

Triple therapy of Kaposi's sarcoma using oral propranolol, oral zinc sulfate and oral acyclovir as new initiative study

Khalifa E. Sharquie, Raed I. Jabbar*

Department of Dermatology, College of Medicine, University of Baghdad/ Medical City Teaching Hospital, Baghdad, Iraq.

* Department of Dermatology, Fallujah Teaching Hospital, Al-Anbar Health Directorate, Anbar, Iraq.

Abstract

Background Kaposi's sarcoma (KS) in Iraq had been reported as sporadic cases in elderly of Iraqi population but after the Gulf War 1991, there was marked increase in cases of classic KS among Iraqi people, in concordance with the rise of incidence of other hematological and skin malignancies.

Objective To introduce triple therapy for Kaposi's sarcoma using oral propranolol, oral zinc sulfate and oral acyclovir as new innovative therapy.

Methods This is case series and therapeutic trial in which seven cases with histopathological proved Kaposi's sarcoma were included over a twelve months period from 2021 to 2022. All patients were treated by oral propranolol tablet 20mg three times a day, with oral zinc sulfate 100 mg three times a day and acyclovir tablet 800mg three times a day. The duration of therapy continued for three months apart from one case in which the treatment continued for one year. Patients were watched carefully for response to therapy and any adverse reactions were recorded.

Results A total of 7 cases of Kaposi's sarcoma enrolled in this study during one-year period (2020-2021). The age of the patients ranged from 50-60 years with 6 (85.71%) males and one (14.28%) female. The duration of the skin lesions ranged from 2 to 13 months with a mean±SD of 7.85±3.97 months. The lower limbs were the most commonly involved site in 4 (57.14%) cases. In all patients the improvement to therapy was started two weeks after starting the treatment. After 3 weeks, all patients showed obvious decrease in the size of the skin lesions with marked reduction in the size of the lesions achieved after 1.5 months. Ultimately, the lesions and associated signs and symptoms were completely vanished after three months leaving only hyperpigmented macules or patches.

Conclusion This is new effective innovative triple therapy for Kaposi sarcoma using oral propranolol, oral zinc sulfate and oral acyclovir. This new regimen of treatment has both therapeutic and prophylactic effects. Further studies are highly recommended using large series of patients and longer duration of therapy to have more confirmed therapeutic response.

Key words

Kaposi's Sarcoma, triple therapy, zinc sulfate, propranolol, acyclovir.

Introduction

Kaposi's sarcoma (KS) is a vascular tumor with cutaneous and extracutaneous involvements.¹ There are four clinical subtypes of KS: Classic, African endemic, Iatrogenic and AIDS

associated. Skin lesions can vary from pink patches to dark violet plaques, nodules or polyps, depending on stage and clinical variant. Human herpes virus-8 (HHV-8) was observed as the causative agent in all clinical types and now KS is regarded as a virally induced disease.²

Previous researches have revealed that in more than 95% of KS, Kaposi's sarcoma-associated herpes virus (KSHV) is present regardless of HIV condition.³⁻⁵ Now, KSHV has been established as the primary and vital part in the development of KS.^{3,6}

In Iraq, KS has been sporadic disease of elderly individuals⁷ but after American attack and exposure to depleted uranium radiation in early 1991, the frequency of the disease is increasing with earlier onset, wider spread of lesions and aggressive course resulting in more morbidity and mortality.⁸

There are no treatments helping to cure the disease but most medications directed to improve and stop the progression of the disease.^{1,9}

Many topical therapies have been used to treat limited mucocutaneous disease such as: radiotherapy, excisional surgery, laser, cryosurgery, vinblastine, bleomycin, intralesional injections with Interferon-alpha (IFN- α) or vincristine.^{1,2,9}

Systemic cytotoxic medications such as vinblastine, etoposide, doxorubicin bleomycin, Interferon, liposomal agents, gemcitabine and vincristine, but unluckily no one gives complete cure and remission of KS lesions.^{1,2,9}

Propranolol has been used in the treatment of infantile haemangioma (IH) but the mechanism

of action has not been fully clear but could be through inducing vasoconstriction, inhibiting the vasculogenesis and induction of cell apoptosis.¹⁰

Zinc sulfate has been employed to treat different cutaneous diseases such as leishmaniasis,¹¹ burn scar,¹² viral warts,¹³ as it has immunomodulator, antioxidants, antimicrobial and cytotoxic actions.¹⁴ While, acyclovir, a synthetic guanine analog, was seen as the start of a new era in antiviral therapy. It is primarily used for the treatment of herpes viruses and it is safe and well tolerated for longer period as it has been used for Herpes simplex virus prophylaxis for 6 months or even longer.¹⁵

A combination therapy of oral propranolol and zinc sulfate has been suggested by Sharquie in the treatment of KS with promising results.¹⁴

So, the aim of this study is to introduce triple therapy for KS using oral propranolol, oral zinc sulfate and oral acyclovir as new innovative therapy.

Patients and Methods

This is case series and therapeutic trial in which seven cases with histopathological proved KS were included over a twelve months period from 2021 to 2022. Formal consent was taken from each patient before starting the study. A full history and physical examination were achieved for each case including: name, age, sex, residence, occupation, site, size and distribution of the lesions, duration of the disease, previous medical and surgical history, family history and drug history. In addition, lymph nodes and mucous membrane examinations were carried out. The following investigations were done; complete blood count (CBC) and erythrocyte sedimentation rate (ESR), anti-human immunodeficiency virus (HIV) anti- body titre, renal function test, liver function test, abdominal

Address for correspondence

Professor Khalifa E. Sharquie,
Department of Dermatology, College of Medicine,
University of Baghdad, Iraqi and Arab Board of
Dermatology and Venereology, Center of
Dermatology and Venereology, Baghdad Teaching
Hospital, Medical City, Medical Collection Office,
P.O. BOX 61080, Postal code 12114,
Baghdad, Iraq.
Ph: 009647901468515
Email: ksharquie@ymail.com



Figure 1 Fifty-two years old male patient with Kaposi's sarcoma before therapy (A). The same patient after 3 months of therapy showing complete clearance of rash leaving hyperpigmented patches (B).

ultrasound, x-ray of the chest and skin biopsies for histopathological examination to prove the diagnosis were carried out.

All patients were treated by oral propranolol tablet 20 mg three times a day, with oral zinc sulfate 100mg three times a day and acyclovir tablet 800mg three times a day. The duration of therapy continued for three months apart from one case in which the treatment was lasted for one year. Patients were watched carefully for response to therapy and any adverse reactions were recorded.

Results

A total of 7 cases of KS enrolled in this study during one-year period (2020-2021). The age of the patients ranged from 50-60 years with a mean±SD of 55.85±3.71 with 6 (85.71%) males and one (14.28%) female and male to female ratio 6:1.

The duration of the skin lesions ranged from 2 to 13 months with a mean±SD of 7.85±3.97 months. The skin lesions were dusky red macules, papules, patches, or plaques. These lesions were asymptomatic in 5 (71.42%) cases

but 2 (28.57%) cases mentioned mild itching. While edema of the feet was observed in 3 (42.85%) cases. Histopathological results were positive for KS while serological tests for HIV were negative and none of our cases recorded an immunologic dysfunction.

The lower limbs were the most commonly involved sites in 4 (57.14%) cases, both upper and lower extremities in 2 (28.57%) cases, and generalized including upper and lower limbs, trunk and neck in one (14.28%) case. In some cases, the rash was mimicking hypertrophic lichen planus and were treated initially as such.

Neither mucosal nor visceral involvement was seen in any patient and all laboratory investigations were within the normal range. Palpable lymph nodes were seen in the groins in one (14.28%) case.

In all patients the improvement was started two weeks after starting the treatment as mentioned by the patients and noticed during follow-up. After 3 weeks, all patients showed obvious decrease in the size of the skin lesions while marked reduction in the size of the lesions was achieved after 1.5 months. Ultimately, the lesions and associated signs and symptoms were completely vanished after three months leaving only hyperpigmented macules or patches (**Figure 1**). One patient continued his therapy for one year with no relapse. No new lesions appeared during the course of therapy and no significant systemic adverse effects were noticed during treatment.

Discussion

Kaposi's sarcoma was rarely encountered tumor in Iraq, but marked upsurge in cases of classic KS has been recorded following the Gulf War (1991). There are few previously published articles regarding KS in Iraq. In the first study,

21 cases with KS were included over a ten years period from 1974 to 1984.⁷ The second study that carried during the period from 1999 to 2001, recorded an upsurge of new cases of KS in Iraq as 20 cases of KS were diagnosed in a period of less than two years.¹⁶ While in the third study 50 cases were included over a six years period from 2012 to 2018.¹⁷ since then, this upsurge of KS continued.

In addition, and since the Gulf War 1991, the incidence of mycosis fungoides and many hematological malignancies were significantly raised.¹⁸⁻²⁰ Marked increase in cases of classic KS had also been described in concordance with the rise of incidence of other hematological malignancies.^{21,22} This upsurge in the frequency of cases is not clear but it could be attributed to increased exposure to depleted uranium and chemical weapons during the subsequent wars that Iraq had faced since 1991.

The present study recorded that KS was most common in males (85.71%) and this result was comparable to other published Iraqi studies.^{16,17}

The mean age of our patients was 55.85 years which is similar to Al-Waiz *et al.* study¹⁶ in which the mean age was 54 years and lower than Sharquie *et al.* study¹⁸ in which the mean age was 64 years.

The mean duration of the disease was 7.85 months which is comparable to Sharquie *et al.* study¹⁷ in which the mean duration was 9 months and lower than Al-Waiz *et al.* study¹⁶ where the mean duration was 19 months. This difference in the mean duration between our study and Al-Waiz *et al.* study¹⁶ may be attributed to changing in the disease presentation or the long time between the two studies.

Lower extremities were the most commonly involved site in 57.14% of our patients and this

result was comparable to previous studies.^{16,17,23} Why KS is common on the lower extremities, could not be well explained.

No mucosal involvement was seen in any case, this result differed from Sharquie *et al.* study¹⁷ and Al-Waiz *et al.* study¹⁶ where mucosal involvement was seen in 4% and 10% of cases respectively. Palpable regional lymph nodes were detected in 14.28% of cases, which is in the same line with the other studies.^{16,17}

In the current study, visceral involvement was not discovered in any case on thorough work-up. This result similar to Sharquie *et al.* study¹⁷ and differs from Al-Waiz *et al.* study¹⁶ in which 20% of cases had visceral involvement.

Sharquie has used a combination of oral zinc sulfate and oral propranolol in the treatment of different types of KS with promising results.¹⁴ These results encouraged us to add oral acyclovir to this combination as HHV-8 has been established as the primary etiologic infectious agent in all variants of KS aiming to provide more consistent promising results with faster response and in a shorter time period.

The present work showed a novel treatment option for KS by combining three therapeutic medications of different mechanism of actions as zinc sulfate acts through its immunomodulatory effects, antimicrobial and cytotoxic actions.¹⁴ Propranolol, is a non-selective beta blocker, and it prevents the progression and spread of KS via induction of apoptosis, vasoconstriction and inhibition of angiogenesis.¹⁰ Furthermore, in the previous years, propranolol has been found to be effective in the treatment of IH and now is the drug of choice in the treatment of vascular lesions.^{24,25} As KS is a vascular tumor, we supposed that in vitro, propranolol would decrease the proliferation of KSHV infected endothelial

cells.²⁶

HHV-8 is always associated with all types of KS.^{3,6} Results from different in vitro and animal researches proposed that antiviral drugs prevent the replication of HHV-8, and, therefore, their use could provide a potential strategy for both treatment and prevention of HHV-8 associated diseases.²⁷ Acyclovir is a nucleoside antiviral drug acts mainly against herpes viruses. In a most recent study, showed that HHV-8 seems to be common among Iraqi population as 86.6% of people donating blood were positive for HHV-8 IgG antibodies.²⁸ So we hypothesized that oral acyclovir would act against HHV-8 via treatment of infected cells and preventing new lesions. Hence, the synergistic effect of this combination will treat the present lesions of KS and prevent the formation of new lesions thus stopping the progress of the disease. Hence, the current study proved that this triple combination had both therapeutic and prophylactic effects.

In the present work, the duration of treatment was 3 months with very satisfactory results. In all patients, the improvement began two weeks after treatment and the lesions were completely vanished after three months leaving only hyperpigmented macules or patches. In comparison to Sharquie *et al.* study¹⁴ in which a dual combination of oral propranolol and oral zinc sulfate was used for the treatment of KS and the improvement started few weeks after treatment while patients needed 6-12 months treatment to achieve complete remission.

In addition, this combination is safe, non-costly and without significant side effects when compared to multi-sessions of radiotherapy, laser, chemotherapy or cryotherapy. The current study proved that this combination had both therapeutic and prophylactic effects as complete remission was achieved during therapy with no appearance of new lesions.

A limitation of this study is the small number of patients enrolled, with relatively short period of follow-up.

Conclusion

This is new effective innovative triple therapy for Kaposi's sarcoma using oral propranolol, oral zinc sulfate and oral acyclovir tablets. This new therapeutic trial has both therapeutic and prophylactic effects with no significant side effects. Further studies are strongly recommended using large series of patients and longer duration of treatment to support the present interesting findings.

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