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Intralesional vinblastine vs. 3% sodium tetradecyl sulfate for the treatment of oral Kaposi's sarcoma. A double blind, randomized clinical trial

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Abstract

In this double-blind, randomized trial, we compared the clinical efficacy of intralesional vinblastine (VNB) and 3% sodium tetradecyl sulfate (STS) in the treatment of oral Kaposi's sarcoma (OKS). Subjects with OKS were randomly assigned to receive a single intralesional injection of either VNB or STS, at a standard dose (0.2 mg/cm^2). Differences were evaluated by the Mann–Whitney U and Fisher's exact tests. Sixteen HIV-infected patients were included, eight received VNB and eight received STS; clinical response was evaluated at days 7, 14, and 28 following treatment. Tumor size reduction was 0.68 and 0.61 cm in the VNB and STS groups, respectively ($P = 0.80$). Two VNB patients had complete or partial response whereas four STS subjects had partial responses ($P = 0.61$). Patients in both groups experienced minimal toxicity. We conclude that intralesional vinblastine or STS are adequate for the management of OKS. The benefits of STS are its low cost and ease of use.

Keywords: AIDS; Kaposi's sarcoma; Vinblastine; Sodium tetradecyl sulfate; Oral

1. Introduction

Kaposi's sarcoma (KS), a disease of heterogeneous presentation, is the most common AIDS-associated malignancy [1,2]. KS has been associated to a recently discovered DNA virus, named HHV-8, a member of the gammaherpesvirus subfamily [3,4]. HHV-8, is principally acquired sexually, particularly among men who have sex with men [5,6]. In recent reports, HHV-8 has been detected in the majority of oral KS lesions in patients with AIDS [7]; also, it has been found in other oral lesions such as nonspecific ulcers, normal oral mucosa in HIV disease and saliva [8–11].

Although the incidence of KS in American men with AIDS has decreased, KS is still a frequent complication of HIV infection [2,12,13]. In developed countries the incidence of KS has declined, perhaps associated to the effect of current combination of antiretroviral therapy and the introduction of highly active antiretroviral agents with protease inhibitors [14,15]. However, neither HHV-8 nor KS have disappeared from the HIV population [12].

In Mexico, as in other developing countries [16,17], KS is still a frequent finding in AIDS patients, being present in 5% of them [18]. According to the AIDS National Registry in Mexico, during the period of 1983–1997, of 33,632 AIDS cases reported; 2308 (6.8%) corresponded to malignancy, of which 1685 (73%) were KS [18].

Oral KS (OKS) lesions may be the first clinical sign of KS in 22% of cases and were found to occur concomitantly with skin and visceral involvement in 45% of patients [7,19]. Oral lesions appear as red to purple macules and nodules that can ulcerate, causing pain, dysphagia and bleeding and thereby interfering with the ability to eat and with daily functioning. OKS

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can also become cosmetically displeasing [7,19]. Early diagnosis and management are important to avoid or minimize severe symptoms.

At present, no curative therapy is available for AIDS-KS. However, palliative therapy can eliminate or reduce cosmetically unacceptable lesions, reduce painful or unsightly edema or lymphadenopathy, shrink symptomatic oral lesions, and relieve symptoms caused by visceral involvement. For the management of limited disease, local therapy is recommended, while systemic therapy is appropriate for the disseminated form of this malignancy [20–22].

Local treatment of OKS, with intralesional administration of vinblastine (VNB) or 3% sodium tetradecyl sulfate (STS) has been used [21–23]. VNB is a natural vinca alkaloid. The primary cytotoxic effect of the vinca alkaloids is to prevent mitotic activity [24]. The mode of action of STS is induction of ischemic necrosis and causes intimal inflammation, with thrombus formation, and is often followed by fibrotic obliteration [22,25]. It has been used in the treatment of varicose veins, varicosities, and vascular and venous malformations [25,26].

The use of intralesional injections of VNB for the management of OKS in open-labelled studies, using different dosages and multiple courses of drug, has proven to be useful, obtaining adequate clinical response of the OKS lesions, and is considered as the intralesional treatment of choice [21,27–32]. STS was also introduced as a local treatment for OKS [33,34]. Although clinical observations using STS showed it was as effective as VNB [33,34], it was not clear whether these preliminary observations were inherent to the patients, or to the lesions or whether they were related to dose and/or volume of injected drug. Therefore, we developed a double-blind randomized comparative clinical trial using the same dose and volume per size of lesion, in a specific region of the mouth, and considering a standardized size of the lesion, compared the clinical efficacy of intralesional injections of VNB and STS in the treatment of OKS lesions.

2. Patients and methods

This study was performed from April 1997 to January 1999, at the AIDS Clinic in the Infectology Department of the Instituto Nacional de Cancerologia (INCan), which is a national referral oncological center in Mexico City. This study was approved by the Human Subject's Research Committee at the INCan.

HIV-infected adult subjects, >18 years old, with clinical and histological diagnosis of Kaposi's sarcoma, were enrolled in the study. AIDS patients with nodular KS lesions on the hard palate, that measured 1–2 cm in diameter, were included in this trial. Demographic and baseline clinical data were obtained. Body mass index was calculated as weight divided by the square of the height. Informed, written consent was obtained from all the patients who indicated willingness to participate in the study.

Exclusion criteria were the presence of ulcerated OKS lesion, oral candidosis, history of radiotherapy in the head and neck region, administration of systemic therapy for KS, known or suspected allergy to test medications, inability to keep follow-up appointments and refusal to participate in the study.

Patients were enrolled consecutively. Using random number tables, an external monitor assigned to receive a single intralesional injection of either vinblastine (Velbe®) or 3% sodium tetradecyl sulfate (Sotradecol®) at a standard volume and dose of 0.2 mg/ml per 1 cm^2 of OKS lesion. The drugs were supplied by University of California, San Francisco and the INCan.

Changes in size, color, and appearance of OKS lesions were evaluated during the study period. Tumor size was assessed based on the largest diameter of the OKS lesion. Color of the lesions included purple, brown, or similar to adjacent mucosa. Appearance evaluation considered changes from nodular to plaque or macular lesions. When multiple palatal lesions were present only one lesion was included in the trial. Other OKS lesions were treated at the end of the study when necessary. Photographs were taken of the target lesions.

Baseline oral evaluation of patients was performed independently by two oral pathologists (LEP & ERG), previously calibrated in the diagnosis of HIV-related oral lesions [35]. Clinical evaluation of the OKS lesion and assessment of adverse effects were also done by the two examiners, on days 7, 14 and 28 (± 2 days) after treatment.

In order to preserve the double blinding, after initial examination an operator researcher (VRA) prepared the study drug in a separate room. Subsequently, after local anesthesia was achieved, the treatment drug was administered to the patients by VRA, in the absence of the two evaluators. Vinblastine was injected intralesionally, while STS was injected perilesionally.

Systemic evaluation of the patient was performed by a physician from the Department of Infectious Diseases. Prophylactic and antiretroviral therapy was continued during the study period. In the case of patients using protease inhibitors, the patient should have initially received these drugs at least 90 days prior to the baseline examination.

In the event of a serious adverse effect, no clinical response or worsening of the lesion, the patient was removed from the study and offered conventional management, as required by the institutional review board (IRB), followed by a written report.

The primary end point of this study was complete response, defined as 95–100% remission of signs and symptoms of the KS target lesion after 4 weeks of

treatment. Partial response was considered as 50–95% remission of signs and symptoms of OKS at 4 weeks of follow-up, and minimal response was considered as $<50\%$ remission of signs and symptoms. If there was no change or an increase in size of the OKS lesions during the trial, it was considered as no response.

Adverse events included the evaluation of pain and development of ulceration. A visual analog scale for evaluating pain, with a range from 0 to 3 used, in which, 0 was no pain, 1 was considered slight pain, 2 was moderate, and 3 was severe pain. Ulceration was assessed according to its presence and size; slight ulcerations were considered those with a diameter of less than 1.5 cm, moderate from 1.5 to 2.4 cm, and severe those with a diameter of $\geqslant 2.5$ cm.

2.1. Statistical analysis

At the end of the study, an average of the measurements of the variables registered by each examiner was calculated and used for statistical analysis. Subsequently, the assignment codes were opened.

The efficacy of the treatment was evaluated according to the reduction in tumor size of OKS in both groups. Tumor size reduction was obtained by comparing the final tumor size against the baseline measurement. Mann–Whitney U test was used to identify differences in the comparison of reduction between the two groups. To compare proportions of outcomes between the two treatment groups, the exact Fisher's test was used. Differences were considered statistically significant when the P value was equal or <0.05.

3. Results

Sixteen HIV-infected male patients were enrolled in the study. Eight subjects were assigned to receive VNB and eight to receive STS. Baseline demographic and clinical characteristics of both groups were similar (Table 1). One individual in the VNB group was drug-naïve. The rest of the patients received antiretroviral therapy, six of them in the VNB group and five subjects in the STS group were receiving two nucleoside analogue reverse transcriptase inhibitors (NRTIs) and one patient in each group received NRTI and a protease inhibitor. The median CD4 lymphocyte count of patients was 67.5 (range 5–271) cells/mm^3.

OKS lesions at the baseline exam were purple nodules in all cases. The changes observed in OKS are described in Table 2. In both groups, oral lesions showed reduction in size, with the exception of one patient in each group, in whom the OKS lesions increased in size during the study period. Only one patient, who received VNB, had complete response of the OKS lesion (Table 2).

At the end of the study, the mean tumor reduction size was 0.68 cm (range 0.25–1.25 cm) in the patients who received VNB, and 0.61 cm (range 0.25–1 cm) in the group who received STS ($P=0.80$). The summary of response in both groups to the drugs at the end of 28 days of follow-up after treatment is shown in Table 3; two patients who received VNB had complete or partial response to the drug (Fig. 1a,b) compared with four subjects in the STS group who had partial response (Fig. 2a,b); the difference was not statistically significant ($P=0.61$).

Adverse events of intralesional injections during the trial are shown in Table 4. After 1 week of follow-up, most patients in both groups experienced pain, which was transient and disappeared during the following weeks.

Half of the patients in both groups developed ulceration at the site of the injection during the first week after treatment. The median ulcer size was 0.625 cm in both cases, with a range of 0.5–1 cm for VNB and 0.5–2 cm for the STS group. During the trial, none of the patients in either group developed opportunistic infections, and the median CD4 counts remained unchanged, 66 cells/mm^3 (range 9–261) at the end of the study. Three

Table 1
Baseline demographic and clinical characteristics of patients with oral Kaposi's sarcoma

	Vinblastine ($n=8$)				3% Sodium tetradecyl sulfate ($n=8$)			
	No. patients	Median	S.D.	Range	No. patients	Median	S.D.	Range
Age (year)		32.5	7.7	25–47		35	6.9	28–49
Weight (kg)		58.2	11.2	48–78		55	9.7	45–72
Body mass index		21.8	2.6	17–24		19.5	3.3	17–26
CD4$^+$ T cell count (per mm^3):		63.5	92	10–271		67.5	54.5	5–129
>200	1				–			
<200	7				8			
Opportunistic infection[a]	4[b]				2[c]			
Smokers	2				2			

[a] History of opportunistic infection.
[b] Oesophageal candidosis, toxoplasmosis, histoplasmosis, tuberculosis.
[c] Salmonellosis.

Table 2
Changes observed in 16 patients with oral Kaposi"s sarcoma lesions after 4 weeks of treatment

Drug	Patient	Tumor size			Final color	Final aspect	Response
		Basal (cm)	Final (cm)	Reduction[a] (cm)			
Vinblastine	1	1.5	1.0	0.5	Purple	Macule	MR
	2	1.5	1.25	0.25	Brown	Plaque	MR
	3	1.75	1.0	0.75	Purple	Macule	MR
	4	2.0	1.25	0.75	Purple	Plaque	MR
	5	1.0	0.75	0.25	Purple	Nodule	MR
	6	1.75	0.5	1.25	Pale purple	Macule	PR
	7	1.0	0	1.0	Brown	Macule	CR
	8	1.0	1.5	–	Purple	Plaque	NR
	Mean (S.D.)	1.4 (±0.39)	0.91 (±0.48)	0.68 (±0.37)			
3% Sodium tetradecyl sulfate	9	1.5	1.0	0.5	Brown	Plaque	MR
	10	1.5	1.0	0.5	Brown	Macule	MR
	11	1.5	1.25	0.25	Purple	Plaque	MR
	12	1.5	0.5	1.0	Purple	Macule	PR
	13	1.25	0.5	0.75	Purple	Macule	PR
	14	1.0	0.5	0.5	Brown	Macule	PR
	15	1.25	0.5	0.75	Purple	Plaque	PR
	16	1.0	1.25	–	Purple	Nodule	NR
	Mean (S.D.)	1.3 (±0.22)	0.81 (±0.48)	0.61 (±0.24)			

[a] Patients with no response were excluded. CR, complete response; PR, partial response; MR, minimal response; NR, no response.

Table 3
Comparative response of oral Kaposi's sarcoma lesions to the treatment at the end of the study

Treatment	Change in size					Change in color	Change in appearance
	100%	50–75%	25–49%	<25%	NR[a]		
Vinblastine	1	1	4	1	1	3	7
3% Sodium tetradecyl sulfate	–	4	2	1	1	3	7
Total	1	5	6	2	2	6	14

[a] NR, no response.

patients did not complete the 28 days of follow-up. The status of two deteriorated due to KS involvement in other organs; the third patient started combination therapy that included a protease inhibitor.

4. Discussion

Currently employed systemic strategies for the management of KS has been single- and multi-agent cytotoxic chemotherapy [20,36]. The administration of immunotherapy, highly active antiretroviral therapy, thalidomide, and retinoids have also been associated with regression of KS lesions [22,36]. Recently, the use of some anti-herpesvirus drugs, such as foscarnet and ganciclovir, have shown some activity in preventing the appearance of KS [36,37]. However, all these drugs have clinically significant systemic side effects such as fever, rash, alopecia, neuropathy, nausea, vomiting, anemia, mucositis, cytopenias, abdominal pain, diarrhea, flu-like symptoms, and bodyweight loss, and are generally unsuitable for long term use [36].

Some of the reported treatments of OKS include surgical excision and radiation therapy [21,22]. Surgical procedures in the management of OKS may cause discomfort and bleeding and are high in cost [22]. Radiotherapy may produce mucositis, xerostomia and development of oral infections [21,22]. In contrast, in some series [27–34], including the present study, intralesional injections of VNB or STS have proven to be efficacious in reducing the size and symptoms of OKS, with mild adverse effects.

In this first comparative double-blind clinical trial, VNB and STS were shown to be similar in efficacy and adverse events. The intralesional application of a single dose of a cytotoxic agent (VNB) or a sclerosing agent (STS), used in a standard volume of injected drug, produced a reduction in size and a change in appearance of oral KS, with minimal toxicity in most cases of both groups. All but one patient in each group, had a

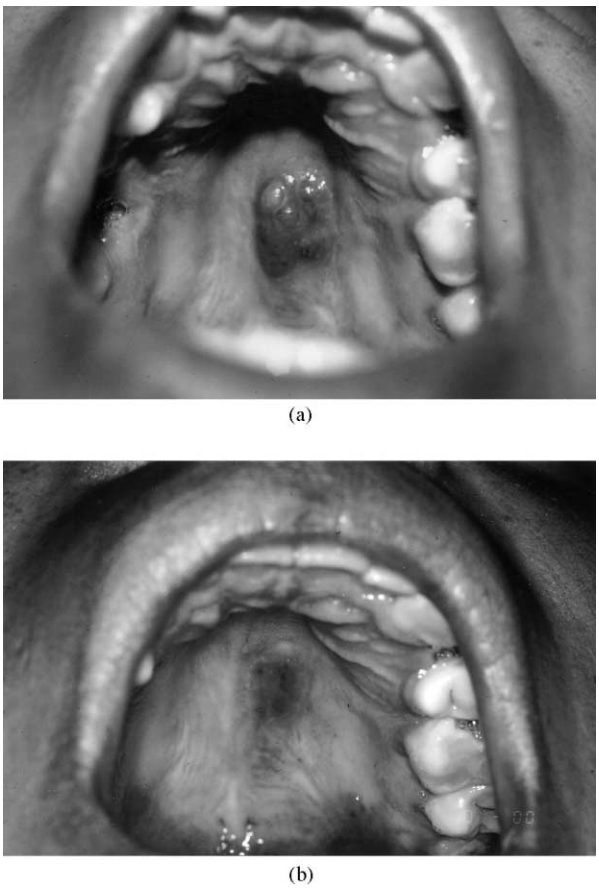

Fig. 1. Nodular Kaposi's sarcoma lesion involving hard palate. (a) Prior to vinblastine treatment. (b) At day 28 following one intralesional vinblastine treatment.

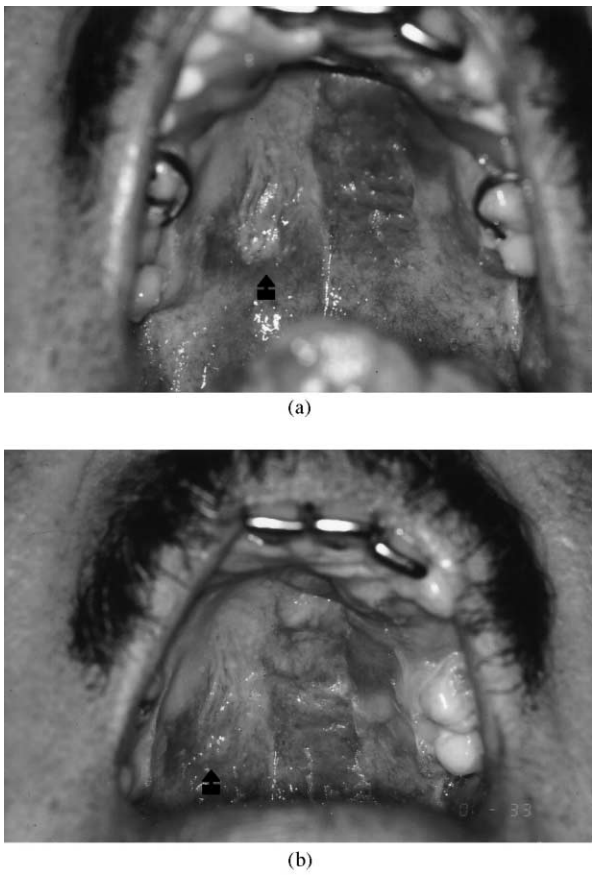

Fig. 2. Nodular Kaposi's sarcoma lesion involving right side of the hard palate. (a) Prior to 3% sodium tetradecyl sulfate treatment (black arrow). (b) At day 28 following one intralesional 3% sodium tetradecyl sulfate treatment (black arrow).

reduction in size of the oral lesions; fully 37% of patients achieved a more than 50% reduction in the oral lesions.

As described in Table 5, VNB has generally been applied by multiple injections, performed once or several times [27–32]. In previous studies [28,30], the highest proportion of complete responses was achieved with periodic injections until evidence of clinical resolution, with a mean number of 2.4 treatment visits. In contrast, in another study that has reported a complete response proportion of 48% [29], the patients received one single VNB treatment, as in the present clinical study.

A comparison among the studies that have used intralesional injections for OKS treatment is difficult because of the variations in the clinical appearance and site of OKS studied, the different doses and number of intralesional injections used, the various criteria for the clinical response and the diverse periodicity of visits and time to follow-up. To facilitate comparisons of treatment approaches between studies, a proposal for clinical staging of OKS has been suggested [21]. This classification also guides the selection of treatment, based on the evaluation of size of the lesion, sites involved and symptoms associated.

Minimal complications of VNB intralesional injection have been reported. In our trial, moderate pain was a common complaint during the first week, which persisted with lower intensity or disappeared during the following weeks. Similarly, most authors [28–32] have described mild and transient pain. In our study, where the same volume and dose per size of lesion was used (0.2 mg/ml per 1 cm of lesion), superficial and small ulcers developed in the majority of cases. Also, in other studies [29–31], ulcer development seemed to be associated with minimal discomfort.

Though the reports that describe intralesional STS are few [33,34], they indicate that this sclerosing solution is an effective alternative drug for the treatment of OKS lesions. A complete resolution from 33 to 60% [33,34] of OKS lesions has been reported with repeated injections of STS (Table 5). In the present study, with a single treatment, half of the oral cases showed more than 50% reduction in size.

As with VNB, during the first week after treatment with STS, temporary pain was reported by the patients of this trial; others have described no associated pain or transient pain [33,34]. Also, ulcer formation with

Table 4
Adverse effects observed during the follow-up in 16 patients with oral Kaposi's sarcoma

	Vinblastine			3% Sodium tetradecyl sulfate		
	7 days ($n=8$)	14 days ($n=6$)	28 days ($n=7$)	7 days ($n=8$)	14 days ($n=8$)	28 days ($n=6$)
Pain						
No	2	3	5	–	6	6
Slight	–	3	2	–	2	–
Moderate	6	–	–	7	–	–
Severe	–	–	–	1	–	–
Ulceration						
None	4	4	6	4	4	4
Slight (<1.5 cm)	4	2	1	3	4	2
Moderate (⩾1.5–2.4 cm)	–	–	–	1	–	–

Table 5
Intralesional Vinblastine (VNB) and 3% sodium tetradecyl sulfate (STS) for the treatment of oral Kaposi's sarcoma[a]

Drug	author	Patients	Lesions	Site	Dosage	Treatments	Visits	Response type	%	Pain	Ulceration
VNB	McCormick [27]	18	35	Palate 51%, alveolus 14%, tongue 6%, gingiva 6%, others 23%	0.3 mg/ml	1–3	1 week	(100%)	100	ND	ND
	Flaitz et al. [28]	50	144	Palate 56%, gingiva 22%, maxillary tuberosity 6%, tongue 4%, lip 3%, others 8%	0.1 mg/cm^2	1–6	2 weeks	(96–100%) (76–95%) (51–75%) (26–50%) (< 25%) NR	74 12 11 3 0.7 0	72	22
	Epstein [29]	42	42	Palate 74%, tongue 14%, gingiva 9%, tonsils 2%	0.1 ml/0.5 cm^2	1	2–4 weeks	(75–100%) (50–75%) (25–50%) (<25%) NR	48 26 21 5 0	90	14
	Nichols et al. [30]	24	82	Palate 52%, gingiva 23%, tongue 7%, maxillary tuberosity 6%, lip 4%, others 6%	0.1 mg/cm^2	1–6	2 weeks	(100%) (66%)	70 30	80	21
	Epstein et al. [31]	10	10	Palate	0.1 ml/0.5cm^2	1–2	2 weeks	(75–100%) (50–75%) (25–50%) NR	40 20 40 0	80	40
	Epstein and Scully [32]	17	21	Palate, gingiva, tongue	0.2 ml/0.5 cm^2	ND	1–2 weeks	⩾50%	57	ND	ND
	Present study	8	8	Palate	0.2 ml/cm^2	1	1 week	(96–100%) (50–95%) (<50%) NR	12.5 12.5 62.5 12.5	75	50
STS	Lucatorto and Sapp [33]	12	15	Palate 86%, gingiva 7%, maxillary tuberosity 7%	0.04–0.6 ml	1–2	1 week	CR PR	60 40	8	100
	Muzyka and Glick [34]	12	12	ND	ND	⩾1	ND	CR	33	0	0
	Present study	8	8	Palate	0.2 ml/cm^2	1	1 week	(96–100%) (50–95%) (<50%) NR	0 50 37.5 12.5	100	50

[a] CR, complete response; PR, partial response; NR, no response; MR, minimal response; ND, no data.

minimal discomfort after the first week of treatment was a common finding in another study and in our results [34]. The benefits of the use of STS are its low cost and easy application and handling. Because there is no need for extra needles or saline solution as for VNB, this drug may be an important treatment alternative for populations that cannot afford high cost therapy, or where needles and saline solution are not available.

In conclusion, we found that intralesional injections of either VNB or STS are effective therapies for the management of OKS, with minimal adverse side effects such as transient pain and superficial ulceration. Even with one intralesional injection of either drug, as in the present study, changes were observed in the majority of OKS lesions. The standard treatment for KS lesions, such as radiotherapy, surgery, chemotherapy, immunotherapy and antiretrovirals, not only have serious adverse events but also are high in cost and require sophisticated techniques and equipment.

Further studies of intralesional therapy should consider additional follow-up time in order to assess time period for recurrence and recurrence rate. Also, future studies should compare the administration of several doses of these drugs, assess thickness of the lesions and compare if early treatment is more effective than the management of already symptomatic lesions.

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