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EDITORIAL

HIV+ patients and HIV eradication – allogeneic transplantation

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Antiretroviral therapy (ART) was the major breakthrough in the management of infection with human immunodeficiency virus (HIV), leading to a significant benefit in the survival of the patients. Nevertheless, this treatment is not sufficient to remove the virus from the body, and viral rebound is commonly observed after discontinuation of antiretroviral medication. Since the discovery of the HIV as causative for the acquired immune deficiency syndrome (AIDS) in the 1980s, allogeneic cell therapy, which has shown efficiency in patients with hematological malignancies, has been considered as a potential treatment option for infected individuals [1]. Patients in the stage of AIDS show a profound lack in peripheral lymphocytes and, especially, in T-helper lymphocytes. In this situation, the life-limiting factors for these patients in the state of AIDS are complications from opportunistic infections due to the deep immune deficiency. From a hematological point of view, it would make sense to substitute immune cells like lymphocyte or granulocyte concentrates from healthy donors. This technique of cell transfer is established and effective in patients with temporary cytopenia together with life-threatening infection, e.g. during cancer chemotherapy treatment. Adoptive T-cell transfer in patients with HIV infection was also sufficient to increase the amount of circulating lymphocytes for a limited period of time but did not last for a longer period and was without remarkable impact on the course of infection [2].

HIV invades predominately bone marrow-derived cells carrying both the CD4 receptor and a suitable chemokine receptor (commonly CCR5). Taking into account that the HIV infection is primary limited to bone marrow-derived target cells, it is not completely fallacious to call HIV a hematological infection. In consequence, effects from stem cell transplantation (SCT) in hematological malignancies could also improve the course of HIV infection. However, this approach is still limited to HIV+ patients with concomitant malignancies. There is some evidence that the maintenance of the infection is mostly limited to T-lymphocytes, and the eligible question in terms of eradication is: does the eradication potency of SCT differ between HIV-infected T-cells and transformed cells in patients with, e.g. T-cell lymphoma? The latter can effectively be cured by elimination of the malignant cell clone after allogeneic SCT which is a very powerful tool to remove patient's immune system. After

engraftment, these newly arising cells effectively eliminate and replace the recipient's hematopoietic system and all stem cell-derived cell sources like T-cells, macrophages, dendritic cells, and microglia cells. Similar to the well-described donor versus cancer effect, a donor versus HIV effect was proposed [3]. However, in practice, previous attempts to eradicate HIV by allogeneic SCT were not successful. In the first period until the ART was established, donor-derived cells were re-infected from HIV rapidly after transplantation. But even after the introduction of ART as a standard procedure to suppress the viral burden, SCT failed to show a significant impact on the control of the viral replication as well as on the elimination of the viral reservoir. Today, we can look back on experiences of more than 60 reported case reports of patients with HIV infection after allogeneic transplantation. In those cases where ART was discontinued, the virus rebounded within a few days or weeks even in patients with completely undetectable viremia [4].

This phenomenon was most distinctly emphasized in the report of the 'Boston patients' [5]. Both patients with HIV were cured from their hematological disease by allogeneic SCT. Both received ART over a period of years after transplantation. Even after operating the most sensitive techniques of analysis, there were no traces of virus detectable in any compartment tested. However, despite the fact that the patients seem to be virus-free, both rebounded from HIV after the antiretroviral medication was discontinued. Interestingly, in these patients, the rebound appeared after several months (instead of days), indicating that the allogeneic SCT and concomitant immunosuppression may have reduced the size of the reservoir but in the end was not powerful enough to eliminate the virus completely. It may also be assumed that HIV may hide in places outside the immune system unaffected by the transplantation procedure and also unaffected by circulating T-cells in terms of the postulated graft versus HIV effect, but as far as we know, these tissues do not harbor replication-competent virus [6].

Taken together, the idea of an immunological treatment of HIV infection by transfer or transplantation of alloreactive, cytotoxic T-cells to eliminate the reservoir of latent infected cells has failed to show sustained efficiency. In contrast, the case of the transplantation in an HIV patient with a donor who was

homozygous for the CCR5-d32 deletion (and therefore unsusceptible for HIV) guides us to another concept of eradication. In this so-called 'Berlin patient', the transfer of CCR5-deficient stem cells during the treatment of leukemia led to a stable engraftment of an HIV-resistant immune system. Over a period of 9 years up to date, during ART was discontinued, all attempts to detect the traces of residual replication-competent HIV in this patient were unsuccessful [7]. The 'Berlin patient' is commonly be assigned as the first iatrogenic HIV cure, and the lesson we have learned could be that withdrawal of the HIV target over a longer period may lead to a spontaneous elimination of the HIV reservoir, for example, by natural cell turnover. This 'stoichiometric treatment' was probably the predominant mechanism of eradication in the 'Berlin patient' more over any immunological effect. However, to verify this theory, more experiences from other patients receiving similar treatments with CCR5-deficient allogeneic cell sources are mandatory. Although several attempts have been undertaken to repeat this approach, most published cases were not evaluable because patients receiving the CCR5-deficient stem cells died from procedure side effects or cancer relapse soon after transplantation [8]. One patient who received CCR5-deficient stem cell but harbored a non-CCR5 using HIV strain before transplantation rebounded after SCT with this mutant variant, indicating the natural limitation of this CCR5-based approach [9]. To investigate and to prove the immunological versus the stoichiometric treatment potency of allogeneic SCT, the European consortium EpiStem was founded in 2015 to offer participating transplant centers to submit patient's data and samples to evaluate the effects of transplantation in HIV patients with and without CCR5-deficient stem sources (www.epistem-project.org/). Allogeneic SCT in HIV patients has been performed from various stem cell sources including related and unrelated adult donors, cord blood, haploidentical donors, and combination treatment with cord blood and haploidentical donors, but it is still open whether this or the choice of the conditioning regimen has an effect on HIV latency [10,11]. A further point in discussion is the impact of different regimen of ART during transplantation and engraftment, whereas the addition of CCR5 inhibitors (like maraviroc) during the transplantation and engraftment period was without beneficial effect [12,13].

The most promising approach in mimicking the CCR5-d32 transplantation in the 'Berlin patient' is the gene editing of autologous peripheral T-cells or stem cells. A spoil of choice in different techniques of CCR5 knock-down like sh-RNA, zinc-finger nucleases, or clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 are available and already clinically tested [14,15]. Even there are some preliminary reports on the safety and efficiency of these approaches, and it is far too early to make final conclusion whether the proposed aim, the eradication, can be achieved with these new developments. It is also not devious that a combination of allogeneic SCT and gene therapy might be superior to autologous approaches.

Current improvements in the development of antiviral medication as well as the finding of an HIV vaccine in the

future will not cure the millions of people living already with HIV. Based on our present knowledge, the cell-derived HIV therapy has a great potency to gather a deeper insight into HIV pathogenesis and thereby may be valuable to develop new strategies to cure this disease.

Declaration of interests

G Hütter is employed at Cellex, a company which provides allogeneic cell collections. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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