COMMENTARY

Harnessing the Power of Existing Therapeutic Strategies to Treat Cutaneous T-cell Lymphomas

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Harnessing the power of allo-HSCT in advanced CTCL

Mycosis fungoides (MF) and Sézary syndrome (SS) are rare cutaneous T-cell lymphomas (CTCL) with very poor prognosis in advanced stages and a high tendency to relapse.[1,2] Five-year survival rates decrease from 94% in early stages (stage 1A) to only 18% in advanced disease (stage 4B).[3] Mainstay treatment strategies for early-stage CTCL include first-line topical therapies or oral agents, while systemic therapies are typically reserved for more advanced-stage disease.[4,5]

My last editorial highlighted the efficacy of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in high-risk patients with advanced MF or SS.[6] According to the current recommendations of the European Organisation of Research and Treatment of Cancer (EORTC), allo-HSCT should be considered in patients with advanced MF and SS and poor prognosis but without significant comorbidity, with complete or near-complete remission achieved prior to transplantation.[7] Previously, data presented at the 64th ASH Annual Meeting and Exposition in 2022 showed that allo-HSCT is a powerful therapeutic strategy in selected patients with advanced CTCL that might improve the prognosis of advanced-stage CTCLs. A retrospective analysis of allo-HSCT outcomes for 57 CTCL patients demonstrated 5-year overall survival (OS) and disease-free survival (DFS) rates of 57.6% and 37.9%, respectively, associated with low toxicity.[8,9] Now, additional data from the CUTALLO study demonstrates a survival advantage of allo-HSCT treatment in people with advanced-stage and poor prognostic CTCL.[10]

CUTALLO (ClinicalTrials.gov: NCT02520908) is an ongoing French prospective study investigating the effect of allo-HSCT compared with non-HSCT therapy on the outcome of individuals with advanced-stage CTCL.[10] The study enrolled patients with advanced-stage MF or SZ and at least one poor prognostic criterion; participants who had disease progression shortly after enrollment were subsequently excluded. At a median follow-up of 12.6 months, de Masson et al. (2023) reported that patients with advanced CTCL receiving allo-HSCT had prolonged progression-free survival (PFS) (primary endpoint) versus matched patients receiving investigator-selected

non-HSCT therapy.[10] Median PFS was 9.0 months (95% confidence interval [CI]: 6.6–30.5 months) in the matched HSCT group versus 3.0 months (95% CI: 2.0–6.3 months) in the matched non-HSCT group (hazard ratio [HR]: 0.38 [95% CI: 0.21–0.69]; p<0.0001). Importantly, the authors of this study concluded that allo-HSCT should be made available for high-risk, advanced-stage MF or SS individuals who achieve pretransplant disease remission.[10]

Immunotherapy represents a promising avenue for CTCL management. The efficacy and safety of mogamulizumab, a monoclonal antibody targeting C-C chemokine receptor 4 (CCR4) was shown in a phase III MAVORIC trial[11] and confirmed in a recent retrospective, real-world OMEGA trial[12] in patients with advanced MF and SS. While the use of mogamulizumab before allo-HSCT may decrease disease burden, a higher risk of transplant complications including graft versus host disease (GVHD) has been reported in patients with adult T-cell lymphoma/leukemia who received mogamulizumab within a short time before HSCT, likely due to depletion of CCR4+ regulatory T cells.[13-15] These data suggest the need for maintenance of the recommended interval between mogamulizumab and allo-HSCT and close monitoring of patients for early signs of transplant-related complications.

Harnessing the power of topical calcineurin inhibitors in early CTCL

Topical calcineurin inhibitors (TCIs) such as tacrolimus and pimecrolimus are used widely as corticosteroid-sparing agents in the treatment of various cutaneous diseases such as atopic dermatitis and other skin diseases.[16] Although a very small increase in the absolute risk of lymphoma has been reported with TCI use, no increased risk of skin cancers has been observed.[16, 17] Moreover, evidence from the literature has reported that individuals with MF have mutations in the calcineurin pathway.[18] A recent Spanish study reported by Ortiz-Romero et al. (2022) assessed the activity and safety of topical pimecrolimus (1% cream) in patients with early MF.[19] PimTo-MF is the first clinical trial evaluating the treatment of CTCL with a calcineurin inhibitor.[19] This phase II study was conducted across six medical centers in Spain in adults with histologically confirmed early MF. The median follow-up after baseline was 5.7 years.[19] More than half of the study participants (56%) responded positively to pimecrolimus cream application (one complete response [CR], 21 partial responses [PR]), and it was well tolerated.[19] These initial results suggest that topical pimecrolimus seems active and well tolerated in patients with early-stage MF.[19]

Despite recent advances in targeted treatment options for CTCLs, there remains an unmet need for effective therapies with good safety profiles for early- and late-stage CTCL. Harnessing the power of allo-HSCT, a potentially curative treatment for several hematological malignancies, shows

promise for high-risk, advanced-stage MF or SS individuals. In addition, harnessing the power of existing atopic dermatitis treatments such as calcineurin inhibitors may be effective in early CTCLs but longer follow-up is required to confirm efficacy and safety.[20]

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Conflict of interest

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