Autologous and Allogeneic Hematopoietic Cell Transplantation in Peripheral T/NK-cell Lymphomas

A Histology-Specific Review

Tejaswini M. Dhawale, MD, Andrei R. Shustov, MD*

KEYWORDS

- Peripheral T-cell lymphoma • Natural killer/T-cell lymphoma
- Hematopoietic stem cell transplantation • Histology • Pathophysiology
- Molecular biology • Treatment

KEY POINTS

- Peripheral T-cell lymphomas and natural killer/T-cell lymphomas (PT/NKCL) comprise a biologically diverse subgroup of rare non-Hodgkin's lymphomas characterized by an aggressive clinical course and dismal outcomes.
- The use of hematopoietic stem cell transplantation in the treatment of PTCL remains controversial owing to the absence of randomized controlled trials.
- Careful consideration of disease biology, history of response to prior therapies, individual patient preferences, and overall treatment goals should guide treatment approaches for every patient.
- Improved understanding of unique biology of each subtype of PTCL and studies incorporating novel agents into treatment regimens may further identify which patients may benefit most from hematopoietic stem cell transplantation.

INTRODUCTION

Peripheral T-cell lymphoma and natural killer (NK)/T-cell lymphomas (PT/NKCL) comprise a diverse subgroup of rare non-Hodgkin's lymphomas that are thought to arise from mature T or NK cells. With a few exceptions, the majority of PT/NKCL are characterized by an aggressive clinical course and historically dismal outcomes. The most common PT/NKCL include peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell

Disclosure Statement: The authors have nothing to disclose.
Department of Medicine, University of Washington School of Medicine, SCCA, 825 Eastlake Avenue East, M-Box G3-200, Seattle, WA 98109, USA
* Corresponding author.
E-mail address: ashustov@seattlecca.org

Hematol Oncol Clin N Am 31 (2017) 335–357
http://dx.doi.org/10.1016/j.hoc.2016.11.003 **hemonc.theclinics.com**

lymphoma (ALCL, ALK-positive and ALK-negative), and extranodal NK/T-cell lymphoma, nasal type.[1] The clinical behavior and prognosis of the different histologic subgroups of PT/NKCL are widely variable and indicative of their individually unique biology. The histology-specific prognosis of the PT/NKCL can be summarized as follows: favorable, 5-year overall survival (OS) of 70% or greater (ALK-positive ALCL, primary cutaneous ALCL); intermediate, 5-year OS of 50% to 70% (ALK-negative ALCL, subcutaneous panniculitis-like TCL [SPTCL]); poor, 5-year OS of 25% to 50% (AITL, PTCL-NOS, nasal NK cell lymphoma); and dismal, 5-year OS of 20% or less (HSTCL, ATL/L, NK/T-cell lymphoma nasal type, aggressive/unclassifiable NK cell leukemia, other extranodal gamma-delta T-cell lymphomas).[2,3] Recent molecular analysis of the PT/NKCL has identified genetic signatures that not only distinguish between specific disease subtypes, but can also inform prognosis.[4] Insights into the biological behavior of these lymphomas has contributed to the development of targeted therapies for these diseases. As appreciation for the molecular fingerprint of PTCL and NKCL increases, it is anticipated that more "personalized" treatment approaches will be available and revolutionize the treatment landscape for these diseases.

Current treatment strategies for the PTCL an NKCL are focused on curative intent and the need to maintain remission given the aggressive nature of these diseases and the frequency with which they relapse. Unfortunately, owing to the absence of any randomized, controlled trials in this setting, there is presently no consensus regarding the optimal therapy for patients with newly diagnosed or relapsed or refractory PT/NKCL. It has been particularly difficult to understand the benefit of hematopoietic stem cell transplantation (HSCT) in these patients as most published studies involving HSCT in the upfront or relapsed setting have been retrospective and/or nonrandomized in nature. Moreover, these studies have often focused on small populations characterized by mixed histologies, varying disease status at transplantation, and treatments with diverse regimens. Selection bias has further limited the interpretation of these results, because many studies have excluded patients with chemorefractory or poor-risk disease who are not eligible for HSCT.

For the purpose of this review, we have focused our attention on the best-available evidence evaluating the role of HSCT in PT/NKCL using a histology-specific approach. We show that certain subtypes of PTCL and NKCL may benefit more from the application of high-dose therapy (HDT) and HSCT than other subtypes and that this benefit is likely a result of their unique clinical characteristics and underlying biology. Ultimately, however, prospective randomized controlled trials are needed to clarify the optimal type and timing of HSCT in patients with PT/NKCL.

PERIPHERAL T-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED

PTCL-NOS is the most common subtype of PTCL, accounting for 25% of all PTCL.[5] The term PTCL-NOS encompasses a heterogeneous group of mature T-cell lymphomas that do not meet criteria for any of the defined T-cell entities in the World Health Organization classification system.[1] PTCL-NOS follows an aggressive clinical course and may present as both nodal and extranodal disease. Most patients with PTCL-NOS have advanced stage disease at diagnosis and in some cases exhibit symptoms of hepatosplenomegaly, pruritus, hemolytic anemia, or hemophagocytic syndrome.[6] The malignant cells in PTCL-NOS are typically characterized by $CD4^+/CD8^-$ expression, frequent antigen loss of CD5 and CD7, T-cell receptor (TCR) gene rearrangement and variable cytotoxic granule expression.[5,7] Recent biological insights into PTCL-NOS have identified frequent mutations in the TET2 gene as well as activation of JAK/STAT, mammalian target or rapamycin, and PI3K pathways in varying subsets of