What to Look Out for when Transplanting T-Cell Prolymphocytic Leukemia

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T-cell prolymphocytic leukemia (T-PLL) constitutes a rare and aggressive mature T-cell leukemia, often associated with rapid progression and a poor prognosis (median overall survival [OS] <2 years). At diagnosis about 2/3 of patients already present with exponentially rising lymphocytosis, clinically relevant bone marrow infiltration, splenomegaly, and lymphadenopathy. Most treatments containing chemotherapeutics such as alkylating agents or purine analogs are of limited efficacy. The best results are currently achieved with the monoclonal anti-CD52 antibody alemtuzumab. As a single agent or in more toxic combinations with chemotherapy, it induces overall response rates of 75–92% with 48–81% complete remissions (CRs) [1]. However, these responses are short-lived (median ≈12 months) and available second-line options are mostly inefficient. Recent advances in the molecular concept of T-PLL helped to identify new vulnerabilities (i.e., p53 reactivation by nutlin derivatives and inhibitors of protein deacetylation or BCL2 antagonization by BH3 mimetics); however, their clinical implementation still needs to be seen [2, 3].

Long-term disease control has been observed so far only in a minor subset of patients. The most promising

results were achieved in those who underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT), preferably as a consolidation in first CR (with a 6-week wash-out period after alemtuzumab). Several retrospective studies indicated that allo-HSCT can improve progression-free survival (PFS) and OS in T-PLL patients, e.g., 21–40% OS at 3 years [4–7]. However, with a median age at diagnosis of 66 years, only 40–60% of T-PLL patients are eligible for an allo-HSCT procedure. Furthermore, the prolonged survival, confined to a 10–20% subset of allo-grafted patients, is obtained at the cost of a high transplantation-related mortality of 31–41% within the first 3 years [4–7]. The main causes of this considerable nonrelapse mortality (NRM) are graft-versus-host disease and infections, which seem to be independent of the intensity of the applied conditioning regimens. Acute and chronic graft-versus-host disease is seen in about 50% of allo-transplanted T-PLL patients [4, 7].

There is still a disappointing relapse incidence of 41–70% at 3 years after allo-HSCT in T-PLL, although these numbers also include cases transplanted in the salvage setting [4–6]. Several studies indicated that a total body irradiation (TBI) as part of the conditioning might positively affect the relapse-free survival [4, 5, 8]. Most of the relapses in these few retrospective series occurred shortly after transplantation (median time from transplantation to relapse 10–16.5 months) [4, 5, 9, 10]. A long period

from diagnosis to transplantation had a negative impact on event-free survival (time to progression or death from any cause) [4].

Importantly, there are recent data from an EBMT prospective observational study that evaluated allo-HSCT (predominantly as a primary consolidation after an alemtuzumab-containing induction) in a cohort of 37 T-PLL patients [8]. Here the 4-year PFS was 30% with a 4-year OS of 42%. In their better predefined cohort (age 18–65 years, HLA matched, etc.) than the retrospective series, the endpoints of median PFS (19.2 months) and median OS (27.8 months) appeared only slightly improved, while NRM seemed lower (32% at 4 years). The 4-year relapse incidence was 38% with 11/13 (85%) of the recurrences occurring within 24 months after transplantation. A TBI with >6 Gy was shown to reduce relapse incidence and an interval between diagnosis and transplantation of >12 months was associated with lower NRM [8].

Given these data, is there something new to learn from retrospective data on allo-HSCT in T-PLL? In this issue of *Acta Haematologica*, Shumilov et al. [11] report a retrospective single-center analysis of 10 T-PLL patients who received an allo-HSCT between 2004 and 2019 after a median time from diagnosis to transplantation of 6 months. All 10 patients had an alemtuzumab-containing induction or re-induction regimen. Seven of them received alemtuzumab exclusively, while 1 CHOEP failure was salvaged by alemtuzumab and 2 alemtuzumab failures were brought to transplantation by polychemotherapy. Conditioning was fludarabine/cyclophosphamide based (notably no TBI). Seven patients entered the HSCT in CR. The 3 relapsed/refractory patients died within the first month after transplantation (2 in progressive disease (PD), 1 from infection).

The authors observed PD (5/10) or NRM (5/10) in all 10 patients and the 2-year OS of 30% and the 4-year OS of 20% was below the OS in the prospective EBMT series [8]. The high NRM in this series [11] was primarily caused by fatal infections, underlining the relevance of infectious complications in the post-transplantation management. CMV reactivations were observed in 6 (60%) patients with a lethal infection in 1 case.

The value of this series is to raise awareness of the occurrence of late relapses after initial remissions post-allo-HSCT. In 3 of their patients, all transplanted in CR and initially showing a complete donor chimerism, PD was observed at 12, 59, and 84 months after transplantation. These relapses were rapidly progressive and mostly extranodal. They displayed a pronounced resistance to salvage therapies (i.e., DLIs, bendamustine, pentostatin). Also,

re-exposure to alemtuzumab could not prevent further progression despite expression of CD52.

Although most relapses develop within the first 2 years after allo-HSCT [4, 8] and stable long-lasting (>10 years) remissions are described in T-PLL [10], Shumilov et al. [11] illustrate that late progression is not uncommon [5, 11]. In these cases, persistence of T-PLL often remains undetected by conventional monitoring of donor chimerism. A PCR-based assessment of minimal residual disease (MRD) kinetics was reported by Sellner et al. [12] and confirmed the presence of graft-versus-leukemia effects in T-PLL. In line with the results by Shumilov et al. [11], they observed a significant reduction of MRD levels upon immunomodulation in 7/10 patients, but with complete MRD clearance in only 2 patients.

Overall, although currently being the best available option in T-PLL, the systematic data on allo-HSCT indicate only marginal improvements of disease control and NRM over the past 2 decades when transplantation was performed as primary consolidation after alemtuzumab induction. Therefore, allo-HSCT and peri-transplant anti-leukemic therapies require profound optimizations. The depth of remission before entering transplantation is a main parameter that needs improvement. Further analyses also need to better identify patients who are likely to benefit from allo-HSCT versus those for whom alternative treatment approaches (e.g., targeted therapies) are more suitable. Other immuno-therapeutic options for T-PLL are to be explored as well [2]. As for now, allo-HSCT continues to be a challenge, providing long-term disease control only for a small subset of eligible patients and being associated with considerable side effects.

Disclosure Statement

M.H. holds patents on TCL1 monoclonal antibodies (research and diagnostic use) with royalties paid.

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Author Contributions

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