients with widespread but slowly progressive disease be treated with single agent therapy; and 3) patients with advanced and rapidly progressive disease be treated with combination chemotherapy (18). However, some difficulties are encountered in evaluating treatment modalities of EKS. Because AIDS is a relatively recent phenomenon, the natural history of EKS has not been well defined; hence the natural progression of the disease versus that caused by manipulation of treatment regimens is hard to assess. While the NYU staging system is used by some investigators, it is not universally accepted (4,18). Therefore, meaningful evaluation of various treatment regimens is difficult.

The single agents most widely used are the vinca alkaloids and the epidophyllotoxin etoposide. Several recent trials are summarized in Table 2 (19-26).

At Henry Ford Hospital, 31 patients have been diagnosed as having epidemic Kaposi's sarcoma. Their treatment has been quite variable, including combinations with the vinca alkaloids, vinblastine, vincristine, bleomycin, and VP-16. The median survival of these 31 patients has been 11 months from their diagnosis of AIDS. Seven of the 31 patients have died as a result of Kaposi's sarcoma. Eight other patients died of opportunistic infections. The remaining 16 patients are still alive.

Because opportunistic infections are a major problem in EKS patients on combination chemotherapy, several investigators have developed protocols that are less myelosuppressive. Wernz et al (25) treated 31 patients with alternating weekly doses of vinblastine and bleomycin. Many patients had "B" symptoms (as defined in Table 1), prior opportunistic infections, or received prior treatment. Fifteen patients developed their first opportunistic infection while on treatment. Twenty-four patients achieved a partial response (7), four had stable disease, and two had no response.

Chemotherapy given as either a single agent or in combination is effective as palliative therapy in many patients with EKS (Table 2). Because our knowledge of the natural history of this disease is limited, it is unclear whether the administration of chemotherapy confers any survival advantage. Clearly, the underlying immune defect and subsequent opportunistic infection remain a major problem in these patients.

Table 3
Interferon Trials in Epidemic Kaposi's Sarcoma

Interferon	Dose	No. of Patients	Percent of Objective Response	Percent of CR*	Percent of PR†
Recombinant Interferon Alpha (28)	36 to 54 × 10^6 U/day intramuscularly (IM) 4 to 8 weeks	36	38	23	15
	3 × 10^6 U/day IM 4 to 8 weeks	39	3	0	3
	(No response, escalate to higher dose)	33	17	10	7
Recombinant Interferon Alpha (29)	1 × 10^6 U/m^2/day subcutaneously; alternate weeks for 8 weeks if no response	10	20	—	—
	Escalate to 50 × 10^6 U/m^2/day intravenously; alternate weeks for 8 weeks	10	40	—	—
	50 × 10^6 U/m^2/day intravenously; alternate weeks for 8 weeks	20	32	—	—
	30 × 10^6 U/m^2/day subcutaneously for 8 weeks	64	31	—	—
Human Lymphoblastoid Interferon (30)	7.5 × 10^6 U/m^2 IM daily for 28 days	9	11	0	11.1
	15 × 10^6 U/m^2 IM daily for 28 days	10	0	0	0
	25 × 10^6 U/m^2 IM daily for 28 days	10	30	30	0
	Overall response	29	13	10	3
Human Lymphoblastoid Interferon (31)	20 × 10^6 U/m^2 IM for 28 days or 2 months	12	67	33.3	33.3

*CR = complete response: total regression of all signs of tumor.
†PR = partial response: greater than 50% regression of each tumor lesion.

The natural properties of interferon make its use appealing in epidemic Kaposi's sarcoma. Specifically, interferon has known antiproliferative, antiviral, and immunomodulatory effects (27). Investigators have hoped that the antiproliferative properties might combat the rapidly progressive EKS. The antiviral effects of interferon might combat the underlying causative agent of AIDS or other clinically important viral infections, and perhaps the immunomodulatory effects of interferon might improve the underlying immune defect in these patients.

Most interferon investigations in EKS have used either recombinant interferon alpha or lymphoblastoid interferon. Real et al from the Memorial Sloan-Kettering Cancer Center (MSKCC) studied the use of both low and high doses of recombinant leukocyte α interferon in 75 patients (28). Patients were staged according to a MSKCC staging system and excluded if there was an ongoing infection or previous treatment with recombinant interferon. The doses and results are depicted in Table 3, along with three other interferon trials. In this study a positive correlation occurred between response to interferon treatment and a history of previous opportunistic infection, but no association was found with tumor burden or visceral involvement. In addition, a highly significant survival difference was observed in responders versus nonresponders.

Volberding and Mitsuyasu (29) evaluated several dose levels of recombinant alpha interferon (Table 3). Clinically poor prognostic factors, ie, "B" symptoms and opportunistic infection, affected response to therapy. Human lymphoblastoid interferon was studied in several dose ranges at the National Cancer Institute (30). Interestingly, all patients receiving the highest dose level required a 75% dose reduction due to toxicity, so that all patients received between 6 and 15 × 10^6 U/m^2 daily by the second week of therapy. In this study, patients with no history of opportunistic infections or chronic CMV viremia and with higher total lymphocyte counts and absolute T4 counts had a better chance at a response.

Clearly, recombinant interferon and human lymphoblastoid interferon are active in treating patients with epidemic Kaposi's sarcoma. Several factors seem to enhance response rates: the lack of "B" symptoms (29), the absence of opportunistic infections (28-30), and the lack of endogenous acid-labile alpha interferon (29-32). While tumor burden was an important prognostic variable in one study (31), it had no effect in another (28). Similarly, while some immunologic parameters correlated with response in one study (30), this has not been a universal finding (32). The actual mechanism whereby interferon induces tumor regression is unknown.

Many questions regarding the natural history and treatment of epidemic Kaposi's sarcoma remain unanswered. While chemotherapy and interferon treatments are active treatments for the disease, a true long-term survival benefit has not been documented. Persistent observation and study, including prospectively randomized therapy trials, are essential to continue the progress against this disease.

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