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Received: 28 December 2016; accepted: 12 January 2017.

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DOI:10.1097/QAD.0000000000001413

Transient HIV-specific T cells increase and inflammation in an HIV-infected patient treated with nivolumab

Immune checkpoint inhibitors (ICIs) can reverse T-cell anergy and boost immune responses against tumours. Nivolumab, an ICI directed against programmed death-1 (PD-1), has become the new standard of care for second-line treatment of advanced nonsmall cell lung cancer (NSCLC) [1–3]. It is thought to be an even clever therapeutic option in HIV-infected patients [4], as the overexpression of PD-1 on exhausted HIV-specific T cells allows ICIs to reactivate PD-1\textsuperscript{+} T cells and to improve HIV-specific immune responses [5–7].

So far, two case reports involving HIV-infected patients with melanoma treated with ICIs have shown encouraging safety results but distinct viral effects [8,9]. Upon ipilimumab treatment, CD4\textsuperscript{+} and CD8\textsuperscript{+} cell counts, as well as the cell-associated HIV-RNA transiently increased [9]. Upon pembrolizumab, no rebound of HIV viral load was observed [8]. The question of whether anti-PD-1 could be a tool for HIV cure is still pending. Here, we report for the first time the detailed immunovirological evolution upon nivolumab in an HIV-infected patient with lung cancer.

The CD4\textsuperscript{+} and CD8\textsuperscript{+} cell counts were analysed on an FC500 flow-cytometer. Phenotypic and functional analysis used a 5-laser-beam LSR-Fortessa cytometer on the CyPS platform. Intracellular-cytokine-staining assay used 15-mer peptides targeting HIV-Gag, reverse transcriptase and Nef and 9-mer Epstein–Barr virus (EBV) peptides [10,11]. The plasma IL-6 levels were quantified using the Simoa-Quanterix SIMOA HD-1 analyzer (Quanterix Corporation, Lexington, Massachusetts, USA). Plasma viral load was quantified using the Amplicor monitors assay [12]. HIV-1 DNA was amplified in LTR gene by real-time PCR [13].

A 53-year-old man, smoker, HIV-infected since 1993, was diagnosed with advanced NSCLC in May 2014. After a decompressive radiotherapy, six cisplatin/gemcitabine and four taxotere chemotherapy cures, nivolumab was started in September 2015. The patient was virally suppressed with CD4\textsuperscript{+} and CD8\textsuperscript{+} T-cell counts of 204 and 1142 cells/\mu l, respectively, upon abacavir, lamivudine and dolutegravir. Seven nivolumab injections were administered, causing Grade 1 hepatic toxicity. Tumoral stability was reported after six injections. Nivolumab was discontinued after the seventh injection due to disease progression and the patient finally passed away in June 2016.

During follow-up, no significant changes of ultrasensitive HIV viral load were observed, but a slight two-fold increase in HIV-cell–associated DNA levels (116 at D0, 213 copies/10\textsuperscript{8} peripheral blood mononuclear cells at D30, Fig. 1a). The immunological follow-up showed a marked increase of IL-6 plasma levels peaking at D14.
and returning to normal beyond D60. The CD4\(^+\) and CD8\(^+\) cell counts peaked at D60 to 413 and 1380 cells/\(\mu\)l, respectively, returning to baseline values at D120, together with a slight CD4\(^+\)/CD8\(^+\) ratio increase (0.18–0.30 from D0 to D60). The CD4\(^+\) and CD8\(^+\) cell activation status showed discordant changes with a modest CD38 increase on CD8\(^+\) T cells, whereas human leukocyte antigen – antigen D related on CD4\(^+\) and CD8\(^+\) T cells remained within normal values (Fig. 1b). The immune check point expression on total
CD4⁺ and CD8⁺ T cells displayed a marked decrease of both PD-1 and LAG3 at D30 (Fig. 1c, d). In contrast, Tim-3 expression increased on CD4⁺ and CD8⁺ T cells during follow-up and returned to baseline values at D120 (Fig. 1c, d). The almost undetectable IFNγ⁺ Gag-specific CD8⁺ T cells at baseline (below 0.1%) increased at D30 (0.4%) then returned to baseline values, whereas reverse transcriptase-, Nef-specific CD8⁺ T cells remained very low (Fig. 1e). Furthermore, PD-1 expression was down-modulated on IFN-γ⁺ Gag-specific CD8⁺ T cells at D30 (Fig. 1c). Frequencies of IL-2⁺ and TNF-α⁺ HIV and EBV-specific T cells showed no significant modification (data not shown). Finally, the CD4⁺ T cell differentiation status remained stable (Fig. 1f), whereas transitional-memory CD8⁺ population increased (+64%) and RA-re-expressing effector-memory decreased (~41%) 4 months after treatment initiation (Fig. 1g).

We describe here the immunovirological effects of nivolumab in an HIV-infected patient. A slight increase in HIV-specific IFNγ⁺ CD8⁺ cells occurred together with an increase in CD4⁺ and CD8⁺ cell counts, in the CD8⁺ transitional-memory population and in IL-6 plasma levels, contrasting with a decrease of PD-1 expression on T cells. Taken together, these data suggest that nivolumab is successful at enhancing the capacities of HIV-specific CD8⁺ transitional-memory cells to proliferate and to secrete cytokines [5,6,14], expanding the PD-1 low T-cell subset [15]. Those changes had no or little impact on HIV replication or reservoirs. The transient increase in inflammation has not been reported before and might result either from the PD-1/programmed death-ligand 1 (PD-L1) pathway disruption in immune cells or from a rapid HIV replication in tissues that would have immediately been controlled by the stimulated HIV-specific CD8⁺ T cells. These first results are encouraging and remain to be confirmed in other HIV-patients treated with anti-PD-1/PD-L1-blocking antibodies.

Acknowledgements

The authors want to thank the members of the CANCERVH national coordinator. A.G., A.S. and B.A. wrote the article. J.-P.S. is the CANCERVH national coordinator.

Conflicts of interest

There are no conflicts of interest.

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Received: 5 January 2017; revised: 17 January 2017; accepted: 30 January 2017.

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HIV cure strategies: response to ignore the central nervous system at your patients’ peril

We read with interest the recent article published in AIDS by Gama et al. [1], highlighting evidence for a significant central nervous system (CNS) reservoir in simian immunodeficiency virus macaque models despite effective long-term peripheral viral suppression by antiretroviral therapy. This was followed by an informative editorial by Spector and Rappaport [2], cautioning those involved in HIV cure research not to overlook this important viral reservoir. Future cure strategies, which test the impact of interventions on measures of viral reservoir in peripheral body compartments, may not assume that they have the same efficacy in the CNS and thereby mitigate the effectiveness of HIV cure interventions.

Although we acknowledge and fully agree with this potential lack of efficacy for HIV cure strategies if sanctuary sites are overlooked, we would like to highlight additional potential perils facing HIV cure strategists with respect to the CNS; namely adverse CNS outcomes that may include toxicities of HIV cure therapies, direct immune-mediated CNS pathogenesis or the impact of viral reactivation on the brain [3].

Mechanisms of negative outcomes on the CNS and neuronal tissue due to cure strategies could include, first, adverse effects on brain function secondary to the removal or elimination of latently infected neuronal cells with crucial function for brain health, such as microglial cells and astrocytes [4]. Second, neuronal damage from either drug utilized during cure research strategies or neuronal damage from viral proteins, the expression of which may be upregulated during cure treatments. An example being the gene upregulation of the light protein [9], and noninvasive neuroimaging could be practical approaches to consider.

For HIV cure strategists and researchers, consideration of monitoring for CNS adverse events within HIV cure studies will be crucial. Monitoring for CNS adverse events is challenging given the closed anatomical sanctuary site of the brain and the complexity of monitoring nervous system function. Brain biopsies are clearly not possible, and repeated cerebrospinal fluid examinations are costly and not practical for every study. However, monitoring clinical parameters such as cognitive function and patient-related outcome measures of cognitive health, coupled with the monitoring of sensitive peripheral markers of neuronal integrity, such as highly sensitive plasma neurofilament light protein [9], and noninvasive neuroimaging could be practical approaches to consider.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.