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Peripheral T-cell lymphoma: The role of hematopoietic stem cell transplantation

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Abstract

Peripheral T-cell lymphoma (PTCL) is a rare and heterogeneous group of non-Hodgkin lymphomas (NHLs). Whereas the incidence of the disease appears to increase during last decades and the prognosis remains dramatically poor, so far no standard treatment has been

Abbreviations: AaIPI, age-adjusted IPI; ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone, intrathecal methotrexate; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; Allo-SCT, allogeneic stem cell transplantation; AITL, angioimmunoblastic T-cell lymphoma; ATG, anti-thymocyte globulin; ASCT, autologous stem cell transplantation; BEAC, BCNU, etoposide, cytarabin, cyclophosphamide; BEAM, BCNU, etoposide, cytarabin, melphalan; BCNU, carmustine; BEC, busulfan, etoposide, cyclophosphamide; B, busulfan; C, cyclophosphamide; Cyt, cytarabin; CR, complete response (CR1/2 first/second complete remission); CVB, BCNU, etoposide, cyclophosphamide; CEOP, cyclophosphamide, epirubicin, vincristine, prednisone; CHOEP, cyclophosphamide, vincristine, doxorubicin, etoposide, prednisone; CTCL, cutaneous T-cell lymphoma; CVB/CBV, BCNU, etoposide, cyclophosphamide; DFS, disease-free survival; DHAP, dexamethasone, cytarabine, cisplatin; DLBL, diffuse large B-cell lymphoma; EATL, enteropathy-associated T-cell lymphoma; ECVBP, epirubicin, cyclophosphamide, vindesine, bleomycin, prednisone; EFS, event-free survival; E, etoposide; Flu, fludarabine; GVHD, graft-versus-host disease; HSTL, hepatosplenic T-cell lymphoma; IFE, ifosfamide, etoposide; ICE, ifosfamide, carboplatin, etoposide; IPI, international prognostic index; ITTP, intention to treat population; MA/MAC, myeloablative conditioning; MCEC, ranimustine, cyclophosphamide, etoposide, carboplatin; Mito, mitoxantrone; Mel, melphalan; NK/T, natural killer-cell/T-cell leukemia/lymphoma; NK, natural killer cell; NRM, non-relapse mortality; ORR, overall response rate; OS, overall survival; P, cisplatin; PFS, progression-free survival; ProMACE-CytBOM, prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide–cytarabine, bleomycin, vincristine, methotrexate; PR, partial remission; PIF, primary induction failure; RIC, reduced intensity conditioning; TBI, total body irradiation; Thio, thiotepa; TTF, time to treatment failure; TRM, treatment-related mortality; W, weeks; Y, year.

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established. High-dose chemotherapy and autologous stem cell transplantation (HDT–ASCT) has been proven effective in relapsed PTCL, while retrospective studies have shown a survival benefit as first-line treatment in some subsets of PTCL patients.

However, given disease rarity, there is a paucity of randomized trials in both upfront and relapse setting. Here, we critically evaluated eligible prospective and retrospective studies that address the role of ASCT in treatment of PTCL, with respect to quality of design and performance. Additionally, the role of allogeneic transplantation has been reviewed.

The comparison of ASCT with novel agents that emerge or the combination of both, are to be ascertained via prospective randomized trials in this field.

Keywords: Peripheral T-cell lymphoma; PTCL; Autologous stem cell transplantation; ASCT; High-dose chemotherapy; Transplantation

1. Introduction

Peripheral T-cell lymphomas (PTCLs) belong to non-Hodgkin lymphomas (NHLs) and constitute a heterogeneous group of lymphomas. This group accounts approximately 10% of aggressive NHLs in Western countries [1,2]. The incidence of PTCL is rising with nearly 3 times more cases diagnosed in the USA in 2005 than in 1992, whereas 69,740 estimated new cases of NHLs and 19,020 estimated deaths by the disease in 2013 [3,4]. The most recent World Health Organization of Tumors of Hematopoietic and Lymphoid Tissues classification recognizes three most common distinct histopathologic subtypes: peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), which is the most prevalent group of PTCLs (30–60%) [5], the angioimmunoblastic T-cell lymphoma (AITL) and the anaplastic large cell lymphoma (ALCL), where the fusion protein nucleophosmin anaplastic lymphoma kinase (ALK) could be expressed (ALK+) or not (ALK−) [3] (Table 1).

To date, there are not specific immunophenotyping characteristics or genetic features well established. The IPI system that has been used for prediction of long-term survival and as prognostic tool in both B- and T-cell lymphomas, has not shown the same value in certain subtypes of PTCLs [6,7]. Recently, a prognostic system in PTCL-NOS has been developed based on the results of a retrospective multicenter study [8]. This system utilizes four clinical variables (age, PS, LDH, and bone marrow infiltration) and has not been evaluated in prospective randomized trials yet.

In contrast to B-cell lymphomas, patients with PTCLs exhibit more aggressive clinical features, B-symptoms, extranodal disease and other markers of advanced disease which are associated also with poor prognosis, such as increased serum lactate dehydrogenase (LDH), bulky disease, elevated Ki-67, over-expression of p53 [9–13]. Compared to the corresponding aggressive B-cell lymphomas, the prognosis of PTCLs is dramatically inferior, with the notable exception of ALCL ALK (+). Current conventional treatment regimens have not achieved so far, to improve considerably the outcome. The prognosis of PTCLs is very poor, with a 5-year disease free survival below 30%, treated with standard chemotherapy consisted of second and third-generation agents [14,15].

The exact role of high dose therapy (HDT) and autologous stem cell support (ASCT) remains undefined. Although that several retrospective and some prospective studies of ACST have shown improved outcome in PTCLs patients, there are reports with inconsistent results. This mainly results from small size of the patient population in clinical trials, the heterogeneity of PTCLs and the enrollment of patients with ALK (+) lymphomas in some trials, which present a more favorable outcome. The timing of ASCT in the treatment of PTCLs, i.e., either in the frontline setting or in relapsed disease is still a debatable issue; ASCT, the standard treatment for relapsed diffuse large B-cell lymphoma (DBLCL) has shown effectiveness for PTCL in several retrospective studies as salvage treatment but also as part of upfront treatment in many prospective studies.

With respect to allogeneic stem cell transplantation (allo-SCT), there are limited data for its usage in patients with PTCL, as it is reserved for relapsed, heavily pre-treated, and chemo-refractory patients. In an attempt to examine the role of ASCT and allo-SCT in the treatment of PTCL and to clarify if these therapeutic strategies are able finally to improve the clinical outcome, we reviewed available prospective and retrospective studies.

Table 1
The WHO classification of peripheral T-cell lymphomas.

WHO 2008 classification of T-cell lymphomas
Adult T-cell leukemia/lymphoma
Hydroa vacciniforme-like lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Mucosis fungoides
Sezary syndrome
Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Borderline lesions
Primary cutaneous peripheral T-cell lymphomas, rare subtypes
Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous CD38 aggressive epidermotropic T-cell lymphoma
Primary cutaneous CD4+ small/medium T-cell lymphoma
Peripheral T-cell lymphoma, not otherwise specified (NOS)
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma, ALK+
Anaplastic large cell lymphoma, ALK−