# Mature T-cell neoplasms and stem cell transplant: the never-ending story

Emmanuel Bachy
Department of Hematology, Lyon Sud Hospital & Lymphoma Immuno-Biology Team, International Center for Infectiology Research (CIRI), Lyon, France
E-mail: emmanuel.bachy@chu-lyon.fr
*https://doi.org/10.3324/haematol.2022.280658*

Among all controversies in hematology, the role of autologous stem cell transplant (ASCT) in first-line treatment for patients with peripheral T-cell lymphoma (PTCL) is one of the most long-lasting. Several hurdles have prevented a definitive solution being found to the problem. First, and compared to its B-cell lymphoma counterpart, no significant progress, except for brentuximab vedotin (BV) in ALK-positive or -negative anaplastic large cell lymphoma, has convincingly and significantly altered the course of PTCL during the last two decades.[1] Such questions as to whether CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) alone or with etoposide (CHOEP) should be used frontline or whether stem cell transplant should be performed as first- or second-line treatment (if at all) are still hot topics in the field, whereas they might be considered completely outdated in other lymphoma subtypes. Second, despite tremendous efforts to better characterize the disease from molecular and pathological points of view, PTCL is still a highly heterogeneous disease. Combined with its rarity, this makes clinical research very difficult to conduct in order to conciliate the need for sufficient numbers of patients to be treated with homogeneous enough subtypes to be considered as one single disease. As a result and to date, more than five prospective trials and more than 20 retrospective studies have tried to address the benefit of ASCT in the first-line setting for PTCL.[2-7] Let's break the suspense: the study published in this issue of *Haematologica* by Garcia-Sancho and colleagues does not definitely answer the questions, but it does add a significant brick to the wall.[8]

Compared to historical and more recent series showing a poor median progression-free survival of approximately 10 to 12 months in PTCL,[9,10] the results from a prospective trial by d'Amore *et al.* published in 2012 convincingly demonstrated that six courses of CHOEP followed by ASCT in cases of partial or complete responses could yield progression-free survival of up to 44% at 5 years.[3] Since then, numerous retrospective studies have produced conflicting results. For example, data from the Swedish registry were in favor of ASCT in multivariate analysis (for both progression-free survival and overall survival; number of patients in the analyses ~250) but were not adjusted for response status at the end of induction.[11] A study by Cederleuf and colleagues based on Swedish and Danish patients (n=232), and limited to those reaching a complete response at the end of induction, did not find any survival advantage for ASCT in multivariate analysis.[12] Our study from the Lymphoma Study Association (LYSA) also did not find any benefit associated with ASCT in patients (n=269) reaching a partial or complete response after six CHOP-like cycles of therapy when populations were matched based on a propensity-score.[13] On the contrary, results based on patients in the prospective American COMPLETE registry (n=119) found a superiority of ASCT for patients in complete response.[14] Similarly, Savage and colleagues recently reported on the outcome of patients with CD30$^+$ PTCL in complete response following first-line treatment with BV-CHP (BV plus CHOP without vincristine) in the ECHELON-2 trial. Although ASCT consolidation was at the discretion of the treating investigator, *post-hoc* analysis showed a significantly longer progression-free survival for patients who received ASCT than for those who did not.[15]

In fact, numerous irreducible statistical biases hamper proper retrospective comparisons of patients' outcomes when it comes to stem cell transplant in general. Positive biases in favor of the procedure are that patients are usually younger, fitter, in better response at the end of induction, and have experienced lesser toxicity before ASCT; conversely, patients usually exhibit a more aggressive disease at diagnosis. As a result, positive and negative biases in favor and against ASCT make it very difficult to balance comparisons in retrospective studies. Usually, ways to control for those statistical biases are to perform matched-population comparisons, to conduct multivariate analyses, to use intent-to-treat groups (i.e., not comparing patients who actually receive ASCT or not; but comparing those for whom the physician decided before any treatment to go for stem cell transplant or not, information which is usually accessible through a review of medical charts), and to consider patients only in response after induction.

The study by Garcia-Sancho *et al.* uses most of those approaches to try to avoid the usual pitfalls of retrospective comparisons when dealing with the procedure of stem cell transplantation. Imbalances in patients' characteristics are "flattened" by using Cox multivariate analysis, only patients in complete response are considered for comparisons and, most importantly, the response must last at least 3 months to be considered. This circumvents another common problem of many studies since patients who can proceed to ASCT usually benefit from the so-called "guarantee-time

bias", i.e., that a patient needs to be in response until the transplant in the ASCT group, but not necessarily for so long in the non-ASCT group. However, the study is not performed based on an intent-to-treat decision by the local physician before any treatment, meaning that there might still be some uncontrolled biases between the two treatment groups. Finally, positron emission tomography/computed tomography is now frequently used for response assessment in PTCL, especially at the end of induction, but metabolic response was not considered in the study by Garcia-Sancho *et al.*

Nevertheless, the authors report here on one of the largest retrospective cohort of patients (n=174) in first complete response from Spanish and Italian centers and show in multivariate analyses that ASCT is associated with better outcomes (both significantly prolonged progression-free and overall survival). Of note, a sensitivity analysis is performed to show that the benefit still exists when only ALK-negative anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma and PTCL-not otherwise specified are taken into account, which are the usual histologies for which the role of ASCT has been extensively debated.

In the next months, the LYSA academic group will enroll the first patients in the TRANSCRIPT (TRANSplantation after Complete Response In Patients with T-cell lymphoma) trial. This study will randomize 204 transplant-eligible patients (before any treatment) to six cycles of CHOP-like regimens (CHOP, CHOEP or BV-CHP) followed (n=102) or not (n=102) by ASCT for those in complete metabolic response. Only ALK-negative anaplastic large cell lymphoma, T follicular helper-phenotype PTCL and PTCL-not otherwise specified will be considered. Randomization will ensure theoretically similar baseline characteristics, ASCT allocation before induction will ensure intent-to-treat decision, and the positron emission tomography/computed tomography evaluation will ensure robust response assessment. The primary endpoint will be progression-free survival. Will the study finally put an end to an endless story in hematology? Will new therapeutic developments in first-line PTCL make the question obsolete by the time of the final analysis? Time will tell.

**Disclosures**

*EB has received honoraria from Kite, a Gilead Company, Bristol Myers Squibb, Novartis, Pfizer, Incyte; acted in a consultancy role for Takeda, Roche, and Gilead/Kite; received personal fees from Kite, a Gilead Company, Bristol Myers Squibb, Novartis, Pfizer; and received research funding from Amgen.*

# References


1. Horwitz S, O'Connor OA, Pro B, et al. The ECHELON-2 trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma. Ann Oncol. 2022;33(3):288-298.
2. Corradini P, Tarella C, Zallio F, et al. Long-term follow-up of patients with peripheral T-cell lymphomas treated up-front with high-dose chemotherapy followed by autologous stem cell transplantation. Leukemia. 2006;20(9):1533-1538.
3. d'Amore F, Relander T, Lauritzsen GF, et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol. 2012;30(25):3093-3099.
4. Mercadal S, Briones J, Xicoy B, et al. Intensive chemotherapy (high-dose CHOP/ESHAP regimen) followed by autologous stem-cell transplantation in previously untreated patients with peripheral T-cell lymphoma. Ann Oncol. 2008;19(5):958-963.
5. Reimer P, Rudiger T, Geissinger E, et al. Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicenter study. J Clin Oncol. 2009;27(1):106-113.
6. Rodriguez J, Conde E, Gutierrez A, et al. Frontline autologous stem cell transplantation in high-risk peripheral T-cell lymphoma: a prospective study from the Gel-Tamo study group. Eur J Haematol. 2007;79(1):32-38.
7. Wilhelm M, Smetak M, Reimer P, et al. First-line therapy of peripheral T-cell lymphoma: extension and long-term follow-up of a study investigating the role of autologous stem cell transplantation. Blood Cancer J. 2016;6(7):e452.
8. García-Sancho AM, Bellei M, López-Parra M, et al. Autologous stem cell transplantation as consolidation of first-line chemotherapy in patients with peripheral T-cell lymphoma: a multicenter GELTAMO/FIL study. Haematologica. 2022;107(11):2675-2684.
9. Bachy E, Camus V, Thieblemont C, et al. Romidepsin plus CHOP versus CHOP in patients with previously untreated peripheral T-cell lymphoma: results of the Ro-CHOP phase III study (conducted by LYSA). J Clin Oncol. 2022;40(3):242-251.
10. Simon A, Peoch M, Casassus P, et al. Upfront VIP-reinforced-ABVD (VIP-rABVD) is not superior to CHOP/21 in newly diagnosed peripheral T cell lymphoma. Results of the randomized phase III trial GOELAMS-LTP95. Br J Haematol. 2010;151(2):159-166.
11. Ellin F, Landstrom J, Jerkeman M, Relander T. Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. Blood. 2014;124(10):1570-1577.
12. Cederleuf H, Hjort Jakobsen L, Ellin F, et al. Outcome of peripheral T-cell lymphoma in first complete remission: a Danish-Swedish population-based study. Leuk Lymphoma. 2017;58(12):2815-2823.
13. Fossard G, Broussais F, Coelho I, et al. Role of up-front autologous stem-cell transplantation in peripheral T-cell lymphoma for patients in response after induction: an analysis of patients from LYSA centers. Ann Oncol. 2018;29(3):715-723.
14. Park SI, Horwitz SM, Foss FM, et al. The role of autologous stem cell transplantation in patients with nodal peripheral T-cell lymphomas in first complete remission: report from COMPLETE, a prospective, multicenter cohort study. Cancer. 2019;125(9):1507-1517.
15. Savage KJ, Horwitz SM, Advani RH, et al. An exploratory analysis of brentuximab vedotin plus CHP (A+CHP) in the frontline treatment of patients with CD30+ peripheral T-cell lymphomas (ECHELON-2): impact of consolidative stem cell transplant. Blood. 2019;134(Suppl_1):464.