Dermatology Practical & Conceptual

Propranolol: A Promising Therapeutic Avenue for Classic Kaposi Sarcoma

Rasha Mahmoud Genedy[1], Marwa Owais[1], Naglaa Mohamed El Sayed[1]

1 Dermatology, Venereology, and Andrology Department, Faculty of Medicine, Alexandria University, Alexandria, Egypt

Key words: Hemangioma, Kaposi Sarcoma, Lymphedema, Propranolol

Citation: Genedy RM, Owais M, El Sayed NM. Propranolol: A Promising Therapeutic Avenue for Classic Kaposi Sarcoma. *Dermatol Pract Concept*. 2025;15(1):4737. DOI: https://doi.org/10.5826/dpc.1501a4737

Accepted: October 8, 2024; **Published:** January 2025

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Naglaa Mohamed El Sayed, dermatology, venereology, and andrology department, Faculty of Medicine, Alexandria University, AL Khartoum square, Alexandria, Egypt. E-mail: naglaasayed66@outlook.com

ABSTRACT

Introduction: Kaposi sarcoma (KS) is a low grade angio-proliferative tumor of endothelial origin. Human herpesvirus 8 (HHV8) plays a major role in the pathogenesis of KS. Classic Kaposi sarcoma is commonly seen among elderly of Mediterranean origin. It is usually slowly progressive and is rarely fatal. There is no definitive cure for KS. Beta blockers were used with great success in the treatment of infantile hemangioma. Because of some similarity between infantile hemangioma and KS, topical beta blockers were tried with variable success rate.

Objectives: We aimed to assess the efficacy and safety of oral propranolol in the treatment of classic KS.

Methods: Fifteen patients diagnosed with classic KS were prospectively enrolled in the study. Detailed history and full clinical examination were conducted. Histopathological diagnosis with confirmatory immune staining was done for all patients. Oral propranolol in a dose of 60 mg was given per day for 6 months. The patients assessed clinically as complete responders, partial responders, and non-responders.

Results: Nine patients (60%) were partial responders; showed 50% reduction in the number of the existing lesions, and 6 patients (40%) were considered non-responders; 3 with stable disease and 3 with progressive disease. Lymphedema partially improved in 1 patient.

Conclusions: Oral propranolol is a safe and good option for treatment of patients with non-complicated classic KS, especially elderly with multiple comorbidities.

Introduction

Kaposi sarcoma (KS) is a low grade angio-proliferative tumor of endothelial origin. Human herpesvirus 8 (HHV8) plays a major role in the pathogenesis of KS in association with genetic, immunologic, and environmental factors [1]. Clinically, most KS lesions initially appear as violaceous patches that progress into plaques, and later develop into larger nodules (tumor stage). It is important to note that different stages can coexist concomitantly in the same patient. Mucous membrane, lymph nodes and viscera may also be affected [2].

Four distinctive subtypes of KS have been described. They include classic, endemic, iatrogenic, and AIDS-related KS [1]. Classic Kaposi sarcoma (CKS) is commonly seen among elderly of Mediterranean origin. Lesions are usually slowly progressive and located on the distal extremities [1]. Although the disease is rarely fatal, it may be accompanied by various complications such as edema, ulceration, and bleeding [2]. On the other hand, endemic KS is seen in the young population of sub-Saharan Africa and may acquire an aggressive and lethal course [1]. Iatrogenic KS has been reported in patients with solid organ transplants as well as other patients on immunosuppressive treatments. In this variant, the cutaneous lesions usually regress after stoppage of therapy [2]. Finally, AIDS- related KS is an aggressive type which is characterized by multifocal skin affection, frequent visceral involvement, and subsequently carries a poor prognosis [3].

Although there are many available therapeutic options for management of KS there is no definitive cure. Alternatively, the current treatments aim is limited to stopping disease progression, decreasing lesions size, and improving lymphedema. Considering the variable presentations of KS, the treatment approach must be tailored according to the clinical type, the extent of KS lesions, their anatomical location, and the presence of comorbidities. Despite the promising results of the different treatment modalities, the high cost and potential side effects may be a barrier against their use in many patients.

In the last couple of decades beta blockers became part of the treatment armamentarium of dermatologic diseases mostly due to their effectiveness in the treatment of infantile hemangiomas (IH) [4]. Propranolol and timolol were among the first-generation nonselective beta blockers that were effectively used in the treatment of such conditions [5]. Nevertheless, their mechanism of action remains not fully understood. It has been postulated that endothelial cells of IH express beta 2 adrenergic receptors (b2-AR), therefore, beta blockers may act through vasoconstriction and inhibition of vascular endothelial growth factors, which leads to reduction in angiogenesis and induction of endothelial cell apoptosis [6].

The success of beta blockers in treatment of IH has advocated their introduction as a treatment modality in other proliferative vascular lesions, whether as a mono- or as an adjuvant therapy [7]. Since similarities exist between IH and KS including the high B- adrenergic receptor expression and the possible role of vascular endothelial growth factor (VEGF) [8], it is hypothesized that b2-AR antagonists (b2-ARAs) may be useful for the treatment of KS. In this context, topical timolol in different formulations and concentrations has been used in the treatment of iatrogenic, epidemic, and CKS with variable success rates [9,10]. Topical timolol has the advantage of being inexpensive, painless, and well tolerated [9,10]. A recent study demonstrated that topical propranolol 2% cream was more effective than topical timolol gel 0.5% in the treatment of patients with CKS [11]. On the other hand, there are limited reports regarding the use of systemic propranolol in the treatment of KS [12,13].

Objectives

The aim of the present work was to assess the efficacy and safety of oral propranolol in the treatment of CKS.

Methods

Patient Selection

All clinically suspected cases of KS were biopsied for histopathological diagnosis, followed by immunohistochemistry confirmation using HHV8 and D2-40 stains. Only cases diagnosed with CKS were included in this study. All patients underwent a thorough history taking (age, duration of the disease, its progression, present and previous medications, comorbid conditions). Physical examination entailed the type, distribution, and number of the lesions, presence of lymphedema and mucous membrane lesions. Cardiac assessment by a cardiologist was administered to exclude any heart morbidities. Additionally, general examination was done mainly to assess the lymph nodes. Routine blood tests and HIV serology were done for all patients to exclude HIV related KS.

Exclusion Criteria

Patients with symptomatic visceral KS, HIV positive patients, those on immunosuppressive therapies, or on any other KS treatments were excluded. Patients with cardiac abnormalities including abnormal ECG, bradycardia, on other antihypertensive drugs, or having any other contraindications for systemic beta blockers were also excluded from this study. Other exclusion criteria included pregnancy and breastfeeding.

Treatment Protocol

The dose of propranolol was selected based on similar doses used in the treatment of other vascular proliferations [14,15]. Patients were given oral propranolol in a starting dose of 40 mg per day for 2 weeks. Thereafter, the dose was increased to 60 mg per day in 2 divided doses half hour after meals for a total duration of 24 weeks. Cardiac reassessment including heart rate, blood pressure and ECG were done after the initiation of therapy and repeated in the monthly visits throughout the treatment.

Outcome Assessment

Currently there is no accepted response assessment system for CKS. The approved system is from AIDS Clinical Trial Group Oncology Committee [16], which is not entirely suitable to apply for CKS because of its different clinical presentation and different prognosis. So, we depend on assessment methods used in previous publications addressing the treatment of CKS [17,18].

Digital photographs were taken before the start of therapy, during each monthly visit and at the end of the 24 weeks. Response to treatment was assessed clinically and photographically based on the total number, size, and color of the lesions before the start of oral propranolol and during each of the follow-up visits and at end of the treatment. Clinical response to treatment was defined as; complete clinical response; complete resolution of all cutaneous lesions, and no new lesions (complete responders), partial response; a 50% reduction in the total number of cutaneous lesions, and no new lesions, or at least reduction of > 25% in the size of previously existing measurable lesions (partial responders), and (non-responders) which included patients with stable disease; no response to treatment and no new lesions, and progressive disease; a 25% increase in the number or the size of the lesions from the baseline. All drug related adverse events were recorded.

Results

Eighteen patients were clinically and histopathologically diagnosed with KS. However, 3 of them were found to be HIV positive and were subsequently excluded from the study. Thus, the total number of patients enrolled in the present prospective study was 15, all with CKS. Among the participating patients were 13 males (86.7%), and 2 females (13.3%). The average age was 62.6 (range from 48-72 years).

The duration of the disease ranged from 5 months to 36 months. Before enrollment in the study, 6 of the selected patients used nonspecific topical treatments such as topical steroids and moisturizers. Eight patients had received specific treatments in the form of topical imiquimod, local radiation therapy, intralesional chemotherapy and 1 patient received systemic chemotherapy with subsequent recurrence after stoppage of treatment. None were on active treatment for KS.

Dermatologic Examination

Fourteen patients (93.3%) exhibited lesions on their lower extremities, 1 of those patients had additional lesions on the upper extremities, whereas only 1 patient had lesions limited to the upper extremities (6.7%). These lesions manifested as multiple violaceous papules, nodules, and plaques, with 2 patients displaying exophytic lesions and another presenting with ecchymosis-like lesions on one lower extremity. The number of lesions varied from 7 to more than 50 per patient. According to Brambilla et al [19] , 5 CKS patients (33.3%) were classified as stage IA, seven patients (46.7%) as stage IIA, and 3 patients (20%) as stage IIB.

All patients were presented with variable stages of lymphedema, with 1 patient classified as stage 1 (6.7%) and 14 patients classified as stage 2 (93.3%) [20]. Notably, all patients reported that the onset of edema coincided with the appearance of cutaneous lesions. Bilateral inguinal lymphadenopathy was observed in 3 patients. Subsequent lymph node biopsies revealed nonspecific inflammatory infiltrates in these cases.

The detailed demographic and clinical data of the patients is presented in Table 1.

Histopathological examination of the skin lesions showed interlacing bundles of spindle shaped cells, dilated vascular spaces, extravasated red blood cells, and hemosiderin deposition (Figure 1, A-D) Immuno-histochemical staining with HHV8, and D2-40 are presented in Figure 2, A and B.

Therapeutic Outcomes

Out of the 15 patients included in the study, 9 were classified as partial responders, representing 60% of the cohort. These patients exhibited a reduction of more than 50% in the total number of lesions with residual pigmentation. The size of large exophytic lesions was decreased by > 25%, which were subsequently surgically removed (Figures 3-5). Six patients (40%) were considered non- responders; 3 patients (20%) were stable, and the remaining 3 patients (20%) were categorized as stage IIB experienced early progression of lesions within 3 weeks of initiating therapy, prompting immediate referral to Oncology upon discontinuation of treatment. The 3 patients in stable disease declined further referral for alternative therapy. Despite none achieving complete response, 1 patient demonstrated more than 90% disappearance of lesions. Partial responders began showing signs of improvement between the fourth and seventh weeks, with an average of 5.7 weeks, characterized by flattening of some lesions and fading of violaceous coloration. Maximum response was observed between 12 and 16 weeks, with an average of 14.1

Table 1. Demographic and Clinical Data of the Studied Patients.

Patient Characteristics	Total Number of Patients 15
Age (years) Average	48-73 62.6
Gender Male Female	 13 (86.7%) 2 (13.3%)
Duration of the disease (months) Average	Range (5-36) 22.3
Type of the lesions Papulonodular Papulo nodular and Plaques Exophytic lesions Ecchymosis like lesions	 15 (100%) 3 (20%) 2 (13.3%) 1 (6.7%)
Distribution Lower extremities alone Lower extremities and upper extremities Upper extremities alone Other body sites	 13 (86.7%) 1 (6.7%) 1 (6.7%) None
Number of the lesions Less than 10 More than 10	 1 (6.7%) 14 (93.3%)
Lymphedema Yes No	 15 (100%) 0
Lymph nodes Yes No	 3 (20%) 12 (80%)
Mucus membrane Yes No	 15 (100%)
Comorbid conditions Diabetes Liver cirrhosis Chronic obstructive pulmonary disease Hypothyroidism	 6 (40%) 2 (13.3%) 2 (13.3%) 1 (6.7%)
Complications Oedema Heaviness Pain cellulitis	 15 (100%) 7 (46.7%) 2 (13.3%) 1 (6.7%)

weeks. Following completion of the 6-month treatment period, responders continued the same dose of propranolol but were not regularly monitored after the conclusion of the study. Lymphedema showed partial improvement in only 1 patient. No adverse events were reported during the study duration.

Conclusions

High quality evidence for management of KS is confined to the more aggressive AIDS-related KS [21]. Conversely, evidence-based treatment options for other forms of KS are limited, and generally limited to case series or case reports [22], consequently the other forms of KS usually managed in a comparable way.

Considering the chronic, non-aggressive course of CKS, as well as the patients old age and the associated comorbidities, it is important to identify new treatment options with a good safety profile that could be used for a longer period aiming at control of the disease and amelioration of the signs and symptoms rather than cure. Based on previous case reports and series demonstrating the efficacy and safety of topical betablockers in the treatment of KS [9-11], systemic propranolol may have a potential role in the treatment of such cases, and it may add the benefit of treating patients with a large number and disseminated cutaneous lesions.

In the present study, we report the treatment of 15 cases of CKS. Oral propranolol was given in a dose of 60 mg per day for a period of 6 months. The overall response rate was 60%, and no side effects were reported during the study period. Two previous publications report the use of oral propranolol in the treatment of KS. Sharquie and colleague in 2018 demonstrated the successful treatment of 4 cases of CKS with oral propranolol 60 mg per day in combination with oral zinc sulphate 100 mg 3 times per day for a duration of 6 to 12 months [12]. The authors indicated a subtle response following one month of therapy without notable adverse effects. Similarly, Vallejo et al reported on; a case of a refractory classic cutaneous KS with multiple comorbidities [13], 10 mg propranolol was given per day for 7 months. Marked improvement was noted after 6 months with no recurrence up to 20 months of follow-up. Our study builds on the previous reports and has the advantage of including more patients, which further solidifies the beneficial effects of systemic propranolol for control of CKS.

The concept of using propranolol in KS was initially derived from its efficacy in the treatment of other vascular tumors since it is a drug with antiangiogenic activity [23,24]. Angiogenesis plays a key role in KS pathogenesis which is recently more regarded as a reactive rather than neoplastic condition. Ample evidence is seen microscopically in the form of leaky and poorly organized, newly developed vessels, with extravasated blood and hemosiderin deposition which result in the characteristic purple lesions [25] . These findings collectively point to propranolol as a good option for treatment of KS. Chisholm et al [8] demonstrated the expression of the phosphorylated form b2 AR in 60% of their studied KS cases as well as the expression of all three beta adrenergic receptors in all phases of IH, in which the efficacy of propranolol is well documented [5]. This further supports oral propranolol as a potential treatment option for KS.

More evidence supports the utility of propranolol as an effective therapeutic in KS; The role of beta adrenergic

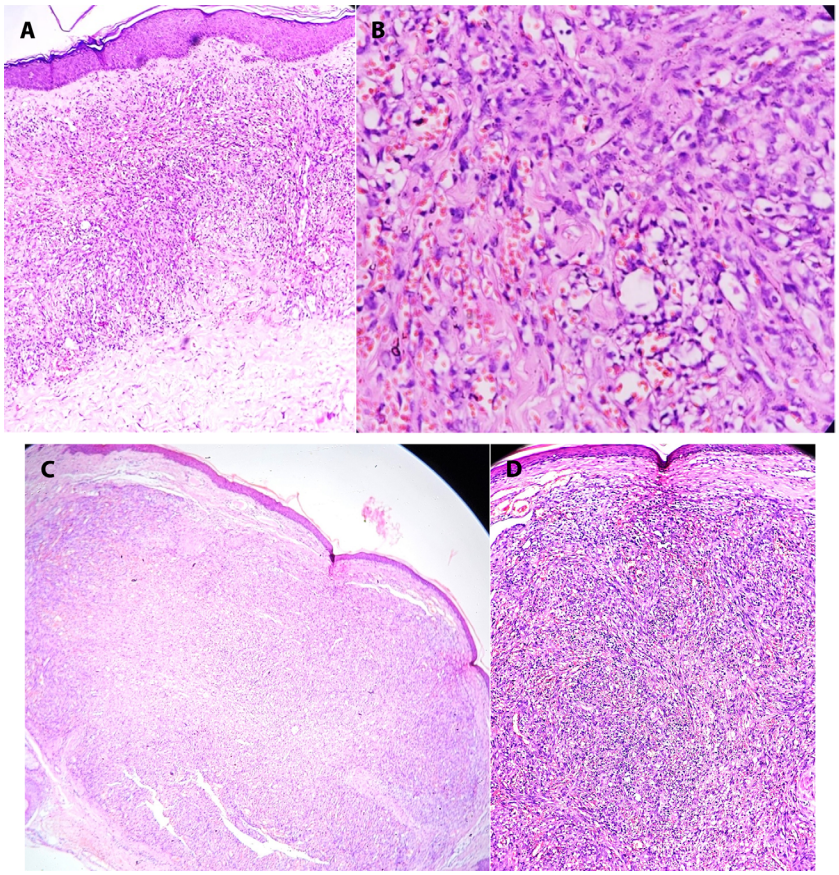

Figure 1. Kaposi sarcoma (KS) histopathology, plaque stage. (A) Diffuse infiltrate occupying the upper and mid dermis (H&E ×100). (B) Higher magnification showing slit-like vascular spaces and extravasated red blood cells (RBCs), admixed with inflammatory cells (H&E ×400). KS nodular stage (C) the whole dermis is expanded with a solid nodule, with thinning of the overlying epidermis (H&E ×40). (D) Storiform pattern of the infiltrated spindle cells, extravasated RBCs (H&E ×100).

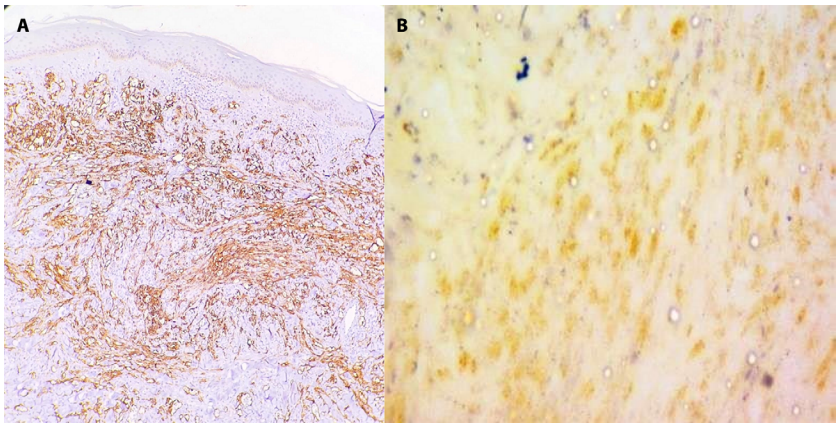

Figure 2. Immunohistochemical staining: (A) diffuse positive staining of both spindle cells and vascular spaces (D2-40 ×100) and (B) positive staining of the spindle cell nuclei for human herpes virus 8 (HHV8; ×400).

signaling in reactivating latent Kaposi sarcoma-herpes virus (KS-HV), a key player of KS pathogenesis has been suggested. Moreover, propranolol was proven to efficiently inhibit reactivation of KS-HV lytic protein and mRNA [26]. It was also hypothesized that propranolol decreases the proliferation of KS-HV-infected endothelial cells and induced KS-HV lytic gene expression in association with downregulation of cyclin dependent kinase 6 (CDK6) [27]. Trials on oral propranolol

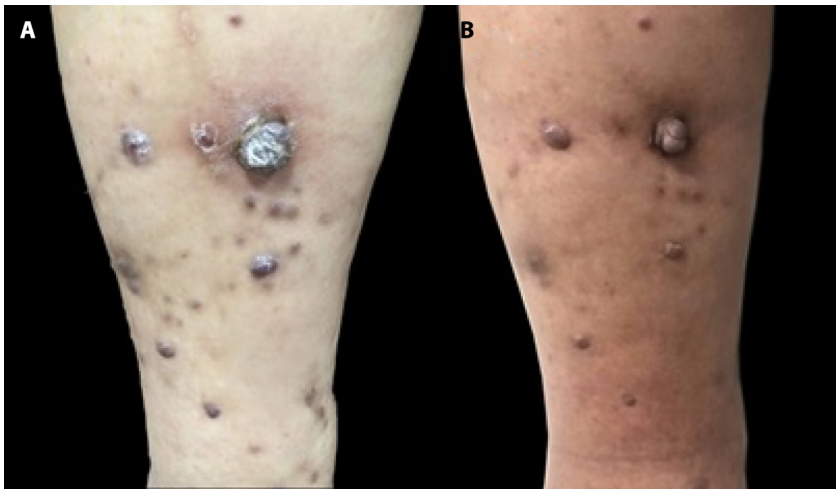

Figure 3. Clinical photo for a classic Kaposi sarcoma (CKS) patient (A) before treatment and (B) after treatment; more than 50% of the nodules faded, with more than 25% reduction in the size of the exophytic lesion.

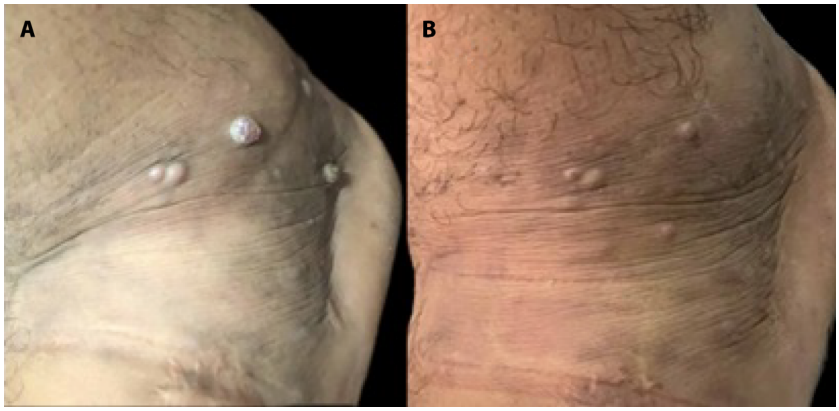

Figure 4. Clinical photo for CKS on the right ankle (A) before treatment and (B) after treatment, evident reduction in the size of the nodules.

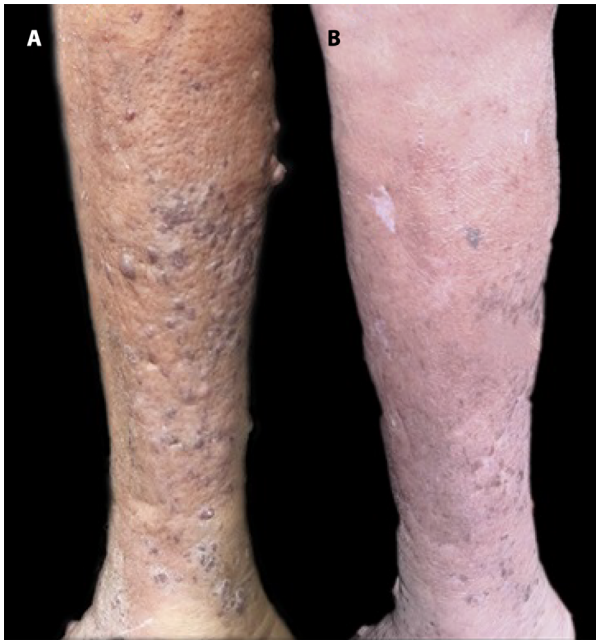

Figure 5. Clinical photo for CKS on the right leg (A) before treatment, and (B) after treatment; more than 90% of the nodules faded.

are further extending to another angio-proliferative more aggressive form of sarcoma, such as angiosarcoma, in which oral propranolol was given as a monotherapy or in combination with chemotherapy drugs with very promising results [24,28]

In the present study lymphedema was present in 100% of our patients and partially improved in one of the partially responders. Lymphedema is a frequent complication of KS [2], its incidence and response to treatment varied between different studies. The exact etiology of lymphedema in Kaposi sarcoma is not known. Leakage from dilated lymphatics, occlusion of lymphatic lumens by proliferated endothelial cells and lymphatovenous anastomosis have been proposed as a possible mechanism [29]. Lymphedema may precede the appearance of KS lesions [2]. Chronic lymph stasis may stimulate angiogenesis, facilitating the onset of HHV8 associated vascular proliferation [30]. Inadequate lymphatic drainage may alter the cell trafficking of T lymphocytes, macrophages, and dendritic cells making the lymphedematous region an immunologically vulnerable area facilitating

the development of KS [31]. In this context Brambilla et al [30] mentioned that limb volume reduction could be useful to improve the prognosis of CKS, and they encouraged the employment of elastic stockings.

There is no agreement on which agent should be selected as a first-line systemic treatment of CKS. The relatively low incidence of the disease, the fact that it usually occurs in old age, and the presence of comorbidities limit prospective studies. In this study, over 50% of the treated patients exhibited a partial response, with one patient achieving near-clearance of lesions. These findings suggest that systemic propranolol represents a safe and effective option for elderly patients with non-complicated, non-aggressive CKS. However, further studies are warranted to determine the optimal dosage and duration of propranolol treatment in such cases. The prospective design of the study and the use of propranolol as a monotherapy help minimize bias regarding its efficacy, particularly when used in combination with other drugs. The limitation of the present study is the small number of patients included, which can be attributed to the rarity of the disease. Additionally, the limited duration of the study may have restricted the ability to observe long-term outcomes and fully assess the efficacy of the treatment.

References

1. Ruocco E, Ruocco V, Tornesello ML, Gambardella A, Wolf R, Buonaguro FM. Kaposi's sarcoma: etiology and pathogenesis, inducing factors, causal associations, and treatments: facts and controversies. *Clin Dermatol*. 2013;31(4):413-422. DOI: 10.1016/j.clindermatol.2013.01.008.PMID:23806158.PMCID:PMC7173141.
2. Schwartz RA, Micali G, Nasca MR, Scuderi L. Kaposi sarcoma: A continuing conundrum. *J Am Acad Dermatol*. 2008;59(2):179-206. DOI:10.1016/j.jaad.2008.05.001. PMID: 18638627.
3. Liu Z, Fang Q, Zuo J, Minhas V, Wood C, Zhang T. The worldwide incidence of Kaposi's sarcoma in the HIV/AIDS era. *HIV medicine*. 2018 May;19(5):355-364. DOI: 10.1111/hiv.12584
4. Püttgen K, Lucky A, Adams D, et al. Topical timolol maleate treatment of infantile hemangiomas. *Pediatrics*. 2016; 138(3): e20160355 DOI: 10.1542/peds.2016-0355
5. Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. *N Engl J Med*. 2015; 372(8):735-746 DOI: 10.1056/NEJMoa1404710
6. Storch CH, Hoeger PH. Propranolol for infantile haemangiomas: insights into the molecular mechanisms of action. *Br J Dermatol*. 2010; 163(2): 269–274 DOI: 10.1111/j.1365-2133.2010.09848.
7. Cuesta AM, Gallardo-Vara E, Casado-Vela J, Recio-Poveda L, Botella LM, Albiñana V. The Role of Propranolol as a Repurposed Drug in Rare Vascular Diseases. *Int J Mol sci*. 2022;23(8):4217. DOI: 10.3390/ijms23084217
8. Chisholm KM, Chang KW, Truong MT, Kwok S, West RB, Heerema-McKenney AE. β-adrenergic receptor expression in vascular tumors. *Mod Pathol*. 2012;25 (11):1446-1451.DOI:10.1038/modpathol.2012.108
9. Meseguer-Yebra C, Cardenoso-Alvarez ME, Bordel-Gomez MT, Fraile-Alonso MC, Perez-Losada ME, Sanchez-Estella J: Successful treatment of classic Kaposi sarcoma with topical timolol: report of two cases. *Br J Dermatol*. 2015;173 (3):860-862. DOI: 10.1111/bjd.13746
10. Alcantara-Reifs CM, Salido-Vallejo R, Garnacho-Saucedo GM, Velez Garcia-Nieto A: Classic Kaposi's sarcoma treated with topical 0.5% timolol gel. *Dermatol Ther*. 2016; 29:309-311.
11. Cmr G, Licata G, Briatico G, et al. Comparison between propranolol 2% cream versus timolol 0.5% gel for the treatment of Kaposi sarcoma. *Int J Dermatol*. 2021; 60: 631–633. DOI: 10.1111/ijd.15407
12. Sharquie KE, Noaimi AA. Treatment of Kaposi's Sarcoma by Combination of Zinc Sulfate and Propranolol. *Journal of Cosmetics, Dermatological Sciences and Applications*. 2018;8 (4):249-255. DOI: 10.4236/jcdsa.2018.84026.
13. Salido-Vallejo R, González-Menchen A, Alcántara-Reifs C, España A. Treatment with Oral Propranolol for Refractory Classic Cutaneous Kaposi Sarcoma. *JAMA dermatology*. 2022;11 (7): 832-834. DOI:10.1001/jamadermatol.2022.1278
14. Mine T, Koike Y, Ehara D, Murota H. A case of bilateral plantar pseudo-Kaposi sarcoma successfully treated with propranolol. *JAAD Case Reports*. 2021;18:74-78. DOI: 10.1016/j.jdcr.2021.09.032
15. Horst C, Kapur N. Propranolol: a novel treatment for angiolymphoid hyperplasia with eosinophilia. *Clin Exp Dermatol*. 2014; 39(7): 810-812. DOI:10.1111/ced.12412
16. Krown SE, Metroka C, Wernz JC. Kaposi sarcoma in the acquired immune deficiency syndrome: a proposal for uniform evaluation, response, and staging criteria. AIDS Clinical Trials Group oncology committee. *J Clin Oncol*. 1989;7(9):1201–1207
17. Ramaswami R, Polizzotto MN, Lurain K, et al. Safety, activity, and long-term outcomes of pomalidomide in the treatment of Kaposi sarcoma among individuals with or without HIV infection. *Clinical Cancer Research*. 2022; 28(5):840-850. DOI: 10.1158/1078-0432.CCR-21-3364
18. Paksoy N, Khanmammadov N, Doğan İ, et al. Weekly paclitaxel treatment in the first-line therapy of classic Kaposi sarcoma: A real-life study. *Medicine*. 2023; 102 (5):e32866. DOI: 10.1097/MD.0000000000032866
19. Brambilla L, Boneschi V, Taglioni M, Ferrucci S. Staging of classic Kaposi's sarcoma: a useful tool for therapeutic choices. *Euro J Dermatol*. 2003; 28 (1):83-86.
20. Greene AK, Goss JA. Diagnosis and staging of lymphedema. *Semin Plast Surg* . 2018;32(1):012-016. DOI: 10.1055/s-0038-1635117
21. Benajiba L, Lambert J, La Selva R, et al. Systemic Treatment Initiation in Classical and Endemic Kaposi's Sarcoma: Risk Factors and Global Multi-State Modelling in a Monocentric Cohort Study. *Cancers*. 2021; 13 (11):2519. DOI: 10.3390/cancers13112519
22. Régnier-Rosencher E, Guillot B, Dupin N. Treatments for classic Kaposi sarcoma: a systematic review of the literature. *J Am Acad Dermatol*. 2013;68(2):313-331. DOI:10.1016/j.jaad.2012.04.018
23. Lamy S, Lachambre MP, Lord-Dufour S, Béliveau R. Propranolol suppresses angiogenesis in vitro: inhibition of proliferation, migration, and differentiation of endothelial cells. *Vascul pharmacol*. 2010; 53(5-6):200-208. DOI:10.1016/j.vph.2010.08.002
24. Stiles JM, Amaya C, Rains S, et al. Targeting of beta-adrenergic receptors results in therapeutic efficacy against models of

hemangioendothelioma and angiosarcoma. *PloS one*. 2013;8 (3): e60021. DOI: 10.1371/journal.pone.0060021

25. Gramolelli S, Schulz TF. The role of Kaposi sarcoma-associated herpesvirus in the pathogenesis of Kaposi sarcoma. *J pathol*. 2015; 235 (2):368-380. DOI: 10.1002/path.4441
26. Chang M, Brown HJ, Collado-Hidalgo A, et al. β-Adrenoreceptors reactivate Kaposi's sarcoma-associated herpesvirus lytic replication via PKA-dependent control of viral RTA. *J virol*. 2005; 79(21):13538-13547. DOI:10.1128/JVI.79.21.13538–13547 .2005
27. McAllister SC, Hanson RS, Manion RD. Propranolol decreases proliferation of endothelial cells transformed by Kaposi's sarcoma-associated herpesvirus and induces lytic viral gene expression. *J virol*. 2015;89(21):11144-11149. DOI: 10.1128 /jvi.01569-15
28. Amaya CN, Perkins M, Belmont A, et al. Non-selective beta blockers inhibit angiosarcoma cell viability and increase progression free-and overall-survival in patients diagnosed with metastatic angiosarcoma. *Oncoscience*. 2018; 5 (3-4):109-119. DOI: 10.18632/oncoscience.413
29. Santos M, Vilasboas V, Mendes L, Talhari C, Talhari S. Lymphangiectatic Kaposi's sarcoma in a patient with AIDS. *An Bras Dermatol*. 2013; 88(2):276-278. DOI 10.1590/S0365-05962013000200019
30. Brambilla L, Tourlaki A, Ferrucci S, Brambati M, Boneschi V. Treatment of classic Kaposi's sarcoma-associated lymphedema with elastic stockings. *J dermatol*. 2006; 33(7):451-456. DOI: 10.1111/j.1346-8138.2006.00108.x
31. Montero Pérez I, Rodríguez-Pazos L, Álvarez-Pérez A, et al. Kaposi sarcoma following postmastectomy lymphedema. *J Cut Pathol*. 2015; 42(11):889-893. DOI: 10.1111/cup. 12573