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Role of Intralesional Vinblastine Administration in Treatment of Intraoral Kaposi's Sarcoma in AIDS

C.M. Flaitz, C.M. Nichols and M.J. Hicks

The purpose of this clinical study was to determine the effect of intralesional vinblastine administration on intraoral Kaposi's sarcoma (KS) in AIDS patients. One hundred and forty-four KS lesions in 50 HIV-positive homosexual males (mean CD4 count 64/mm^3) were treated periodically with intralesional vinblastine injection (0.1 mg/cm^2) until lesion resolution or no further reduction in lesional area. The most common lesion sites were: palate 56% (hard palate 42%, soft palate 14%); gingiva 22% (maxillary 15%, mandibular 7%); and maxillary tuberosity 6%. The mean lesion area was 4.6 cm^2 (range = 0.1–35 cm^2). Complete resolution occurred in 74%. The mean reduction in lesional area was 93% for all lesions. Lesions with only a partial response (26%) to vinblastine had a mean reduction in the lesional area of 69%. The mean number of treatments was 2.4 (range = 1–6). The recurrence rate was 26% with a mean disease-free period of 12.9 weeks. Recurrence rates were highest for nodular (40%) and purple macular lesions with focal nodularity (36%). The most frequent complications were transient pain (72%), superficial mucosal ulceration (22%) and transient paresthesia (12%). Intralesional vinblastine administration produced complete resolution in a substantial number of intraoral KS lesions and represents a well-tolerated treatment regimen for localised control of intraoral KS lesions. Owing to a 25% recurrence rate, re-evaluation is necessary for treatment of recurrent and new Kaposi's sarcoma lesions.

Keywords: AIDS, HIV, Kaposi's sarcoma, vinblastine, oral

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INTRODUCTION

KAPOSI'S SARCOMA represents the most common malignant neoplasm in individuals with acquired immunodeficiency syndrome (AIDS) and occurs in approximately 10–15% of AIDS patients [1–5]. The oral cavity is involved in 80% of cases with lesions most frequently found in mucosa supplied by the palatine arteries [6, 7]. Perhaps more importantly, intraoral Kaposi's sarcoma may be the initial sign of human immunodeficiency virus (HIV) infection or progression from HIV infection to AIDS [8, 9]. Early lesions in Kaposi's sarcoma appear as asymptomatic erythematous macules involving the superficial aspect of the oral mucosa and gingiva [8–10]. With maturation, the deeper aspect of the tissue becomes involved and a nodular pattern emerges. Lesion colour is transformed from erythematous to violaceous, owing to deposition of haemosiderin within the submucosal tissue.

Intraoral Kaposi's sarcoma produces significant symptoms in HIV-infected patients and may contribute to the overall health and well-being of these individuals [8, 9]. Typical symptoms in advanced lesions are localised pain, dysphagia and bleeding from the lesions [8, 9]. Frequent concerns by the patients are the presence of the mass itself and esthetic concerns. Owing to the compromised nutritional status of these patients and the mass effect of these lesions, nutritional intake may be impaired. In addition, traumatisation and/or rapid growth of the lesions may lead to mucosal ulceration and result in secondary infection. Erosion of the underlying bone with involvement of the maxilla and mandible by Kaposi's sarcoma may also occur [11]. Both speech pattern and physical appearance may also be affected and result in stigmatisation of the patient. Intralesional vinblastine was first used in 1989 as a treatment for oral Kaposi's sarcoma [12–14].

The purpose of this ongoing clinical study [8] was to evaluate the effects of intralesional vinblastine administration on intraoral Kaposi's sarcoma in AIDS.

Correspondence to C.M. Flaitz.
C.M. Flaitz is at the Department of Stomatology, Division of Oral Pathology, Dental Branch, University of Texas–Houston Health Science Center; C.M. Nichols is at the Department of General Dentistry, Dental Branch, University of Texas–Houston Health Science Center, Houston, Texas; M.J. Hicks is at the Department of Pathology, Texas Children's Hospital, Baylor College of Medicine, and Division of Pediatric Dentistry, Dental Branch, University of Texas–Houston Health Science Center, Houston, Texas, U.S.A.
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MATERIALS AND METHODS

Study population

Fifty HIV-positive males with 144 intraoral Kaposi's sarcoma lesions were included. These patients had biopsy-proven oral and/or cutaneous Kaposi's sarcoma and were referred by their physicians for treatment of their intraoral lesions. All patients were classified as having AIDS according to CDC criteria with a mean CD4 count of 63.9/mm^3 (CD4 $\leq$ 100/mm^3 in 78% of patients). The risk factor for HIV infection was men who have sex with men. The mean age was 34.1 years (range 26–50 years). A number of medications were being taken. Antiretroviral and antiviral medications were being taken by 90% and 42% of patients, respectively. Anti-tuberculosis drugs were prescribed for 26% and prophylactic medication for *pneumocystis carinii* pneumonia was being taken by 66%. Both systemic (38%) and topical (24%) antifungal agents had been prescribed for prophylaxis and/or treatment of candidiasis. *Pneumocystis carinii* pneumonia was the most frequent (44%) opportunistic infection, followed by intraoral candidiasis (42%). Tuberculosis, cytomegaloviral infection, varicella and cryptococcal meningitis were reported as prior opportunistic infections in 10–16% of subjects. Recurrent herpes simplex, hairy leukoplakia, toxoplasmosis, cryptosporidiosis, histoplasmosis and pseudomonal pneumonia had occurred in 2–8% of patients. Almost two-thirds of subjects had experienced sexually transmitted diseases with 14% experiencing three or more sexually transmitted diseases. The most frequently encountered diseases were gonorrhea (34%), hepatitis B (26%), syphilis (24%), anogenital condyloma (14%) and herpes simplex type II (14%).

Table 1. Intraoral locations of Kaposi's sarcoma

Location	Frequency
Palate	55.6%
Hard palate	(41.7%)
Soft palate	(13.9%)
Gingiva	22.2%
Maxillary	(14.6%)
Mandibular	(7.6%)
Maxillary tuberosity	5.6%
Tongue	4.2%
Dorsum of tongue	(2.8%)
Ventral tongue	(1.4%)
Lip	3.5%
Maxillary lip	(2.8%)
Mandibular lip	(0.7%)
Tonsillar pillar	3.5%
Retromolar pad	2.8%
Floor of mouth	1.4%

Treatment

Each of the 144 lesions were placed into one of five categories [8] based upon clinical appearance. These categories were: purple macular, purple macular with focal nodularity, nodular with mucosal colour ranging from normal to purple, red macular and red macular with focal nodularity. Each lesion was photographed before and after treatment. The surface area of the lesion was measured during each clinical examination and photographs were taken to document the lesion type and response to therapy.

Local anaesthesia (0.5% bupivacaine with 1:200,000 epinephrine) was administered prior to treatment with intralesional vinblastine at a dosage of 0.1 mg/cm^2 using a 0.2 mg/ml solution of vinblastine sulphate in sterile saline. At 2-week intervals, the patients were recalled to assess response to treatment by determining the effect on lesional area. At these recall visits, Kaposi's sarcoma lesions were treated again with vinblastine (0.1 mg/cm^2) if the lesions were responding to treatment, as determined by a decrease in lesional area and/or if lesion pigmentation decreased. If mucosal ulceration was present, treatment was delayed for 1 week. The amount of vinblastine administered and post-treatment complications were recorded at each treatment visit. Treatment was discontinued if no clinically detectable lesion remained or if there was no interval reduction in lesional area and lesion pigmentation was stabilised. The percentage reduction in lesional area was determined for each lesion. The lesions were classified as complete clinical resolution (no residual lesion), partial resolution (<25%, 26–50%, 51–75%, 76–95% lesional area reduction) or no treatment response. The total amount of vinblastine administered and number of treatments were also determined.

All patients were followed at 4-week intervals following the final intralesional vinblastine treatment for up to 64 weeks (mean follow-up 14.1 weeks) to assess recurrence and disease-free status. No patients were lost to follow-up; however, 19 patients died of AIDS-related diseases during this study.

RESULTS

Kaposi's sarcoma involved both keratinised and non-keratinised oral mucosa (Table 1); however, the vast majority of lesions involved keratinised oral mucosa. The most common location was the palate, with the hard palate being more frequently involved than the soft palate. The mean lesional area (Table 2) was 4.6 cm^2, ranging from 0.1 to 35.0 cm^2. Recurring lesions had a larger mean lesional area (5.3 cm^2) when compared with non-recurring lesions (4.3 cm^2). Intralesional vinblastine administration resulted in complete clini-

Table 2. Intralesional vinblastine administration in Kaposi's sarcoma

	All lesions	Non-recurring lesions	Recurring lesions
Vinblastine administered (per treatment)	0.08 mg/cm^2 0.37 mg/lesion	0.08 mg/cm^2 0.34 mg/lesion	0.07 mg/cm^2 0.37 mg/lesion
Mean lesional area (mean)	4.6 cm^2	4.3 cm^2	5.3 cm^2
Mean number of treatments	2.4	2.3	2.8

Table 3. Treatment response of Kaposi's sarcoma to intralesional vinblastine administration

Clinical response to intralesional vinblastine	
Complete clinical resolution	73.6%
Partial clinical resolution	26.4%
(76–95% reduction)	(11.8%)
(51–75% reduction)	(11.1%)
(26–50% reduction)	(2.8%)
(<25% reduction)	(0.7%)
No clinical response	0%
Mean reduction in lesional area	
All cases ($n=144$)	93.0%
Partial resolution cases ($n=38$)	68.8%
Recurrence rate	25.7%
Mean disease-free period (period to recurrence)	12.9 weeks
Complications following treatment	
Transitory pain	72%
Mucosal ulceration	22%
Paresthesia	12%
Sinusitis	6%
Fever	2%
Ischemia, localised	2%

cal resolution (Table 3) in slightly less than 75% of lesions. All lesions were judged to have either a complete or partial clinical response to vinblastine treatment. The mean reduction in lesional area for all lesions was slightly greater than 90% (Figs 1–4). With the lesions that had a partial clinical response, an almost 70% reduction in lesional area occurred. The mean number of treatments for all lesions was 2.4, ranging from one to six treatments. The recurrence rate following the final vinblastine administration was slightly over 25% with a mean disease-free period of 12.9 weeks. Comparison of vinblastine administered per treatment was similar for both non-recurring and recurring lesions. The number of treatments required to reach complete clinical resolution or no additional response was greater for recurring lesions. The clinical appearance (Table 4) was somewhat different between recurring and non-recurring lesions. A greater proportion of recurring lesions were classified as purple macular with focal nodularity and nodular when compared with non-recurring lesions. Recurrence rates within these two lesion types were also the highest among the five lesion types. Non-recurring lesions were more frequently found within the red macular with or without nodularity types when compared with recurring lesions. The lowest recurrence rates were seen with red macular lesion types.

Intralesional vinblastine administration resulted in transitory pain in 72% of patients. Of these patients, 70% required

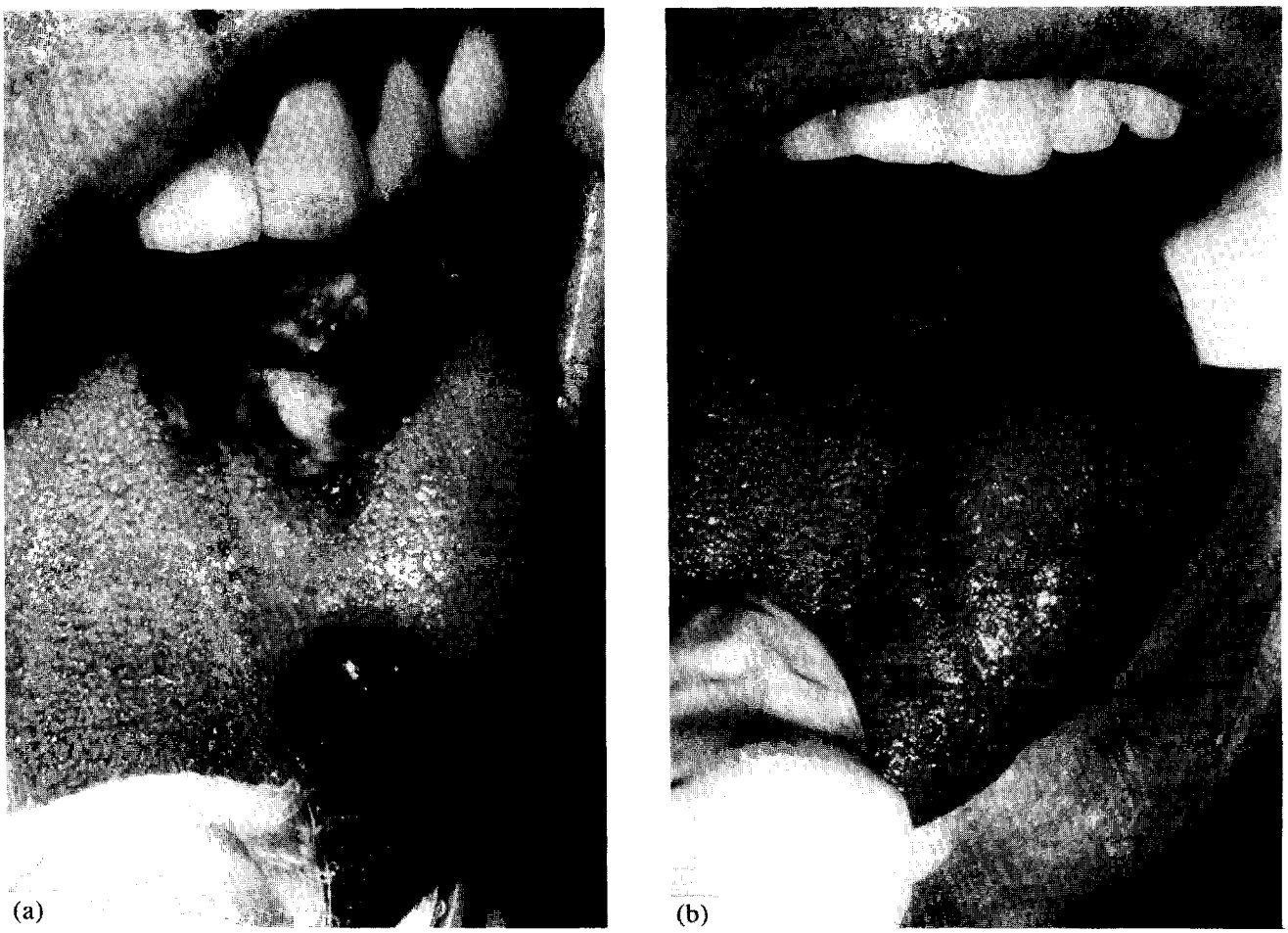

Fig. 1. Nodular Kaposi's sarcoma lesion involving dorsal tongue prior to (a) and following (b) three intralesional vinblastine treatments.

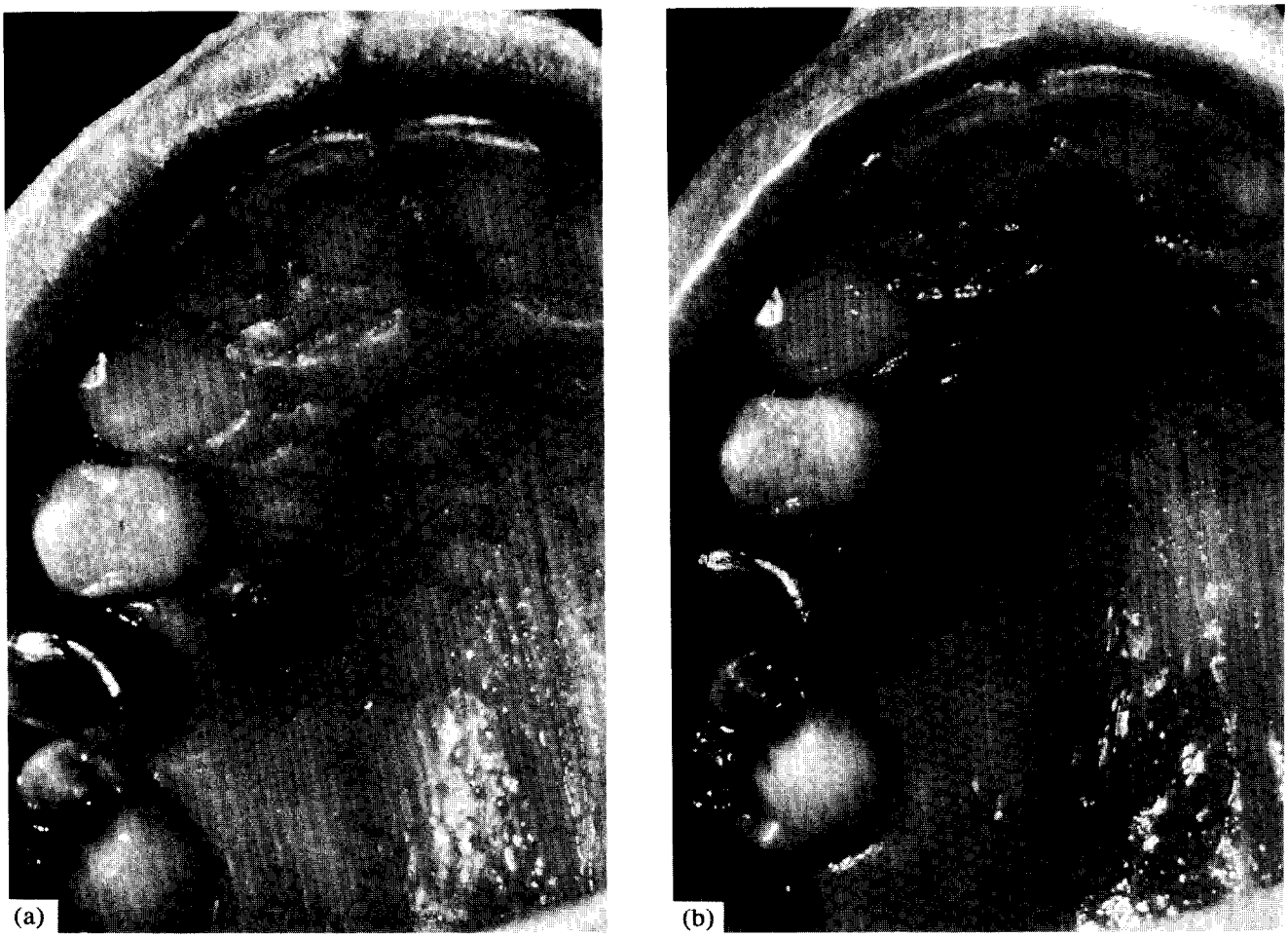

Fig. 2. Nodular Kaposi's sarcoma lesion involving hard palate prior to (a) and following (b) two intralesional vinblastine treatments.

codeine-containing analgesics for relief of pain symptoms. Less frequent complications of vinblastine treatment were mucosal ulceration (22%), temporary paresthesia (12%), sinusitis (6%), fever (2%) and localised ischemia (2%). Pain was most frequently reported following the first vinblastine treatment. 19 patients died of AIDS-related diseases. Disseminated Kaposi's sarcoma was the cause of death in 5 patients. Atypical tuberculosis ($n=7$), *pneumocystis carinii* pneumonia ($n=4$) and cytomegaloviral infection ($n=3$) were the proximate cause of death in the remaining 14 patients.

DISCUSSION

Intralesional vinblastine administration in oral Kaposi's sarcoma provides a means for palliation of symptoms while producing a considerable disease-free period in AIDS patients [8, 12–14]. The clinical outcome from the present study compares favourably with previous studies [12–14]. However, in the present study, a higher proportion of lesions were classified as complete clinical resolution. This may be due to the study protocol which required that periodic treatment be carried out until there was clinical resolution or no change in lesional area. The number of vinblastine treatments varied from as few as one treatment to as many as six treatments. Other studies [12–14] have used a single vinblastine treatment design with most patients, while only a subset of patients received more than one treatment. In general, periodic intralesional vinblastine administration until resolution or no further reduction in lesion size resulted in an over 90% reduction in lesional area with slightly less than 75% of lesions classified as undergoing complete clinical resolution. However, one-quarter of lesions did recur with a mean disease-free period of about 3 months. This compares quite favourably with another study [12] in which there was a 57% recurrence rate with a mean disease-free period of about 4 months following a single vinblastine treatment. The reduction in the rate of recurrence in the present study may be secondary to the fact that the present study allowed for multiple treatments until clinical resolution or no change in lesional area was achieved.

The complications associated with this type of treatment are transitory and well-tolerated [8, 12–14]. The most frequent complaint was transitory pain (72%) which was readily alleviated by analgesics containing codeine. When these post-injection complications are compared with the potential side-effects of other treatment modalities for localised Kaposi's sarcoma [9, 15–21], the complications associated with intralesional vinblastine are short-lived and do not affect adjacent oral mucosa or salivary gland function. Fractionated radiotherapy for intraoral Kaposi's sarcoma may result in severe mucositis and decreased salivary flow levels, even at relatively low radiation dosages (300 cGy) [15–17]. Radiotherapy is also

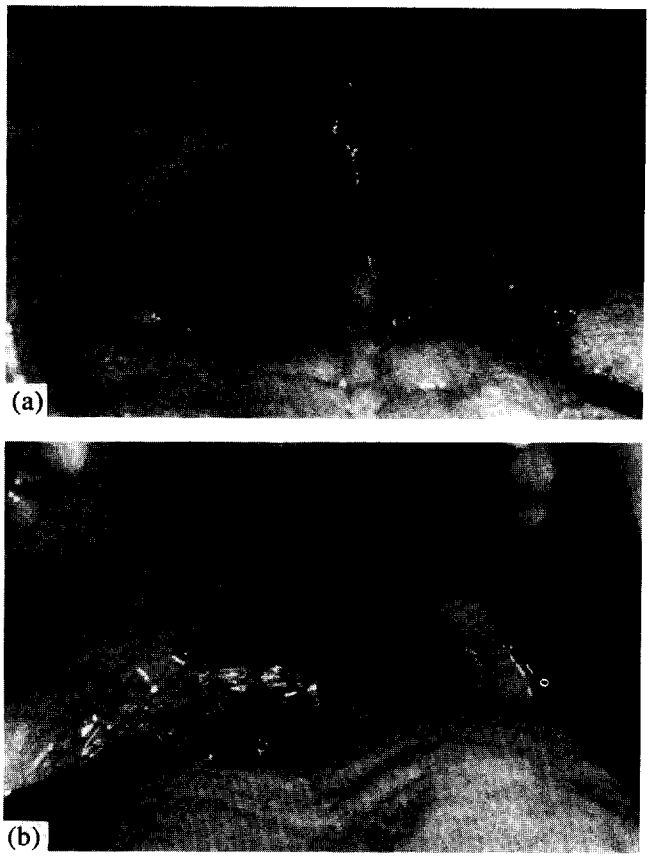

Fig. 3. Macular Kaposi's sarcoma lesion involving tonsillar pillar prior to (a) and following (b) two intralesional vinblastine treatments.

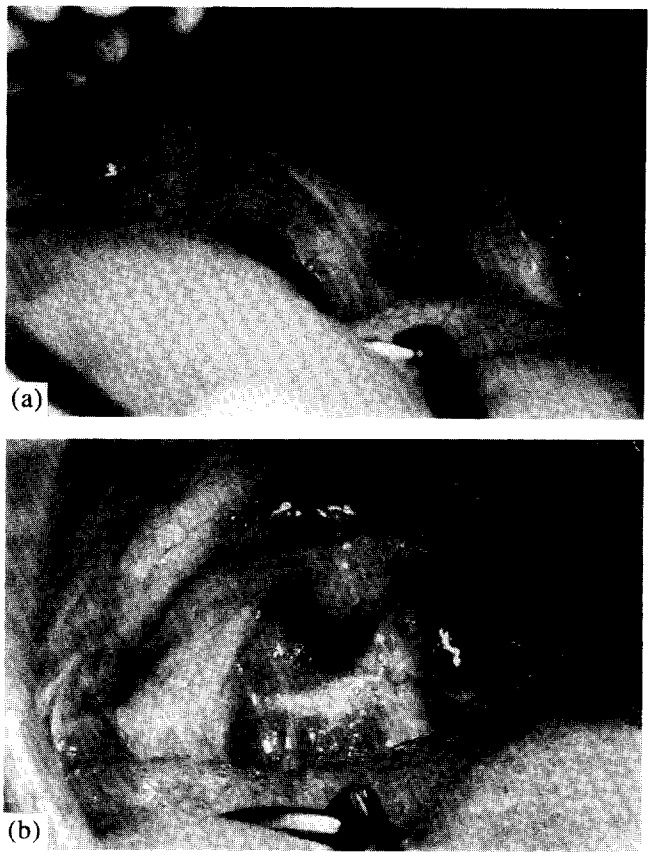

Fig. 4. Exophytic nodular Kaposi's sarcoma lesion involving soft palate prior to (a) and following (b) four intralesional vinblastine treatments.

a palliative measure with only a 20% complete remission rate and relapse within 4–6 months [16, 17]. Once the maximum dosage has been given, further radiotherapy is prohibited. Likewise, systemic chemotherapy may not be well-tolerated and contraindicated due to the fragile health status in AIDS patients. Mucositis, myelosuppression and opportunistic infections are associated with systemic chemotherapy [8, 9, 18–20]. Although systemic chemotherapy provides a response rate of 72–88%, complete remission is achieved in only 30% [19, 20]. Once chemotherapy is terminated, relapse occurs. Surgical resection of Kaposi's sarcoma is indicated when the lesions are localised, resectable and accessible [8, 9]. With many patients, multifocal lesions are often present and these lesions are extensive with involvement of the deep submucosal tissues which obviates surgical management. Laser fulguration has also been promoted, but this treatment modality is best suited for exophytic lesions and is not effective in treating diffuse infiltrative lesions [8]. The advantage of laser therapy is the degree of hemostasis achieved and reduction in postoperative discomfort.

The clinical appearance of Kaposi's sarcoma lesions may help determine which lesions recur more frequently and help direct follow-up and future therapy. Both nodular (40%) lesions and purple macular lesions (36%) with focal nodularity had the highest recurrence rates in the current study. These lesions may represent well-established, long-standing Kaposi's sarcoma lesions [8–10]. In addition, the lesions may be infiltrative and involve the deep submucosa. Although clinical resolution was achieved with these lesions, a residual microscopic tumour which would not be detected clinically may have remained [8]. Recurring tumours had a greater mean lesional area (5.3 cm^2) when compared with non-recurring tumours (4.3 cm^2) and required additional intralesional vinblastine treatments to reach clinical resolution. Prophylactic treatment of tumours which are more prone to recur after clinical resolution may be necessary to eradicate microscopic residual disease and provide the longest possible disease-free state.

The difficulty in developing a treatment regimen for AIDS-Kaposi's sarcoma is the fact that the pathogenesis is not known. Several factors [8, 22] have been implicated in tumorigenesis in AIDS-Kaposi's sarcoma including: (1) HIV-induced immunosuppression; (2) genetic predisposition (HLA-DR5 major histocompatibility group expression); (3) HIV-tat gene insertion with direct effect on cellular transformation; (4) co-infection with pathogens transmitted by sexual practices (cytomegalovirus); and (5) cytokines produced by HIV-infected cells which induce proliferation. Athough the pathogenesis of AIDS-Kaposi's sarcoma is still being defined, an efficacious palliative treatment modality is available [8, 12–14]. Intralesional administration of vinblastine [8, 12–14] has been shown to produce a marked reduction in lesional area, induce clinical resolution and result in a considerable disease-free period. Major advantages of this palliative method are that it requires minimal expenditure and that this technique may be performed in a typical general dentistry practice setting. The

Table 4. Clinical appearance of Kaposi's sarcoma and relationship to recurrence

	Purple macular	Purple macular/ nodular	Nodular	Red macular	Red macular/ nodular
All lesions ($n=144$)	37.5%	23.6%	15.9%	17.4%	5.6%
Recurring lesions ($n=37$)	35.2%	40.5%	16.2%	8.1%	0%
Non-recurring lesions ($n=107$)	38.4%	24.2%	8.4%	21.5%	7.5%
Recurrence rate	22.8%	36.5%	40.0%	11.5%	0%

necessity of a major medical centre with an oncology/radiotherapy service, operating suites and laser equipment required for other therapies in palliation of intraoral Kaposi's sarcoma is eliminated. Finally, if the lesion recurs, intralesional vinblastine therapy may be easily re-instituted with transitory localised side-effects without the concern for myelosuppression, mucositis, increased risk of opportunistic infections or deterioration in salivary dysfunction which may occur with chemotherapy and/or radiotherapy.

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