AIDS

Efficacy of Nivolumab in HIV patient with melanoma brain metastases

--Manuscript Draft--

Manuscript Number:	AIDS-D-20-00223
Full Title:	Efficacy of Nivolumab in HIV patient with melanoma brain metastases
Article Type:	Correspondence
Section/Category:	
Keywords:	melanoma, HIV, nivolumab
Corresponding Author:	Ilaria Proietti Latina, ITALY
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	
Corresponding Author's Secondary Institution:	
First Author:	Ilaria Proietti
First Author Secondary Information:	
Order of Authors:	Ilaria Proietti
	Nevena Skroza
	Simone Michelini
	Alessandra Mambrin
	Ersilia Tolino
	Nicoletta Bernardini
	Veronica Balduzzi
	Anna Marchesiello
	Salvatore Volpe
	Patrizia Maddalena
	Davide Bellini
	Simone Vicini
	Concetta Potenza
Order of Authors Secondary Information:	

Title: Efficacy of Nivolumab in HIV patient with melanoma brain metastases

Proietti Ilaria[1], Skroza Nevena[1], Michelini Simone[1], Mambrin Alessandra[1] , Tolino Ersilia[1], Bernardini Nicoletta[1] , Balduzzi Veronica[1], Marchesiello Anna[1], Volpe Salvatore[1], Maddalena Patrizia[1], Bellini Davide[2], Vicini Simone[2], Potenza Concetta[1].

[1] Department of Medical-Surgical Sciences and Biotechnologies, Dermatology Unit "Daniele Innocenzi", Sapienza University of Rome, Polo Pontino, Italy.

[2] Department of Radiological Sciences, Oncology, and Pathology

"Sapienza" - University of Rome

Diagnostic Imaging Unit - I.C.O.T. Hospital, Latina – ITALY

Key Words: melanoma, HIV, nivolumab,

Words count: 746

Figures: 1

***Corresponding author**

Dr. Ilaria Proietti

Dermatology Unit "Daniele Innocenzi", "A. Fiorini" Hospital,

Via Firenze, 1, 04019, Terracina (LT), Italy

+39 0773 708811

proiettilaria@gmail.com

The authors declare that there is no conflict of interest regarding the publication of this article.

Main text

The interesting article by Spano et al.[1] offers an understanding regarding the efficacy and safety of anti-PD1 in patients living with HIV and cancer in clinical practice. In this case report, we detail a case of a patient with melanoma and chronically infected with HIV who is successfully treated with anti-PD1 after ineffective treatment with BRAF-MEK inhibitors.

In April 2015 a 69-year-old Caucasian patient with HIV is treated with efavirenz 600mg, abacavir 600mg, and lamivudine 300mg. The patient has a baseline CD4 count of 370/mm^3 and an undetectable HIV viral load. An excisional biopsy on the right back region resulted in nodular melanoma, 13mm Breslow, no ulceration, positive for S100, Mart1 and HMB45. Subsequent wide local excision had a negative result however sentinel lymph node biopsy revealed one lymph node involved. No metastases were found in a successive full-body PET.
In May 2017 a brain MRI showed a 3cm parietal lesion and multiple bilateral pulmonary lesions. CT showed a single T9 vertebral lesion. Due to the presence of BRAF V600E mutation, Dabrafenib-Trametinib therapy was initiated.

Between 2017 and 2018 routine brain MRI documented the progressive development of small encephalic lesions which were treated successfully with Gamma Knife radiosurgery. The pulmonary and vertebral secondary lesions remained stable. Unfortunately, in January 2019, the patient developed a new unresectable cerebellar lesion. Due to the documented disease progression, Dabrafenib-Trametinib therapy was discontinued and Nivolumab (240mg/2w) was instituted.

The subsequent brain MRI in July 2019, demonstrated a reduction in dimension and contrast-enhancement of all the lesions, especially those in the para-hippocampal and anterior horn of the left lateral ventricle regions (Fig.1). The HIV viral load remained undetectable and the CD4 count was 420/mm^3.

Treatment of cancer has been revolutionized by Immune Checkpoint Inhibitors (ICI). This kind of therapy is particularly effective in melanoma, because of its high immunogenicity. Antagonizing PD-1 or CTLA-4 proteins on the surface of T-cells, tumor-induced T-cell anergy is prevented, leading to a greater antitumor response by the host immune system.

However patients with HIV infection have been excluded from clinical studies of immunotherapy, so there is a lack of clinical data on the efficacy and safety of ICI therapy in these patients.

Cancer is the leading cause of death among non-AIDS-defining illnesses in patients with chronic HIV infection, particularly the most immunogenic ones such as melanoma[2]. Furthermore, HIV patients experience shorter disease-free and overall survival than the immunocompetent ones[3]. Immunodeficiency associated with chronic HIV infection increases the risk of developing cancer and causes the worst prognosis by disabling patients from mounting an effective immune response against tumor cells. HIV infection leads to CD4-T cells anergy, amplifying the expression of different immune checkpoint molecules on their surface.[4]

Our patient was treated with: Efavirenz 600mg, Abacavir 600mg, and Lamivudine 300mg. In particular, Efavirenz is known to induce CYP3A4 while Dabrafenib is metabolized by the same enzyme. Efavirenz may lower the levels of Dabrafenib reducing its antitumor activity. This may explain the disease progression during Dabrafenib-Trametinib treatment in our case. The strict correlation between HIV and melanoma therapy is underlined by the efficacy of Nelfinavir, a protease inhibitor, in the prevention of BRAF melanomas growth, in combination with either MEKi or BRAFi, and of NRAS mutant melanomas in combination with MEK5. Further studies are needed to assess the mechanisms, the efficacy and safety of targeted therapy in HIV patients. Instead, there is no evidence immune checkpoint inhibitors interact with HAART supporting the good response in our patient. A point of interest is the improvement of our patient's CD4 cell count. The protracted antigen exposures during HIV chronic infection leads to an overexpression of PD-1 in HIV-specific T-cells with consequent cells functional exhaustion, lower proliferation, cytokine production, and cytotoxic

abilities. In addition, HIV-specific CD8+ T-cells express multiple inhibitory receptors like CD160, 2B4, TIM-3, and LAG-3. Furthermore, viral load is related to PD-1 expression that is reduced in patients undergoing effective HAART. PD-1 pathway inhibition seems to restore exhausted CD8+ T-cells activate B-cell producing virus-specific antibody, enhancing antiviral immune response and viral control[6].

According to some authors, the activation of the T-cell reservoir could increase the autoimmune phenomena in HIV population [7] but recent reviews of the literature indicate there are no differences compared with HIV-uninfected population[2-8.] Further studies are needed to clarify this aspect.

In conclusion, ICI therapy may be considered as a beneficial option for HIV-infected patients with advanced melanoma leading to an important antitumor response and preventing HIV induced T-cell anergy.

Prospective studies are needed to validate this evidence.

REFERENCES

1. Spano et al. Immunotherapy for cancer in people living with HIV: safety with an efficacy signal from the series in real life experience, AIDS, 2019, 33:F13–F19
2. Safety and Efficacy of Immune Checkpoint Inhibitor Therapy in PatientsWith HIV Infection and Advanced-Stage Cancer A Systematic Review Michael R. Cook, MD; Chul Kim, MD, MPHL. JAMA oncology, 2019, doi:10.1001/jamaoncol.2018.6737
3. K. Rodrigues, B. J. Klencke, K. Vin-Christian et al., "Altered clinical course of malignant melanoma in HIV-positive patients," Archives of Dermatology, vol. 138, no. 6, pp. 765–770, 2002.
4. Q. Leng, Z. Bentwich, E. Magen, A. Kalinkovich, and G. Borkow, "CTLA-4 upregulation during HIV infection: association with anergy and possible target for therapeutic intervention," AIDS, vol. 16, no. 4, pp. 519–529, 2002.
5. Hyungsoo Kim et al. HIV Drug to Aid Melanoma Therapies, Cancer cell, 2016, Vol 29, ISSUE 3, 245-246
6. Vijayakumar Velu et al. Role of PD-1 co-inhibitory pathway in HIV infection and potential therapeutic options Retrovirology (2015) 12:14
7. Chang et al. Nivolumab Treatment for Cancers in the HIV-infected Population J Immunother 2018;41:379–383

8. ABBAR et al. Immune checkpoint inhibitors in people living with HIV: What about anti-HIV effects? AIDS. 2020 Feb 1;34(2):167-175. doi: 10.1097/QAD.0000000000002397.

Fig. 1. (A, B) Post-contrast T1-weighted axial and coronal brain MR images performed in April 2019 at the start of the treatment with Nivolumab showing multiple enhancing brain and cerebellar lesions with leptomeningeal involvement in the right fronto-parietal and para-hippocampal regions (arrow), associated with involvement of the anterior horn of the left lateral ventricle. (C, D) Follow-up MRI of the same patient reveals marked decrease in size and contrast-enhancement of the metastatic lesions seen in the right para-hippocampal region and in the anterior horn of the left lateral ventricle 3 months after Nivolumab treatment (arrows).

Figure 1

Click here to download Figure Immagine1.jpg