Correspondence

Comparison between propranolol 2% cream versus timolol 0.5% gel for the treatment of Kaposi sarcoma

Dear Editor,

Kaposi sarcoma (KS) is an angioproliferative disorder associated with human herpesvirus 8 (HHV-8) infection. Due to the KS heterogeneity, there are no standard therapeutic guidelines, and several different options are available for KS treatment.[1] Many topical agents have been used with mixed results. Recently, beta-blockers (β-blocker) such as propranolol and timolol have also been used with excellent results.[2] From May 2019 to September 2020, 12 volunteer patients of both sexes exhibiting clinical/dermoscopic and histopathological diagnosis of KS, aged between 68 and 83 years, were randomly enrolled in the study. The patients had never done systemic therapy for KS; informed consent was obtained from each patient. The patients selected were HIV-negative, without acute disease, and without oral β-blockers intake. Dermatological examination showed cutaneous nodules and plaques of KS on the distal lower extremities and feet. Patients were randomly divided into two treatment groups; six patients were treated with timolol maleate 0.5% gel (available for ophthalmic use), while the remaining patients were treated with 2% propranolol cream (galenic preparation). The two different treatments were applied by the respective groups, twice daily, with a gentle massage and without occlusion. Follow-up visits were every 2 weeks, and the treatment was stopped after 12 weeks. At the end of the treatment, the results obtained in the two treatment groups were evaluated and compared. Clinically, all participants showed significant improvement in KS after treatment without adverse reactions. Patients treated with 0.5% timolol gel showed partial response after 12 weeks of treatment (more than 50% of the lesions regressed) (Fig. 1a–b). In the group treated with 2% propranolol cream, five of six patients showed complete response of the treated lesions (Fig. 2a–b), while only one patient had partial response after 12 weeks of treatment. For partial responder patients (timolol group and one patient of propranolol group), we decided to start therapy with elastic stocking. After 6 months of follow-up, there was no evidence of regrowth in the propranolol group and a noticeable clinical improvement in all other patients (Table 1). In the last years, there has been an emerging interest in the role of β-blockers as therapeutic option in a wide variety of proliferative vascular disorders. The mechanism of action of β-blockers for the treatment of angioproliferative neoplasms is not well known. It has been hypothesized that they act in three consecutive steps: at first vasoconstriction, subsequently the inhibition of pro-angiogenic signals, and finally the promotion of endothelial cell apoptosis. In a recent study, Chisholm *et al.*[3] found a strong expression of beta-adrenergic receptors in up to 75% of KS lesions. Furthermore, Chang *et al.*[4] demonstrated that in infected lymphoid cells, the reactivation of HHV-8 occurred in the presence of an adequate concentration of catecholamines and that this was dependent on β-adrenergic signaling. This would explain the efficacy of β-blockers in treating KS. In our study, all patients had a significant improvement in their clinical conditions; no side effects were detected. Furthermore, comparing the results of the two treatment groups, it came out that the group treated with 2% topical propranolol cream showed complete clinical response compared to the group treated with 0.5% topical timolol gel in which only a partial clinical response was achieved. This could be explained by the different mechanism of action of the two drugs. We suppose that timolol may perform its effect

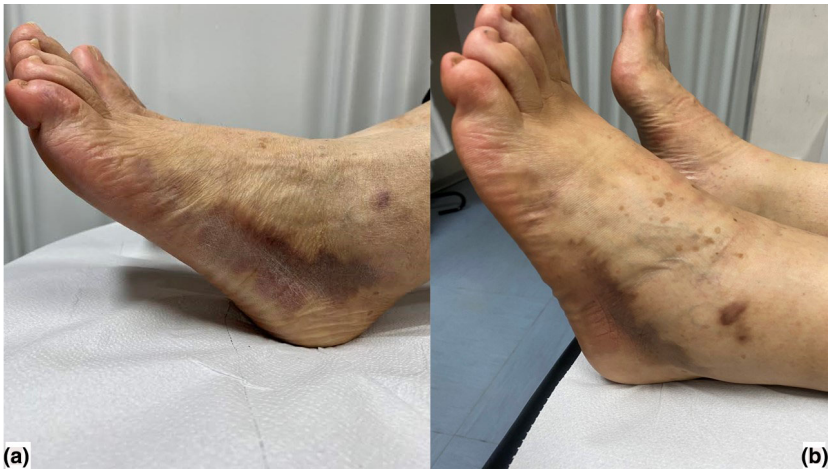

Figure 1 (a–b) Partial response after 12 weeks of treatment with 0.5% timolol gel

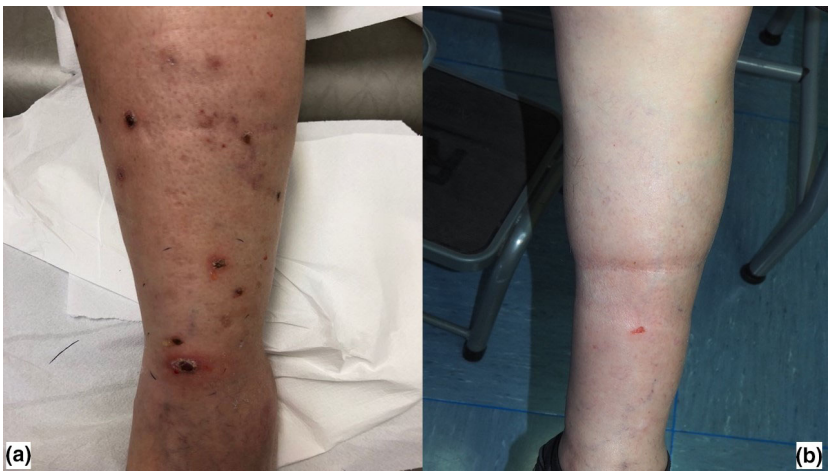

Figure 2 (a–b) Complete response after 12 weeks of treatment with 2% topical propranolol cream

Table 1 Demographics of the patients, treatment groups, and follow-up visit

Name	Age	Location	Comorbidities	Treatment	Side effect	Partial resolution	Complete resolution	Follow-up visit at 6 months
C.C	64	Legs	Hypertension	Propranolol	None		100%	No evidence of regrowth
D. T	81	Ankles and feet	Hypertension, Diabetes	Timolol	None	70%		Elastic stocking
A.P	73	Legs and feet	None	Timolol	None	70%		Elastic stocking
C.R	78	Feet	Hypertension, COPD	Propranolol	None	70%		Elastic stocking
S.E	83	Legs	Diabetes	Propranolol	None		100%	No evidence of regrowth
A.A	75	Ankles and feet	None	Propranolol	None		100%	No evidence of regrowth
C.G	82	Legs	Hypertension	Propranolol	None		100%	No evidence of regrowth
G.L	69	Feet	Diabetes	Timolol	None	50%		Elastic stocking
A.D	80	Legs	None	Propranolol	None		100%	No evidence of regrowth
A.G	75	Feet	Hypertension	Timolol	None	50%		Elastic stocking
S.P	80	Legs	None	Timolol	None	55%		Elastic stocking
I.C	76	Feet	Diabetes	Timolol	None	45%		Elastic stocking

COPD, chronic obstructive pulmonary disease.

through the inhibition of β-adrenergic signaling. Propranolol not only acts on the β-adrenergic signaling, but it decreases the proliferation of KS-associated herpesvirus (KSHV)-infected cells. Additionally, propranolol induces KSHV lytic gene expression in association with downregulation of CDK6. In conclusion, our study confirmed that propranolol shows a superiority in terms of efficacy, measured as clinical resolution, compared to timolol. However, further studies are necessary to confirm these data in a larger number of patients and for a longer follow-up period.

Acknowledgment

The patients in this manuscript have given written informed consent to publication of their case details.

Data Availability Statement

The data that support the findings of this study are openly available in ["pubmed"] at doi.org/

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