counts would need to be established through clinical event end point trials. The IL-2 experience chastened us in this regard.\(^1\)

The infused cells in the Tebas study persisted in patients for up to 5 years, but the half-life in blood was only 5 weeks.\(^1\) The durability of the modified T cells seemed to plateau after 3 infusions. Importantly, engraftment of cells in the gut lymphoid tissue was comparable with that in blood. The basis for the limited half-life of the modified cells compared with other gene therapy approaches is unclear, as humoral or cellular immune responses against the product were not induced. Prolonging the persistence of these gene-modified blood cells and other gene therapy products may require cytoreductive “conditioning” to reduce competition from unmodified cells for trophic factors.\(^1\) Unfortunately, this would increase the risk of toxicity for patients who otherwise have access to extremely effective suppressive chemotherapy.

As with antitumor chemotherapy, gene therapy approaches to inhibiting HIV infection are directed at different steps in the life cycle of the virus (see figure).\(^4\) Transgenes code for either an RNA-based agent, as in this trial, or a protein-based agent. The agent may target the virus or a host cell element needed in the life cycle of the virus. For the latter, the candidate treatment should avoid disruption of essential cell function, and clinical trials need to monitor for this accordingly.

Hematopoietic stem cells (HSCs) have advantages over CD4\(^+\) T lymphocytes as cell targets for HIV gene therapy.\(^4\) They account for all the lineages of cells subject to infection by HIV. Transduced HSCs persist longer than transduced CD4\(^+\) T cells. On the other hand, HSCs do not expand readily ex vivo, thus having a greater need for cytoreductive conditioning in patients for better engraftment. They take longer to proliferate in vivo after infusion, but proliferate widely once they start. The latter property results in a greater risk of insertional oncogenesis.

To enhance cytotoxic T-lymphocyte activity of CD8 T cells, genes can be inserted into CD8 T lymphocytes to create a CD4 extracellular domain, or other HIV envelope–binding molecule or antibody, coupled to the \(\gamma\) signaling chain of the CD3 T-cell receptor (TCR).\(^5\) Another strategy is to redirect the TCRs of the CD8 T cells to target specific HIV antigens. The latter approach has been successful in the treatment of chronic lymphoid leukemia.\(^6\) A risk is potential off-target immunogenicity when modified TCR chains pair with the native chains.

The antitumor effects of the VRX496-modified CD4\(^+\) T cells were modest. Other gene therapy approaches have demonstrated modest antitumor activity.\(^5,7,8\) It is to be expected that, as with antitumor chemotherapy, each treatment approach individually will be incomplete in its ability to fully contain viral replication and that the development of viral resistance will become an important limitation when used alone. Thus, combinations of gene therapy agents may be needed to obtain optimal control of the infection.

Current antitumor therapy is merely suppressive, as HIV establishes latency in the genome of resting memory CD4\(^+\) T lymphocytes.\(^9\) The development of gene therapy for HIV infection holds the promise of creating a body of cells that can resist HIV and permit a longer lasting control of the infection perhaps without the need for antitumor drugs.

Conflict-of-interest disclosure: The author served on a data and safety monitoring board for an HIV gene therapy study sponsored by Sangamo Biosciences.\(\blacksquare\)

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*Comment on Mahlaoui et al, page 1510*

**In Wiskott-Aldrich syndrome, platelet count matters**

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In a retrospective analysis of the French Registry of patients with Wiskott-Aldrich Syndrome (WAS), Mahlaoui et al have identified severe refractory thrombocytopenia (SRT) early in life as a major risk factor for poor outcome.\(^1\)

In an attempt to use phenotypic criteria to define WAS disease severity, Zhu and colleagues proposed a scoring system according to which a score of 5, corresponding to the most severe phenotype, was reserved for subjects developing autoimmunity or malignancies.\(^2\) Initially, the degree and persistence of thrombocytopenia were not used to grade severity of the disease, and were subsequently introduced only to mark the mildest form of the disease, intermittent X-linked thrombocytopenia (score < 1).\(^3\) However, persistent and severe thrombocytopenia is associated with a significant risk of hemorrhage. In particular, in a large, multi-institutional retrospective study of patients with WAS, life-threatening bleeding had been recorded in 30% of the patients.\(^4\) Therefore, Mahlaoui et al have decided to modify Zhu et al’s scoring system by attributing a score of 5 also to patients with SRT, defined as platelet count persistently \(\leq 10^{10}\) /L. In a series of 160 patients with WAS enrolled in the French nationwide registry, they noticed that the risk of developing a score of 5 was significantly higher during the first 2 years of life. Among 26 patients who were attributed a score of 5 during the first 2 years of life, 13 had SRT; for 12 of them...
SRT represented the inaugural manifestation leading to a score of 5. Autoimmune hemolytic anemia and vasculitis were also common, being present in 15 and 6 patients, and marking the onset of severe disease in 9 and 5 patients, respectively. Only 1 of the 26 patients developed malignancies, and major infections, while observed in 12 patients, were not an augural manifestation. By contrast, malignancies were observed in 7 of 21 patients who were attributed a score of 5 beyond 2 years of age; in this group of patients, autoimmune hemolytic anemia and SRT were recorded in only 4 and 3 patients, respectively. These data are novel and important because they indicate that phenotypic features consistent with severe WAS may have a different distribution in infants versus older patients.

In the study by Mahlaoui et al, occurrence of severe disease early in life was associated with high mortality and morbidity risk. Among the 26 patients who reached a score of 5 in the first 2 years of life, hemorrhages involving the brain, gut, and lungs were observed in 9 patients, and all 4 patients who were not treated by hematopoietic cell transplantation (HCT) died of severe hemorrhage. This observation reinforces the notion that profound and persistent thrombocytopenia in WAS represents a major risk factor. Accordingly, the proposal to include SRT among the criteria to score WAS disease severity should be welcomed as a useful and appropriate addition.

The study by Mahlaoui et al confirms that HCT is an effective form of treatment for WAS, and suggests that it should be performed as soon as possible especially in patients who manifest severe disease early in life. A recent multicenter analysis of 194 patients with WAS treated by HCT has confirmed significant improvement of outcome, with a 5-year survival approaching 90% for transplants performed since the year 2000. In particular, excellent results were demonstrated after unrelated donor (URD) HCT. In the study by Mahlaoui et al, all 7 patients with severe early-onset disease who received URD-HCT were reported to be alive and well. In the past decade, improved outcome has also been reported after haploidentical transplantation for WAS. However, this remains a risky procedure. This is also confirmed in the study by Mahlaoui et al; among 12 patients with severe early-onset disease who received haploidentical HCT, 4 died and 1 required a second transplant from a matched sibling donor. Recently, gene therapy has become available for patients with WAS. The first clinical trial with use of a gammaretroviral vector offered proof of principle that gene therapy may cure the disease, but also illustrated the risks of leukemia due to insertional mutagenesis. By then, novel vectors with improved safety profile have been developed for the treatment of WAS, and one such self-inactivated lentiviral vector is currently in use in clinical trials in Milan, Paris, London, and Boston. Gene therapy may be especially attractive for patients with severe disease who lack matched related and unrelated donors.

Development of strategies that may facilitate identification of patients with WAS who would most benefit from HCT or gene therapy and who should be promptly referred to treatment remains an important goal in the clinical management of this disease. In this sense, revision of Zhu et al’s scoring system, as proposed by Mahlaoui et al, may help, because it broadens the spectrum of severe phenotypic features that are associated with poor outcome. However, this approach may not allow identification of patients at higher risk of poor outcome before severe manifestations of the disease have occurred. In addition, in the study by Mahlaoui et al only 4 of the 9 patients with severe early-onset disease who developed severe organ hemorrhages had been diagnosed with SRT, indicating that even inclusion of SRT in the WAS scoring system may not correctly predict the risk of potentially fatal hemorrhagic events. Mahlaoui et al have also reported that analysis of immunologic parameters did not distinguish patients with a score of 5 from those with a lower score, thus demonstrating that assessment of the status and function of the immune system is not sufficient to describe severity of the disease. By contrast, some studies have suggested that presence of null mutations and lack of WAS protein (WASp) expression correlate—albeit not perfectly—with development of a severe clinical phenotype. Unfortunately, incomplete information on genotype and WASp expression was available in the manuscript by Mahlaoui et al, reflecting the retrospective nature of the study, based on registry data. Large prospective studies, with nationwide or even international registries, are needed to validate the possible predictive value of these and other biomarkers.

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REFERENCES

Comment on Riches et al, page 1612

Exhausting T cells in CLL

Thorsten Zenz

In this issue of Blood, Riches and colleagues provide an in-depth characterization of T cells and particularly CD8+ T cells from patients with chronic lymphocytic leukemia (CLL). They demonstrate that CD8+ T cells exhibit defects in proliferation, cytotoxicity, and increased expression of inhibitory receptors and thus exhibit features of ‘T-cell exhaustion.’
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