International Journal of Cutaneous Disorders & Medicine
ISSN: 2961-5839

Academic Strive
Researcher's perception is our reality

Mini Review *Volume 5 Issue 1*

Kaposi's Sarcoma: Current Treatments

Aral HNE[1], Atliya O[2] and Adisen E[3]*

[1]Dermatology and Venereology Department, Gazi University, Turkey

[2]Dermatology and Venereology Department, Gazi University, Turkey

[3]Dermatology and Venereology Department, Gazi University, Turkey

***Corresponding author:** Esra Adisen, Dermatology and Venereology Department, Gazi University Hospital, Ankara, Turkey, Tel: +905386691346; Email: esra31519@gmail.com

Received Date: April 08, 2024; **Published Date:** May 16, 2024

Abstract

Kaposi's sarcoma is a vascular tumor associated with HHV-8. Clinically, there are classical, AIDS-related epidemic, endemic and iatrogenic types. Local, interventional and systemic treatments are available depending on the type of disease, extent and severity of lesions. However, there is no consensus on optimal treatments and this causes difficulties in treatment selection. Topical treatments such as alitretinoin, timolol, imiquimod, silver nitrate application, laser and surgery can be used. In systemic treatment, chemotherapeutics, immune modulators and antiviral agents can be used. Apart from these, successful results have been reported with treatments such as mTOR inhibitors, immune checkpoint inhibitors, PD-L1 inhibitors. In addition, treatments targeting enzymes such as methyltransferase, RNase and nitric oxide synthase are promising.

Keywords: Current Developments, Kaposi's Sarcoma, Treatment

Abbreviations: HHV-8: Human Herpes Virus-8; AIDS: Acquired Immune Deficiency Syndrome; HIV: Human Immunodeficiency Virus; Nd-YAG: Neodymium Yttrium Aluminum Garnet; mTOR: Mammalian target of rapamycin; HIF-1: Hipoxia inducible factor-1; PD1: Programmed cell death 1; PD-L1: Programmed death- ligand 1; CRISPR: Clustered Regularly Interspaced Palindromic Repeats; INOS: Inducible Nitric Oxide Synthase.

Introduction

Kaposi's sarcoma is an angioproliferative neoplasia that can involve all organs and is associated with immunosuppression [1]. It was first described by Hungarian dermatologist Moritz Kaposi in 1872 [2]. Kaposi's sarcoma herpes virus, also known as Human herpes virus-8 (HHV-8), which increases angiogenesis in addition to genetic predisposition, has been found to play a role in its etiopathogenesis [2]. Clinically, it is usually characterized by purplish brown macules, plaques and nodules in the distal lower extremities. Lesion sizes may remain unchanged or may show rapid progression. Also, lymphedema may accompany the affected extremities [3].

Kaposi sarcoma has 4 types: classical, AIDS-related epidemic, iatrogenic and endemic. The classical type is frequently seen in elderly men of Mediterranean and eastern European origin. The endemic type is common in Africa and can also be seen in children. AIDS-related epidemic type is associated with HIV infection and seen in homosexual or bisexual men. The iatrogenic type occurs

Copyright © 2024 Adisen E, et al.

in patients receiving immunosuppressive therapy or solid organ transplantation, especially kidney transplantation. In addition, there is an increasing number of cases of Kaposi's sarcoma in homosexual men without HIV infection [4] and in some publications it may be considered as the fifth type of the disease [5].

Classical Kaposi's sarcoma usually has a chronic and slow course, but sometimes it may show an acute and rapid course leading to mortality [6]. The diagnosis of Kaposi sarcoma is based on clinical, histopathology, HHV-8 serology and immunohistochemical methods [7,8].

Discussion

Treatment aims to restore the immune system, reduce the size of the lesions and prevent lymphedema. On the other hand, the choice of treatment is influenced by the type and extent of the disease, the patient's comorbidities and the experience of the clinician. However, studies on treatment in the literature are generally based on case reports and retrospective case series. Despite many new developments, a definitive algorithm for treatment has not yet been defined. In this review, current approaches in the treatment of Kaposi's sarcoma are presented.

Asymptomatic cases with a limited number of lesions can be followed without treatment, but the disease may progress. In a study of 39 asymptomatic patients with Kaposi's sarcoma, patients were followed up for 2 years without treatment and the rate of patients without progression was only 34% [9].

In the iatrogenic type, the primary goal should be to reduce immunosuppression and regression or even complete remission can be observed by modifying immunosuppression regimens [2]. Also, in the epidemic type associated with AIDS, disease regression can be observed with antiretroviral therapy [10]. At the same time, it has been shown that HIV protease inhibitors can be used in treatment due to their antiangiogenic and anti-tumoral invasion properties different from their antiretroviral effects [11].

Local treatment options should be considered in cases with a limited number of skin lesions. Topical agents such as alitretinoin, imiquimod, timolol can be used in the treatment of lesions limited to a small anatomical area [12]. In local and limited number of symptomatic lesions, excision [13], cryotherapy [13], silver nitrate [14], pulse dye [15] and Nd-YAG laser [16] treatments can be applied. Intralesional injection with systemic treatment agents such as vinblastine, vincristine, bleomycin, doxorubicin, interferon can be performed [14].

Kaposi's sarcoma lesions are highly sensitive to radiotherapy and it is a good option when there are multiple lesions in a limited anatomical area [17]. Although treatment responses are similar, electron beam therapy may be preferable due to lower out of field recurrence rates [18]. Electrochemotherapy can also be used to increase drug penetration into the tumor [19,20].

There is no consensus on the indications for systemic therapy. In general, however, systemic therapy is indicated in symptomatic visceral or mucosal involvement, diffuse symptomatic skin lesions not covered by the radiation field, diffuse nodular disease and moderate to severe lymphedema [14].

In systemic treatment, pegylated liposomal doxorubicin and paclitaxel are recommended in the first line [10]. However, caution should be exercised in patients with cardiac problems. For patients with peripheral lymphedema or disease limited to the skin and oral mucosa, pomalidomide is an alternative to both classical and epidemic chemotherapy. Chemotherapeutic drugs such as paclitaxel, etoposide, bleomycin, vinorelbine, vincristine, gemcitabine can be used alone or in combinations in progressive disease resistant to initial treatment [2]. The choice between these agents should be individualized, taking into account age, comorbidity and personal preference. Immunomodulatory agents such as thalidomide with antiangiogenic and antiinflammatory properties and IFN with antiproliferative and antiviral activity can be used in AIDS-related Kaposi's sarcoma [14].

Molecularly targeted antiangiogenic agents such as mTOR inhibitors like sirolimus and everolimus [21,22], pazopanib [23], bevacizumab [24]; checkpoint inhibitors such as nivolumab [25], HIF-1, MYC dual inhibitors such as echinomycin [26], PD-1 inhibitors such as pembrolizumab [27], histamine blockage [28], CRISPR [29], fecal transplantation [30], N6 methyladenosine modification [31], METTL 16, a newly discovered RNA methyltransferase [32], a catalytic RNA against KSHV immediate early replication and transcription activator [33], iNOS inhibition [34] are among the promising treatments in the future. It has also been observed that nevirapine, ganciclovir, foscarnet and sidefovir have antiviral activity on HHV-8 [35].

In a study by Masood et al, VEGF was shown to be an autocrine growth factor with high levels of expression in AIDS-associated KS cases, and VEGF antisense oligonucleotides inhibited the growth of KS cells in mouse models [36]. There is a case treated with pazopanib [37] and a phase 2 study of bevacizumab in the treatment of KS [38]. Joest et al. showed that PD-L1 positive microenvironment protects the tumor from immune system attack in nodular stage Kaposi Sarcoma and PD-L1 inhibitors such as nivolumab and pembrolizumab are promising in the treatment of KS [39]. It has been shown that histamine, which plays an important role in allergic

reactions, is highly expressed in AIDS-associated KS cases and histamine blockade suppresses lytic replication of HHV8 [28]. Genetic therapies for herpesvirus replication have been targeted with CRISPR, a popular technology of today. In the study conducted by Tian X, et al. [29] it was pointed out that SMCHD1 gene is a restriction factor in herpesvirus replication and that treatments targeting this gene can be used [29]. Fecal transplantation has been shown to increase the effects of immunotherapy agents and contribute to treatment by showing cross reactivity with tumor neoantigens. In melanoma and RCC, tumor size reduction was reported with fecal transplantation without PD-1 inhibitor administration [30]. MEETL16, an RNA methyl tranferase, has been shown to play an important role in the lytic replication of herpesvirus [32]. iNOS expression has been shown to correlate with herpesvirus lytic gene expression and inhibition may be a therapeutic target [34]. MYC and HIF-1 oncoproteins have been shown to be closely associated with herpesvirus replication and oncogenesis. Echinomycin, which inhibits both of these proteins, has been shown to dramatically regress cell growth in vivo and in vitro [26].

Conclusion

The management of Kaposi's sarcoma is still challenging, the type of disease, prevalence and systemic involvement should be considered when making treatment decisions and a multidisciplinary approach is required in collaboration with dermatology, oncology and infectious diseases. There are many new developments in treatment and the clinician's experience, patient preference and comorbid conditions influence the choice of treatment. However, it should be noted that the exact criteria for the initiation of systemic therapy and the choice of treatment modality have not been defined and there is no consensus on optimal treatment. More studies are needed in this regard.

References

1. Etemad SA, Dewan AK (2019) Kaposi Sarcoma Updates. Dermatol Clin 37(4): 505-517.

2. Dupin N (2020) Update on oncogenesis and therapy for Kaposi sarcoma. Curr Opin Oncol 32(2): 122-128.

3. Dauguet M, Lebbé C, Vignes S (2023) Lymphedema and Kaposi sarcoma: A narrative review. J Méd Vasc 48(5-6): 181-187.

4. Lanternier F, Lebbé C, Schartz N, Farhi D, Kérob D, et al. (2008) Kaposi's sarcoma in HIV-negative men having sex with men. AIDS 22(10): 1163-1168.

5. Friedman-Kien AE, Saltzman BR, Cao YZ, Nestor MS, Mirabile M, et al. (1990) Kaposi's sarcoma in HIV-negative homosexual men. Lancet 335(8682): 168-169.

6. Fatahzadeh M (2012) Kaposi sarcoma: review and medical management update. Oral Surg Oral Med Oral Pathol Oral Radiol 113(1): 2-16.

7. Schneider JW, Dittmer DP (2017) Diagnosis and Treatment of Kaposi Sarcoma. Am J Clin Dermatol 18(4): 529-539.

8. Brambilla L, Genovese G, Berti E, Peris K, Rongioletti F, et al. (2021) Diagnosis and treatment of classic and iatrogenic Kaposi's sarcoma: Italian recommendations. Ital J dermatology Venereol 156(3): 356-365.

9. Brenner B, Rakowsky E, Katz A, Gutman H, Sulkes A, et al. (1999) Tailoring treatment for classical Kaposi's sarcoma: comprehensive clinical guidelines. Int J Oncol 14(6): 1097-1102.

10. Lebbe C, Garbe C, Stratigos AJ, Harwood C, Peris K, et al. (2019) Diagnosis and treatment of Kaposi's sarcoma: European consensus-based interdisciplinary guideline (EDF/EADO/EORTC). Eur J Cancer 114: 117-127.

11. Monini CP, Sgadari C, Grosso MG, Bellino S, Toschi E, et al. (2009) Clinical course of classic Kaposi's sarcoma in HIV-negative patients treated with the HIV protease inhibitor indinavir. AIDS 23(4): 534-538.

12. Htet KZ, Waul MA, Leslie KS (2022) Topical treatments for Kaposi sarcoma: A systematic review. Skin Health Dis 2(2): e107.

13. Webster GF (1995) Local therapy for mucocutaneous Kaposi's sarcoma in patients with acquired immunodeficiency syndrome. Dermatol Surg 21(3): 205-208.

14. Esser S, Schöfer H, Hoffmann C, Claßen J, Kreuter A, et al. (2022) S1 Guidelines for the Kaposi Sarcoma. J Dtsch Dermatol Ges 20(6): 892-904.

15. Marchell N, Alster TS (1997) Successful treatment of cutaneous Kaposi's sarcoma by the 585-nm pulsed dye laser. Dermatol Surg 23(10): 973-975.

16. Özdemir M, Balevi A (2017) Successful Treatment of Classic Kaposi Sarcoma with Long-Pulse Neodymium-Doped Yttrium Aluminum Garnet Laser: A Preliminary Study. Dermatol Surg 43(3): 366-370.

17. Quéro L, Palich R, Valantin MA (2022) The Role of Radiotherapy in Treating Kaposi's Sarcoma in HIV Infected Patients. Cancers 14(8): 1915.

18. Nisce LZ, Safai B, Poussin-Rosillo H (1981) Once Weekly

Total and Subtotal Skin Electron Beam Therapy for Kaposi's Sarcoma. Cancer 47(4): 640-644.

19. Ferioli M, Galuppi A, Buwenge M, Cammelli S, Perrone AM, et al. (2021) Electrochemotherapy in Kaposi sarcoma: A systematic review. Mol Clin Oncol 14(4): 64.

20. Niccolò A, Elena M, Nadiane P, Barbara M, Gianlorenzo I, et al. (2023) Electrochemotherapy with bleomycin as an effective local treatment for Kaposi's sarcoma: a case report. Anticancer Drugs 34(4): 589-591.

21. Zhou J, Li Y, Qiu T, Gong X, Yang K, et al. (2023) Long-term outcomes of sirolimus treatment for kaposiform hemangioendothelioma: Continuing successes and ongoing challenges. Int J cancer 153(3): 600-608.

22. Maza-Morales M, Valdés-Loperena S, Durán-McKinster LC, García-Romero MT (2023) The use of mTOR inhibitors for the treatment of kaposiform hemangioendothelioma. A systematic review. Pediatr Dermatol 40(3): 440-445.

23. Zsuzsanna P (2014) Medical treatment of soft tissue sarcomas based on the histological subtype. Magy Onkol 58(1): 53-58.

24. Pria AD, Pinato DJ, Bracchi M, Bower M (2019) Recent advances in HIV-associated Kaposi sarcoma. F1000Res 8.

25. Delyon J, Bizot A, Battistella M, Madelaine I, Vercellino L, et al. (2018) PD-1 blockade with nivolumab in endemic Kaposi sarcoma. Ann Oncol 29(4): 1067-1069.

26. Chen J, Lin Z, Song J, Plaisance-Bonstaff K, James J, et al. (2023) Echinomycin as a promising therapeutic agent against KSHV-related malignancies. J Hematol Oncol 16(1): 48.

27. Lolli I, Valentini AM, Ricci AD, Armentano R (2023) Anaplastic Classic Kaposi Sarcoma: PD-L1 Expression and Response to Immunotherapy: A Case Report and Review of the Literature. J Natl Compr Canc Netw 21(5): 442-448.

28. Chen J, Song J, Plaisance-Bonstaff K, Mu S, Post SR, et al. (2023) Role of Histamine and Related Signaling in Kaposi's Sarcoma-Associated Herpesvirus Pathogenesis and Oncogenesis. Viruses 15(4): 1011.

29. Tian X, Zhou Y, Wang S, Gao M, Xia Y, et al. (2023) Genome-Wide CRISPR-Cas9 Screen Identifies SMCHD1 as a Restriction Factor for Herpesviruses. mBio 14(2): e0054923.

30. Stoff R, Wolf Y, Boursi B (2023) Fecal Microbiota Transplantation as a Cancer Therapeutic. Cancer J 29(2): 102-108.

31. Zhang X, Meng W, Feng J, Gao X, Qin C, et al. (2023) METTL16 controls Kaposi's sarcoma-associated herpesvirus replication by regulating S-adenosylmethionine cycle. Cell Death Dis 14(9): 591.

32. Zhang X, Peng Q, Wang L (2023) N6-methyladenosine modification-a key player in viral infection. Cell Mol Biol Lett 28(1): 78.

33. Liu Y, Chen YC, Yan B, Liu F (2023) Suppressing Kaposi's Sarcoma-Associated Herpesvirus Lytic Gene Expression and Replication by RNase P Ribozyme. Molecules 28(8): 3619.

34. Vladimirova O, Soldan S, Su C, Kossenkov A, Ngalamika O, et al. (2023) Elevated iNOS and 3′-nitrotyrosine in Kaposi's Sarcoma tumors and mouse model. Tumour Virus Res 15: 200259.

35. Goff CB, Dasanu CA (2023) Changing therapeutic landscape in advanced Kaposi sarcoma: Current state and future directions. J Oncol Pharm Pract 29(4): 917-926.

36. Masood R, Cesarman E, Smith DL, Gill PS, Flore O (2002) Human herpesvirus-8-transformed endothelial cells have functionally activated vascular endothelial growth factor/vascular endothelial growth factor receptor. Am J Pathol 160(1): 23-29.

37. Harris BHL, Walsh JL, Neciunaite R, Manders P, Cooper A, et al. (2018) Ring a ring o'roses, a patient with Kaposi's? Pazopanib, pazopanib, it might go away. Mediterranean (classic) Kaposi sarcoma responds to the tyrosine kinase inhibitor pazopanib after multiple lines of standard therapy. Clin Exp Dermatol 43(2): 234-236.

38. Uldrick TS, Wyvill KM, Kumar P, O'Mahony D, Bernstein W, et al. (2012) Phase II study of bevacizumab in patients with HIV-associated Kaposi's sarcoma receiving antiretroviral therapy. J Clin Oncol 30(13): 1476-1483.

39. Joest B, Kempf W, Berisha A, Peyk P, Tronnier M, et al. (2020) Stage-related PD-L1 expression in Kaposi sarcoma tumor microenvironment. J Cutan Pathol 47(10): 888-895.