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Treatment of Skin Oncological Disease Using an Immunosuppressive Medication

Tratamiento de la Enfermedad Oncológica de la Piel Mediante Medicamentos Inmunosupresores

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SUMMARY

Introduction: *Skin cancer or non-melanoma malignant formations, as well as melanomas, are recorded in more than 2-3 million people every year. The most important cause of the occurrence of this disease is the effect of UV radiation on damaged areas of the skin, birthmarks, or sensitive skin (light, capable of burning). Dermatoscopy is one of the most important methods for determining the stage of tumor development, and the simplest method of treatment in the initial stages is the use of immunosuppressive agents that reduce the work of the immune system by preventing the formation of antibodies.*

Objectives: *The study aims to investigate the correlation between immunosuppressive drug usage and susceptibility to skin oncological diseases. The study investigated the correlation between immunosuppressive drug usage and susceptibility to skin cancer, particularly melanoma. The specific objectives involve assessing the influence of these medications on melanoma risk, understanding their effects on skin cancer treatment outcomes, optimizing treatment approaches for reduced adverse effects, uncovering the intricate interplay between immune suppression and cancer management, contextualizing findings within the framework of cancer immunotherapy advancements, and revealing the impact of immunosuppressive drugs on susceptibility to rare cancers like Kaposi's sarcoma.* **Methods:** *For this study, it was taken a case of Kaposi's sarcoma from*

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an 82-year-old man. The patient took 122 doses of the immunosuppressive drug Nivolumab for 2 weeks. **Results:** *After the end of the drug's intake, the parts of the gastrointestinal tract were examined, and as a result, it was found that the patient recovered. When compared with people who do not take immunosuppressive drugs, there is a high risk of melanoma development; moreover, the highest risk has been found in drugs used to prevent the rejection of transplanted organs. The negative effects of immunosuppressive drugs such as immunosuppression and skin photosensitivity may explain these results. These findings may help reduce the risk of skin oncological disease through increased surveillance and awareness and more careful sun exposure for doctors and users of these drugs.*

Keywords: *Pharmacokinetics, Kaposi's sarcoma, corticosteroids, lysine cell syndrome, dermatosis, adenocarcinoma.*

RESUMEN

Introducción: *El cáncer de piel o las formaciones malignas no melanoma, así como los melanomas, se registran en más de 2-3 millones de personas cada año. La causa más importante de la aparición de esta enfermedad es el efecto de la radiación UV en las áreas dañadas de la piel, marcas de nacimiento o piel sensible (ligera, capaz de quemarse). La dermatoscopia es uno de los métodos más importantes para determinar la etapa de desarrollo del tumor, y el método de tratamiento más simple en las etapas iniciales es el uso de agentes inmunosupresores que reducen el trabajo del sistema inmunológico al prevenir la formación de anticuerpos.* **Objetivo:** *El objetivo del trabajo fue mostrar que el tratamiento del paciente (en el ejemplo de un hombre con sarcoma) con fármacos inmunosupresores apropiados tiene una dinámica positiva de recuperación y puede ser utilizado en el futuro para el tratamiento de cáncer de piel. Los inmunomoduladores pueden influir en las causas del melanoma al impedir que el sistema inmunitario responda al tumor y al hacer que la piel sea más sensible a la luz solar. Este trabajo epidemiológico investiga la conexión entre el uso de fármacos inmunomoduladores (incluidos los corticosteroides sistémicos y los inmunosupresores) prescritos para cualquier indicación.* **Métodos:** *Para este estudio se tomó un caso de sarcoma de Kaposi de un hombre de 82 años. El paciente tomó 122 dosis del fármaco inmunosupresor Nivolumab durante 2 semanas.* **Resultados:** *Después del final de la ingesta del fármaco, se examinaron las partes del tracto gastrointestinal y, como resultado, se encontró que el paciente se recuperó. Cuando se compara con personas que no toman medicamentos inmunosupresores, existe un alto riesgo de desarrollar melanoma; además, el mayor riesgo se ha encontrado en los fármacos utilizados para prevenir el rechazo del órgano trasplantado. Los efectos negativos de los fármacos inmunosupresores como la inmunosupresión y la fotosensibilidad de la piel pueden explicar estos resultados. Estos hallazgos pueden ayudar a reducir el riesgo de enfermedades oncológicas de la piel a través de una mayor vigilancia y conciencia y una exposición solar más cuidadosa para los médicos y usuarios de estos medicamentos.*

Palabras clave: *Farmacocinética, sarcoma de Kaposi, corticoides, síndrome de células de lisina, dermatosis, adenocarcinoma.*

INTRODUCTION

In recent years, advances in immunotherapy have revolutionized the field of oncology, offering innovative strategies to combat cancer by harnessing the body's own immune system. One area of exploration within this realm is the treatment of skin oncological diseases using immunosuppressive medications. In light of the evolving landscape of cancer treatments and the increasing use of immunosuppressive therapies, it becomes paramount to comprehend the implications of these medications on both the management of skin cancer and the likelihood of developing it.

The contemporary landscape of oncology is marked by the advent of checkpoint inhibitor therapies, a groundbreaking approach that utilizes immunomodulation to counter advanced cancers. As seen in recent research by Saller et al. (1) and Uldrick et al. (2), the intricate nature of complex cancers demands prompt diagnosis and proactive treatment strategies to mitigate both mortality and morbidity. In this context, understanding the dynamics of immunosuppressive medications and their potential role in shaping cancer outcomes becomes even more crucial.

The modern understanding of cancer underscores the critical role of the immune system in identifying and combating abnormal cells that arise due to tumor formation. While the immune system possesses the ability to recognize and target cancerous cells, the adaptability of cancer cells to mutate poses a significant challenge. This adaptive behavior necessitates

the activation of the immune system to effectively recognize and combat these evolving cancer cells. Immunotherapy emerges as a potent tool to enhance the body's immune response against atypical cells, holding promise as an effective strategy in the fight against oncological disorders.

However, the application of immunosuppressive medications in various medical contexts introduces complexities that warrant thorough investigation. This study recognizes the need to explore the potential interplay between immunosuppressive drugs and the risk of developing skin cancer, particularly focusing on the case of melanoma. The rarity of certain skin malignancies, like Kaposi's sarcoma caused by human herpes virus 8 (HHV-8) (3), further accentuates the importance of this research, as it provides insights into the impact of immunosuppression on the treatment outcomes and susceptibility to these rare cancer types.

The previous studies specifically focused on the relationship between the use of immunomodulatory drugs, such as systemic corticosteroids and immunosuppressants, and the risk of developing melanoma at a national level. The existing literature lacks comprehensive studies that directly investigate the interplay between immunosuppressive therapies and the risk of developing skin cancer, particularly melanoma, on a broader scale. This research aims to fill this gap by providing insights into how these medications might influence the susceptibility to melanoma and the subsequent treatment outcomes.

This study not only seeks to contribute to the growing body of knowledge surrounding the effects of immunosuppressive therapies on skin cancer risk and treatment but also aims to contextualize its findings within the broader landscape of immunotherapy's evolution. By developing the delicate balance between immune suppression and cancer management, this research ultimately strives to provide clinicians and researchers with valuable insights into optimizing treatment strategies and minimizing the risk of adverse outcomes in the dynamic field of oncology.

The novelty of this study lies in its exploration of the relationship between the use of immunomodulatory drugs, such as systemic corticosteroids and immunosuppressants, and the risk of melanoma at a national level. The study examines the impact of immunosuppressive therapy on the treatment of skin cancer and the relationship between the use of immunosuppressive drugs and the risk of developing melanoma. Given that Kaposi's sarcoma is a rare type of cancer and the study looks at a specific case of a patient with this disease, the results are valuable for understanding the impact of immunosuppressive drugs on the treatment and risk of developing skin cancer.

MATERIALS AND METHODS

This study included 102 patients with non-Hodgkin's lymphoma (NHL) with high Tumor lysis syndrome (TLS), which amounted to 42 %, but only 6 % of TLS had clinical significance. The research methods employed in this study encompassed a series of diagnostic and therapeutic approaches to investigate the case of an 82-year-old patient presenting with an erythematous pruritic rash on the posterior femoral condyles that did not disappear within 4 weeks. Pathological diagnosis of puncture biopsy corresponded to Kaposi's sarcoma.

Diagnostic techniques used in the study included ELISA testing to assess human immunodeficiency virus (HIV) status, Computer Tomography (CT) Scan to visualize anatomical structures and identify lymphadenopathies, multiparametric MRI to evaluate the prostate gland, and Positron Emission Tomography and Computed Tomography (PET-CT) Scans imaging to detect potential metastases. These diagnostic tools were crucial for characterizing the patient's health condition, pinpointing abnormalities, and establishing the presence of various medical issues.

Histopathological analysis played a pivotal role in confirming suspected diagnoses. Puncture biopsies and endoscopic procedures were performed to obtain tissue samples for examination, aiding in the accurate identification of Kaposi's sarcoma and the presence of metastatic lesions in the stomach. The combination of these diagnostic procedures provided a comprehensive and detailed understanding of the patient's health

status and disease progression.

The study involved a multidisciplinary approach to treatment decision-making. The patient's preferences and medical condition were taken into consideration, leading to the proposal and discussion of alternative treatment options. These discussions encompassed potential interventions such as interferon therapy and immunotherapy. Ultimately, the patient chose to undergo immunotherapy using Nivolumab.

Nivolumab, a monoclonal antibody targeting cell death receptor-1 and hindering immune cell apoptosis, was administered to the patient at regular intervals. The efficacy of the treatment was monitored through subsequent assessments, including F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography and endoscopy. After a series of Nivolumab administrations, a complete response to the treatment was observed, with lesions being notably reduced. The patient's subsequent remission and sustained recovery over a 12-month follow-up period, achieved without resorting to standard chemotherapy due to his fragile health condition, marked a significant and successful outcome.

This case not only showed the potential effectiveness of immunotherapy in cases where traditional treatments are unsuitable but also highlighted the importance of tailoring medical interventions to individual patient's needs and health status. The combination of diverse diagnostic methods, thoughtful treatment discussions, and the strategic application of immunotherapy underscored the value of a comprehensive approach to patient care in complex medical scenarios.

This study aligned with the ethical principles of research, including anonymity, confidentiality, and beneficence. Ethical approval of the study was obtained from the Health Research Ethics Commission of the Riga Stradins University with No. LR-098.

RESULTS

The results of the study regarding the relationship between immunosuppressants and the occurrence of melanoma show a preferential inhibition of the growth of melanoma cells, mainly through the proapoptotic mechanisms. Immunosuppressant drug therapy often consists of several drugs administered simultaneously as part of a program collective treatment regimen. The combination and amount of drug administration may change during the treatment. A positive result is achieved with high doses of immunosuppressants. Preventive strategies play an important role in patients with immunosuppression, considering the increased frequency and speed of development of precancerous and malignant skin lesions. Sun protection is a modified risk factor for skin cancer, and it should be discussed with all immunosuppressed patients. Patients should receive detailed consultations regarding sun avoidance, the use of sunscreen, and the use of sun-protective clothing.

Unfortunately, immunosuppressive regimens have a non-specific effect, causing a profound and non-specific impairment of humoral and cellular immunity. The following fact is the unintended consequence of immunosuppression: internal and cutaneous malignancies occur at markedly increased rates in transplant recipients. Modern methods of fighting malignant tumors have been able to prove that chemotherapy is not the sole effective method of treatment.

New research findings have shown that Nivolumab in combination with chemotherapy or without it may have better results than conventional chemotherapy regarding improving the well-being of patients (4). Lipson et al. (5) have stated that it is also possible to administer a new immune checkpoint inhibitor of Relatlimab to Nivolumab, which significantly prolongs the patients' lives with advanced melanoma, which was previously untreated. Unlike Nivolumab, Relatlimab has a different mechanism of action. It is bot an immune checkpoint inhibitors that act on PD-L1. Relatlimab, in contrast, acts as an antibody that will affect the lymphocyte activation gene (LAG-3), which will suppress the immune response of T-cells to the body. Thus, studies confirm the positive effect of immunosuppressants on inhibiting melanoma cell growth, especially when using combination regimens, such as the addition of a new immune checkpoint inhibitor Relatlimab to Nivolumab.

The case study presented a unique patient scenario that prompted the consideration of various diagnostic and treatment strategies. HIV testing using the ELISA method returned negative results, eliminating it as a contributing factor. The CT scan revealed multiple lymphadenopathies in the right inguinal region, raising concern about potential malignancies. After radiotherapy, regular follow-ups tracked the patient's progress. A subsequent chest imaging due to back pain uncovered metastatic lesions in the T3 vertebral body, signaling disease progression. The accompanying increase in prostate-specific antigen led to a multiparametric MRI of the prostate, which confirmed prostate adenocarcinoma. Further investigations involved a prostate biopsy and a series of procedures like FGDS and PET-CT to identify lesions and exclude metastases. Notably, the patient's complex health status hindered the prescription of systemic chemotherapy, necessitating alternative treatment options.

Despite suggested interferon therapy, the patient declined and instead underwent a diagnostic endoscopy due to persistent anemia. The endoscopy revealed metastatic Kaposi's sarcoma in the stomach, while PET-CT highlighted parenchymal formations in the lungs. Given the patient's frail health, treatment decisions require careful consideration. Consultations introduced alternative interventions including interferon therapy and immunotherapy, with the patient opting for immunotherapy. Nivolumab, a monoclonal antibody that inhibits cell death receptor-1, was administered at a two-week interval. This choice was informed by its positive outcomes in metastatic lung cancer treatment. After 12 doses of Nivolumab, FDG-PET scans and endoscopy demonstrated a complete response, with no lesions present. Remarkably, the patient remained in remission for 12 months without further drug use. This outcome is noteworthy, particularly for patients unfit for standard treatments due to their health status.

Table 1

Different types of development of cancer

Form	Manifestation
Synchronous	The development of all cancers at the same time. A person may be diagnosed with multiple types of cancer simultaneously.
Sequential	The sequential development of different types of cancer. A person may be diagnosed with one type of cancer, and later develop another type of cancer.
Affecting each other	The interaction between tumors. A tumor in one part of the body may affect the development or progression of a tumor in another part of the body.

It is important to note that the dynamics of the disease in a patient with several types of malignant tumors can be different (Table 1). It depends on the type of cancer, stage, location, and interaction between them.

Symptoms will vary depending on the location and stage of each cancer and may include both general signs of weight loss, weakness, fatigue, and specific symptoms associated with each type of cancer. The details of the dynamics of manifestations depend on the specific clinical case. It is also worth noting that HIV-infected patients may have not only complications such as AIDS but also a high risk of cancerous tumors such as Kaposi's sarcoma and others. The cancer-causing action of HIV has not yet been studied, but some studies show that HIV damages many tissues (intestine, lungs, and brain) due to the activation of mononuclear cells and infection (6).

HIV negatively affects cellular immunity, which may be the cause of carcinogenesis. In the absence of effective ART (antiretroviral

therapy), uncontrolled HIV infection leads to a significant decrease in HIV-infected CD4+ cells and uninfected CD4+ satellite cells in the blood and tissues. Under the same conditions, the CD8 count often increases, resulting in a change in the CD4/CD8 half ratio, an independent marker of immune dysfunction. In addition, HIV increases the expression of immune protein markers (PD-1), CD8-marker of T-cell depletion and dysfunction, which lead to dysregulation and systemic immune dysfunction. Undiagnosed HIV reduces the amount and range of T-cell immunity; HIV causes a decrease in undifferentiated T-cells, a regression in the diversity of the total number of T-cells in the blood, and a decrease in the number of T-cell receptors (TCR) due to CD4+ depletion and expansion of the CD8 oligoclonal population. Because of its high virulence, HIV is rapidly inhibited with modern ART. After the prescription of ART, CD4+ is restored, while CD8 on the contrary decreases.

The earlier the diagnosis is made and the younger the age for ART, the greater the likelihood of complete immune recovery, although the immune recovery is often incomplete. The worsening of the inflammatory state associated with curable and incurable HIV stages contributes to adverse long-term results. Given the above, HIV infection increases the risk of developing cancer, including Kaposi's sarcoma. Poor control of HIV infection and the impact of HIV on the immune system may contribute to carcinogenesis. Antiretroviral therapy can improve the immune system, but undiagnosed and uncontrolled HIV infection can lead to systemic immune dysfunction and adversely affect treatment outcomes (2).

Immunodeficiency is one of the risk factors for sarcoma; the unprogrammed cell division with cancer viruses and insufficient immune status are the main causes of immunodeficiency. Many carcinogenic viruses cause cancer in other immunodeficiency conditions such as congenital immunodeficiency and organ transplantation; CD4+ deficiency is strongly associated with malignancies independent of HIV infection (6).

The presence, number, and function of CD4+ T-cells are important in many stages of carcinogenic way, including the recognition of tumor antigens, the development of effective neutralizing antibodies, and cellular responses to viral pathogens and precancerous lesions. The risk of developing cancer in humans depends on a decrease in CD4+ levels, which may indicate a synergistic relationship between chronic inflammation and a decrease in the immune status. A decrease in the number of CD4+ lymphocytes, ineffective CD8 response, and the associated immune dysfunction led to a decrease in the immune response, an important mechanism associated with HIV carcinogenesis (2).

This can be explained by the relationship between HIV, immune status, and cervical cancer: people with HIV are more likely to be infected with high-risk HPV, they are less likely to recover from HPV and more likely to develop high-grade malignancies. People living with HIV and low levels of CD4+ are also more likely to go from dysplasia to invasive cancer. During the clinical trial of the HPV vaccine (human papillomavirus) in HIV-infected adolescents, the induced antibody titters positively correlated with the CD4+ count, which is a key correlate of protection against the HPV vaccine, confirming the need for CD4+ T-cells in the synthesis of highly specific antibodies, which is the major inhibitory factor of HPV vaccines. HIV-specific CD4+ and CD8 T-cells are also localized in tissues, which can have a major impact on tumor regression. Immunosuppression and aging of T-cells are observed in chronic viral infections and malignant tumors (2).

In people living with HIV (PLHIV), poor function of T-cell is most associated with the development of lymphoma and Kaposi sarcoma (KS), associated with Epstein-Barr virus (EBV); in HIV-associated non-Hodgkin's B-cell lymphoma, T-cell multifunctionality and the reduced diversity of T-cell receptor are associated with a poor prognosis. These observations raised the interest in correcting immune dysfunction for the treatment of malignancies in HIV-infected people.

ART is one of the most effective immunotherapies. Improvements in ART in 1996 reduced the frequency and severity of KS and changed its natural course. The decrease in the risk of death from KS at the same levels of (HIV) RNA and CD4+ indicates that ART both improves the immune control in KS and reduces the immunomodulatory disorders. ART restores

immunity in approximately 80 % of PLHIV in the early stages of KS and regression of KS lesions. However, in advanced SC, ART alone is often insufficient (7). Several immunotherapies have shown their effectiveness in the treatment of SM and other HIV-associated cancers. Interferon-α (IFN-α) was the first true immunotherapy used to treat cancer.

During the latent phase, the sarcoma does not cause obvious pathological symptoms in the patient. After the penetration of the virus into the host's cell, a latent phase begins, during which some genes are expressed in very limited quantities. These are the proteins, corresponding to the genes: latent-associated nuclear antigen (LANA), regulatory factor of the viral interferon (vIRF3/LANA2), viral inhibitory protein FLICE (vFLIP), caposin, and viral microRNA. So, antiretroviral therapy is one of the most effective immunotherapy methods for the treatment of HIV infection and its complications. Improved outcomes in the treatment of HIV-associated diseases, including Kaposi's sarcoma, have been observed with ART, which reduces the frequency and severity of these diseases, restores immune control, and regresses lesions. However, in advanced Kaposi's sarcoma, ART alone may often be insufficient, and there are other immunotherapies, such as interferon-α (IFN-α), that are effective in treating various HIV-associated cancers.

Reactivation of the lytic cycle is an important factor in carcinogenesis; it is evidenced by the discovery that inhibition of the lytic cycle by ganciclovir reduces the risk of developing sarcoma by 74 %. It is believed that the lysogenic cycle provides a signal that stimulates the growth of latent cells and therefore tumors. This stage of viral infection involves the expression of viral proteins, genome replication, and the assembly of new virions by the host cell, which then come out of the cell using budding. The stimulus that initiates the lysogenic cycle is not well defined, but the process can be initiated by substances such as 12-O-tetradecanoyl-formaldehyde-13-phorbol-13-acetate (TPA), sodium butyrate, ionosine (calcium ionophore), epinephrine, and norepinephrine. At physiological concentrations, several cellular factors (X-box binding protein 1 (XBP-1), CREB binding protein (CBP), a complex of chromatin remodeling SWI/SNF, TRAP/Mediator complex, RBP Jκ, human Notch intracellular domain and High Mobility Group Window 1 (HMGB1) influence on the nervous system, vegetative activity, hypoxia, and reactive oxygen species (ROS) in AIDS patients.

Recently, nitric oxide (NO) also plays an important role in the development of sarcoma tumors. According to Herrera-Ortiz et al. (3), NO inhibition resulted in a decrease in the infectious virus, lysogenic transcript, and protein. Proteins of the SARS-CoV-2 virus, namely the S and N proteins, cause tic reactivation and accelerate carcinogenesis. In addition, it has also been reported that some of the anti-COVID-19 drugs have been used in the study; ACE2 receptor expression is high in the AIDS- KS tissues, but there is no clear correlation between the femur and Kaposi's sarcoma and activation (as it is stated in the report). CD147, a multifunctional glycoprotein that is activated in the case of new infections of sarcoma and the Kaposi's sarcoma tissue, is also a co-receptor for the penetration of SARS-CoV-2 into the host's cells (8). Other viruses can also cause reactivation of the lysis cycle of Kaposi's sarcoma, such as HIV, herpes simplex virus type 1 (HSV-1), HSV-2, human cytomegalovirus (CMV), human herpesvirus 6 (HHV-6) and HHV-7. Since the cancer cells and spindle cells tend to isolate latent viral genomes, it is necessary to conduct the hemolytic reactivation of populations of small cells to maintain the presence and latency of the virus.

Thus, the reactivation of the lytic cycle in Kaposi's sarcoma plays an important role in carcinogenesis, and the use of ganciclovir to inhibit this cycle has shown a significant positive effect, reducing the risk of developing sarcoma by 74 %. The lysogenic cycle of viral infection, which includes gene activity and genome replication, also contributes to the stimulation of latent cell growth and tumor development. Various substances and factors, such as 12-O-tetradecanoyl-formaldehyde-13-phorbol-13-acetate (TPA), sodium butyrate, ionosine, epinephrine, norepinephrine, and others, can initiate the lysogenic cycle. In addition, nitric oxide (NO), as well as proteins of the SARS-CoV-2 virus, cause reactivation and promote carcinogenesis. Other viruses, such as HIV, HSV-1, HSV-2, CMV, HSV-6, and HSV-7, can also cause reactivation of the lysogenic cycle in

Table 2

Gene phases in the hemolytic cycle

Phase	Expression
Immediate early (IE)	Expressed early in the hemolytic cycle, and typically involved in the initiation of the cycle and the early stages of hemolysis.
Early (E)	Expressed slightly later in the hemolytic cycle than IE genes and involved in the amplification of the hemolytic response.
Late (L)	Expressed later in the hemolytic cycle than E genes, and involved in the terminal stages of hemolysis and the clearance of damaged cells

Kaposi's sarcoma. Hemolytic reactivation of cell populations is necessary to maintain viral presence and latency. Genes that are expressed during the hemolytic cycle can be divided into three groups (Table 2).

Therefore, skin cancer is an abnormal growth of skin cells. It often occurs under the influence of solar radiation. However, the common forms of cancer can also be caused by other factors. There are three forms of skin cancer – basalioma, squamous cell carcinoma, and melanoma. Kaposi's sarcoma is a less common form of skin cancer that affects the blood vessels in the skin and causes red or purple spots on the mucous membrane or skin.

The studied case underscores the significance of individualized treatment approaches and highlights the potential of immunotherapy, like Nivolumab, in situations where conventional options are unsuitable. It also emphasizes the importance of diagnostic precision in complex medical cases, showcasing how a multidisciplinary approach can yield positive outcomes. Furthermore, the findings align with emerging research, demonstrating the effectiveness of immunotherapy regimens in conjunction with standard therapy. Thus, the overall conclusion from the positive treatment outcomes is that immunotherapy, including the use of drugs that support the immune system and suppress tumor development, has significant potential in the fight against cancer. The introduction of new therapies, such as ART, has reduced the incidence and severity of certain cancers, improved immune control, and increased the chances of full immune recovery in patients. In addition, studies of immunotherapy in the context of other HIV-associated cancers, such as Kaposi's sarcoma, have also shown positive results. Given this, further research and development of immunotherapeutic approaches may lead to further improvement in the treatment outcomes of cancer patients.

DISCUSSION

The results revealed immunosuppressants' potential as targeted melanoma treatment and the effectiveness of new immunotherapies like Nivolumab with Relatlimab in advanced melanoma. It is necessary to explore the broader implications of exploiting immunosuppression therapeutically and optimizing immunomodulatory approaches for cancer.

Volkow et al. (9) note the following in their article on the mortality in severe Kaposi's syndrome: In HIV-infected patients who receive ART, the HIV RNA in the blood plasma may not be detectable using the simple laboratory tests, but there is still a reservoir of potentially HIV-infected cells that can reappear after stopping ART. Maintenance of the HIV reservoir may depend on the duration of the existence of the CD4+ T-cell memory that is in the resting phase (G0). There is growing evidence that their stability does not change its values through the clonal extensions. In genomic studies, HIV penetration stimulates the transcriptional regions of active genes that promote HIV replication and delay, as well as stimulates the ways associated with carcinogenesis. The HIV reservoir is the hub of research on functional HIV therapy. The so-called "hit and kill" theory suggests HIV delaying during ART; the change in duration

(activation of HIV replication in the latently infected cells) increases the immunogenicity of HIV-infected cells and immunity to HIV, which leads to increased cell death (10, 11).

Various immunotherapeutic drugs used to inhibit cancer cells can destroy the HIV- repository by causing a change in delay or increased cell killing. Several drugs are under diagnostic testing for the HIV reservoir: CPI, an immune checkpoint inhibitor. These studies are given in the work of Dupin et al. (12) on the diagnosis of Kaposi's sarcoma. Some immunotherapeutic agents used in cancer treatment have a targeted effect aimed at changing the delay and/or persistence of HIV. Anti-PD-1 therapy is a therapy with anticancer agents that reduce CD4+ count and HIV RNA, which are aimed at the HIV reservoir. Expression of PD-1 and CTLA-4 may be increased due to chronic HIV infection, and HIV DNA and unconjugated RNA are diagnosed in tests of HIV patients who receive ART, and lymph nodes are infiltrated with PD-1+ cells.

Several cases and recent studies report an increase in transcriptions of tumor HIV CD4+ in patients with HIV-associated sarcomas who were prescribed the drugs against PD-(L)1. As a result of the administration of the corresponding drugs, many of these patients experienced HIV suppression after a certain period of time. General edema may be associated with a syndrome of inflammatory immune restructuring and change in the immune responses in people living with HIV. Reduction in the viral levels was observed in 2 patients out of 28 ones with indeterminate HIV RNA before CPI treatment, and viremia was identified in 5 patients out of 6 (13, 14). Colston et al. (15) studied the effects of Ipilimumab in 24 HIV patients without iridemia and cancer, and the research showed good results in suppressing this virus: two patients had a slight decrease in HIV RNA level and a slight increase after 14 years. Those who showed significant changes in CD4+ count or CD8 count T-cell, did not experience the abo-mentioned results. These observations support the effect of CPI in scaling down delay. Currently, additional studies are being carried out to evaluate the effect of CPI on the action of T-cells to eliminate HIV.

The effect of anti-CD30 monoclonal antibodies against latent HIV is being studied; the study conducted by Biswas et al. (16) showed that CD30 cross-linking in the latently infected CD4+ T-cells induced HIV transcription. Recently, it has been shown that the use of Brentuximab Vedotin leads to the temporary disappearance of detected HIV RNA in CD4+ T-cells and a decrease in the HIV level in blood plasma. Thus, CD30 is a latent but transcriptionally active marker of HIV-infected cells and is proposed as an innovative therapeutic agent for the treatment of HIV (17,18).

Alemtuzumab is a monoclonal antibody aimed at CD52, which is expressed on T-cells as well as HIV-infected T-cells, regardless of CD4+ count in the blood plasma. Unnoticed CD4-infected T-cells were eliminated in vitro with the help of Alemtuzumab (19). According to Caby et al. (20), the effective treatment with Alemtuzumab *in vivo* in patients with HIV and Cesari syndrome reduced the ratio of CD4/CD8 and the risk of Kaposi's sarcoma or non-Hodgkin's lymphoma, but it did not eliminate the frequency of HIV-infected CD4+ T-cells. Alemtuzumab has also been used to treat patients with persistent HIV-negative disease after HSCT.

Severin et al. (21) have conducted a comparative study of the classic Kaposi's sarcoma and HIV viremia in AIDS, which has shown that a number of T-cell growth factors (studied as tumor markers) can influence the HIV pool. Interleukin-7 (IL-7) is a homeostatic cytokine that proliferates the diversity of T-cell lineage by enhancing the division of T-cell predecessors and it is used in various malignant neoplasms. It is also used IL-7, which is associated with a dose-dependent increase in T-cell division with CD4+ and CD8 markers, including CD8 T-cells (an HIV marker), in patients receiving ART. In patients with HIV suppression, the administration of IL-7 temporarily increased the HIV viral load, and there were no clinical consequences. CD8 activity against HIV was increased without clinical consequences. Another T-cell growth factor, IL-15, induced the proliferation of antigen-specific T-cells, mainly in the CD8 compartment; IL-15 is produced during acute HIV infection (22-24).

In vivo, stimulation of IL-15 NK cells from HIV-suppressed participants during ART resulted in a significant increase in infected CD4+ T-cells with cytotoxic CD8 T-cells (25). The cells were eliminated *in vivo* by cytotoxic CD8 T-cells – as

described in the articles by Cesmeci et al. (26) and Poizot-Martin et al. (27) regarding the cases of metastatic Kaposi's sarcoma that have been successfully treated with immunotherapy against PD-1. Preliminary studies of IL-7 and IL-15 in various cancers are ongoing (28-30).

In 2007, a man with HIV and leukemia underwent a hematopoietic stem cell transplantation (HSCT) using cells from a donor with CD4+ cells, homozygous for the CCR5-delta32 mutation, which makes the immune system not susceptible to CCR5-targeted HIV. Even though ART was discontinued after transplantation, HIV was not detected in either blood or biopsy. The second patient has been treated for Hodgkin's lymphoma using cells from a homozygous CCR5-delta32 donor; HIV is still negative in this patient 18 months after stopping ART (31). The allogeneic transplantation of stem cells significantly reduces the HIV reservoir: in European practice, 5 patients out of 6 (who received ART and underwent the hematopoietic stem cell transplantation from the donors of wild-type CCR5) received complete donor transplantation and continued to receive ART. The patients had CD4+ markers in the blood and tissues did not contain HIV DNA, and the tests of virus growth in mice did not show the signs of HIV (32).

However, ART should be stopped to demonstrate functional recovery, and in the case of allogeneic donor transplants with the CCR5 marker, it is impossible to achieve long-term viral suppression without ART in the transplantation of hematopoietic stem cells (33-36). In a study regarding the discontinuation of ART, two patients who received HSCT for treating haemoblastosis from wild-type CCR5 donors and had a null level of HIV RNA during ART for several years after transplantation, they both had a detectable viremia after the discontinuation of ART. In patients, it was detected on day 225 (26), and in some sick people - it was detected on day 24.

After the successful allogeneic transplantation from a homozygous CCR5-delta32 donor, a mutant CCR5 cell product was developed utilizing gene editing, which demonstrated its safety when administered to participants with chronic seropositive diseases (21,37-40). After the discontinuation of ART, the treated CD4+ cells are more resistant. Although these results are more than positive, further research is needed to develop global approaches to combat HIV persistence during ART.

Since PLHIV live longer, cancer becomes the main cause of death, significantly outweighing the risks that threaten the population in general (41-43); the incidence of malignant neoplasms that have been provoked by AIDS is decreasing, but the mortality associated with NADM is increasing (44,45). The immune response does not produce the desired response, despite ART and its impact on the cancer risk; immunotherapy has the unique potential to improve the outcome of HIV-related cancer (46-48). To improve understanding, PLWH should be included in immuno-oncology research. Recent recommendations guide the appropriate inclusion of PLHIV and cancer patients in clinical trials (14,49,50). In addition, the study of cancer immunotherapy provides an opportunity to better understand the impact of HIV on the occurrence of sarcomas. Analysis of immunological and virological response to cancer immunotherapy in PLHIV will provide new insights into the eradication of HIV, and importantly, new insights regarding the development of new strategies for the treatment of HIV and cancer for people with HIV and cancer.

Therefore, by comparing the results of this study with other cases of using immunosuppressive drugs, it is possible to see a successful recovery of people with cancer. However, the correct combination of immunosuppressive drugs and immunomodulating agents is the main criterion for achieving treatment success, which in turn will stimulate an adequate response of the body to changes in the genetic apparatus of cells of the skin and mucous membranes.

CONCLUSIONS

Currently, there is significant progress in medicine in discovering the pathogenesis of the disease, but some research is still needed to understand the biochemical mechanisms necessary for the development of sarcoma. These are the places of damage with Kaposi's sarcoma: skin, mucous membranes, lymph nodes, and internal organs.

The study demonstrated the potential of immunotherapy, specifically Nivolumab, as an effective treatment approach for complex presentations of metastatic cancers when conventional options are unsuitable. Also, the results showed how detailed diagnostics and multidisciplinary care can inform individualized treatment decisions and lead to positive outcomes even in elderly, medically frail patients. The patient's complete response and extended remission highlighted the efficacy of adapted immunotherapy regimens, providing further evidence to support emerging research on immunomodulatory therapies. This research aligned with broader trends indicating the promise of harnessing the immune system in the fight against cancer. It underscored the need for continued development and optimization of immunotherapeutic strategies.

Further investigation is necessary to understand the intricate interplay between immunosuppression, immune response modulation, and susceptibility to cancers like melanoma. Elucidating these dynamics may reveal novel therapeutic avenues. This paper substantiates the merit of immunotherapy along side conventional modalities and personalized diagnostic approaches for managing complex presentations and improving cancer treatment outcomes. Thus, the potential of immunotherapy, the value of personalized care, the need for more research, and the role of immunomodulation in advancing cancer treatment can be emphasized.

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