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Controversies in autologous and allogeneic hematopoietic cell transplantation in peripheral T/NK-cell lymphomas

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Peripheral T-cell and NK-cell lymphomas (PT/NKCL) are a heterogeneous group of lymphoid neoplasms with poor outcomes. There is no consensus on the best front line therapy or management of relapsed/refractory disease. The use of autologous and allogeneic hematopoietic cell transplantation (HCT) has been studied in both settings to improve outcomes. Multiple retrospective and several prospective trials were reported. While at first sight the outcomes in the relapsed/refractory setting appear similar in B-cell and T-cell lymphomas when treated with high dose therapy (HDT) and autologous HCT, it is becoming obvious that only specific subtypes of PTCL benefit from this approach (i.e. anaplastic large cell lymphoma [ALCL] and angioimmunoblastic lymphoma [AITL] in second CR). In less favorable histologies, HDT seems to provide limited benefit, with the majority of patients experiencing post-transplant relapse. The use of autologous HCT to consolidate first remission has been evaluated in several prospective trials. Again, the best results were observed in ALCL, but the superiority of this approach over chemotherapy alone needs confirmation in randomized trials. In less favorable histologies, high-dose consolidation resulted in low survival rates comparable to those obtained with chemotherapy alone, and without randomized trials it is hard to recommend this strategy to all patients with newly diagnosed PT/NKCL. Allogeneic HCT might provide potent and potentially curative graft-vs-lymphoma effect and overcome chemotherapy resistance. Only a few studies have been reported to date on allogeneic HCT in PT/NKCL. Based on available data, eligible patients benefit significantly from this approach, with 50% or more patients achieving long-term disease control or cure, although at

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the expense of significant treatment related mortality (TRM). Reduced-intensity conditioning regimens appear to have lower TRM and might extend this approach to older patients. With the recent approval of several novel agents for relapsed/refractory PT/NKCL and their impact on survival of patients after relapse, it is becoming even more difficult to assess the benefit of HCT on overall survival and apply the results of non-randomized studies to clinical practice. Development of effective clinico-pathologic prognostic models might provide the opportunity to better define the role of HCT for patients with various subtypes of PT/NKCL. The first randomized trial comparing upfront autologous and allogeneic HCT was initiated by the German High-Grade Non-Hodgkin Lymphoma Study Group, and the results of this study might help answer some of the controversies for the first time.

Introduction

Before discussing the current evidence for hematopoietic cell transplantation, it is important to review historical data on outcomes in PT/NKCL that is frequently used as a historical control in retrospective and non-randomized studies. PT/NKCLs are a biologically and clinically diverse group of hematologic malignancies that have one thing in common – origin from a mature T- or NK-cell. Beyond this, there are very few commonalities between hepatosplenic T-cell lymphoma (HSTCL) and anaplastic large cell lymphoma; nasal NK-cell lymphoma and enteropathy-associated T-cell lymphoma (EATCL); or adult T-cell leukemia/lymphoma (ATL/L) and angioimmunoblastic T-cell lymphoma (AITL). In fact, as we come to understand these malignancies better, it appears that on the molecular level, they are nothing alike. It is not surprising then, that the recent International T-cell Lymphoma Project demonstrated a striking difference in outcomes between major WHO-defined subtypes of PTCL [1]. For the sake of future discussion, the histology-specific prognosis can be divided into favorable, 5-year OS $\geq$ 70% (ALK-positive ALCL, primary cutaneous ALCL), intermediate, 5-year OS 50–70% (ALK-negative ALCL, subcutaneous panniculitis-like T-cell lymphoma), poor, 5-year OS 25–50% (AITL, PTCL-NOS, nasal NK-cell lymphoma), and dismal, 5-year OS $\leq$ 20% (HSTCL, ATL/L, NK/T-cell lymphoma nasal type, aggressive/unclassifiable NK-cell leukemia, other extranodal gamma-delta T-cell lymphomas). These outcomes are in agreement with numerous prior studies. Aside from histologic subtype, the International Prognostic Index (IPI) is predictive of outcomes in major subtypes of PT/NKCL. Patients with common subtypes of T-cell lymphomas (PTCL-NOS, ALCL, and AITL) and a high-intermediate or high risk IPI score (3 or 4–5), have dismal prognosis, while those with a low or intermediate-low risk IPI score (0 or 1) might have favorable outcomes. Finally, it is becoming apparent that specific therapies significantly affect the outcomes in subtypes of PT/NKCL. As recent examples, L-asparaginase-containing regimens (i.e. SMILE, Aspa-MTX-Dex) showed surprisingly high activity in patients with NK-cell lymphoma [2], while intensified hybrid chemotherapy improved outcomes in EATCL. In a combined analysis of several German High-Grade Non-Hodgkin Lymphoma Study Group trials, addition of etoposide to the standard CHOP regimen significantly improved outcomes in most subtypes of PT/NKCLs [3]. More recently, brentuximab vedotin demonstrated remarkable activity in ALCL [4]. These and other advances are changing the "historical control" benchmark for T-cell malignancies and make interpretation of nonrandomized studies difficult.

Therefore, analyzing the possible benefit of HCT using retrospective and non-randomized prospective trials discussed in this review, one should take into account the prognostic impact of PT/NKCL histologic subtypes, IPI-risk distribution, and types of therapies given to patients included in the reports.

Autologous HCT for PT/NKCL

At the present time, no randomized clinical trials evaluating the impact of HDT and autologous HCT in either newly-diagnosed or relapsed/refractory PT/NKCL have been conducted. The current