T-Cell Prolymphocytic Leukemia: Long-Term Remissions Challenging!

Leopold Sellner^{a, b}

^aDepartment of Internal Medicine V, Heidelberg University Hospital, Heidelberg, Germany;

^bOncology Business Unit – Medical Affairs, Takeda Pharma Vertrieb GmbH & Co. KG, Berlin, Germany

In their article, Shumilov et al. [1] report late-relapse patterns after allogeneic hematopoietic stem cell transplantation (alloHSCT) in T-cell prolymphocytic leukemia (T-PLL) patients. T-PLL is a rare hematological malignancy with a very aggressive clinical course. There is evidence for graft-versus-leukemia effects [2], and long-term remission can be achieved with alloHSCT [3]. However, the curative potential of alloHSCT is still a matter of debate for T-PLL. Indeed, none of the patients reported on by Shumilov et al. [1] was alive at the time of the final analysis. Infections and disease progression were among the most common causes of death. The high non-relapse mortality (NRM) of 50% is in line with previous reports on T-PLL but higher than with other hematological malignancies [3]. The heavily impaired immune system of T-PLL patients may, at least in part, account for these high NRM rates. Furthermore, depletion of healthy T cells with alemtuzumab before alloHSCT is an additional factor promoting infectious complications. Indeed, cytomegalovirus (CMV) viral loads in patients who later had CMV reactivations after transplantation had already been detected during alemtuzumab-based induction. Careful CMV monitoring, as well as the consideration of letermovir-

based prophylaxis in CMV-positive recipients, may further reduce infectious complications in T-PLL patients after alloHSCT.

Considering the high NRM rate, careful evaluation of the alloHSCT-directed curative potential is important. In the study by Shumilov et al. [1], relapse occurred even 7 years after alloHSCT, and not a single patient was “cured.” Late relapses, even after 5 years in complete remission, are not uncommon in T-PLL. Unfortunately, data on long-term follow-up after alloHSCT with careful minimal residual disease (MRD) monitoring are limited to small case series [2]. Larger studies with long-term follow-up, preferably including MRD monitoring, would be desirable and could help us to further improve post-alloHSCT patient care. Nevertheless, currently available data for alloHSCT are still supporting transplantation, which has the potential to achieve longer disease control than alemtuzumab alone, where basically all patients relapse within 2 years [4].

However, 4-year overall survival and progression-free survival rates of 42 and 30%, respectively, with alloHSCT consolidation remain unsatisfactory [3]. In addition, the observation by Shumilov et al. [1] that no durable disease control could be achieved in T-PLL after relapse is in line

with previous findings [4]. Furthermore, fewer than 50% of the T-PLL patients are eligible for alloHSCT, due to advanced age and comorbidities. Therefore, there is an urgent medical need for novel treatment approaches to T-PLL. Possible targets for T-PLL include BCL-2, cyclin-dependent kinases, epigenetic modulation, the JAK/STAT pathway, and reactivation of p53 [4]. However, none of these approaches alone are expected to provide long-term disease control. Drug combination approaches may overcome these limitations. Unfortunately, the conduction of clinical trials is very difficult with an extremely rare disease such as T-PLL. Ex vivo drug screening may be a valuable option for initial hypothesis generation, but it cannot reflect the complex tumor microenvironment in vivo [4, 5]. Nevertheless, important pathway dependencies can be identified and correlated with biomarkers for response [4].

Chimeric antigen receptor T (CAR-T) cells are an emerging treatment modality in the field of cancer immunotherapy. The presence of graft-versus-leukemia effects is highlighting the importance of T-cell-mediated tumor control in T-PLL. However, unique targets for T-cell malignancies are exceptions. The use of pan-T-cell targets will lead to fratricide and prohibit successful CAR-T-cell generation as well as in vivo expansion. Furthermore, in contrast to B-cell eradication in B-cell malignancies, long-term depletion of T cells will be accompanied by severe immunosuppression. Another issue using

CAR-T cells in T-PLL is the impaired generation of healthy T cells and the presence of many malignant T cells in peripheral blood. The use of autologous T cells may not be possible, and, therefore, allogeneic T cells with genetically prohibited T-cell receptor expression or the use of allogeneic CAR-NK cells without the risk of graft-versus-host disease induction may be an alternative for this disease.

In conclusion, current treatment options for T-PLL are extremely unsatisfactory. Novel efficient treatment combinations achieving deep remission together with a favorable safety profile are mandatory. In addition, optimized alloHSCT and other drug- or cell-based consolidation approaches with reduced NRM rates, as well as potent maintenance strategies including MRD-adapted treatment decisions, are key research topics to provide long-term remission to a larger proportion of T-PLL patients.

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