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

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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 precluded from providing a definite answer to the question. 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 (ALCL), has convincingly and significantly altered the course of PTCL during the last 2 decades.\(^1\) Such questions as to whether CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) with or without etoposide should be used frontline or if stem cell transplant should be performed in first or second line (if at all) are then still hot topics in the field; whereas they might be considered as completely outdated in other lymphoma subtypes. Second and despite tremendous efforts to better characterize the disease from a molecular and pathological point of view, PTCL is still a highly heterogeneous disease. Combined to its rarity, this makes clinical research very difficult to conduct in order to conciliate sufficient number of patients to be treated and homogeneous enough subtypes to be considered as one single disease. As a result and to date, more than 5 prospective trials...
and more than 20 retrospective studies have tried to address the benefit of ASCT in 1st line setting for PTCL.\textsuperscript{2-7} Let’s break the suspense, the present study published in Haematologica by Garcia-Sancho and colleagues will not definitely answer the question but it will add a significant stone to the building.\textsuperscript{8}

Compared to historical and more recent series showing a poor median progression-free survival (PFS) of approximately 10 to 12 months in PTCL,\textsuperscript{9,10} the results from the prospective trial of d’Amore et al. published in 2012 convincingly demonstrated that 6 courses of CHOP followed by ASCT in case of partial or complete response (PR or CR) could yield up to 44% of PFS at 5 years.\textsuperscript{3} Since then, numerous retrospective studies have produced conflicted results. For example, data from the Swedish registry were in favor of ASCT in multivariate analysis (both for PFS and OS; number of patients in the analyses ~250) but was not adjusted for response status at the end of induction.\textsuperscript{11} The study from Cederleuf and colleagues based on Swedish and Danish patient populations (N=232), and limited to those reaching a CR at the end of induction, did not find any survival advantage for ASCT in multivariate analysis.\textsuperscript{12} Our study from the LYSA (N=269) also did not find any benefit associated with ASCT in patients reaching a PR or a CR after 6 CHOP-like cycles when populations were matched based on a propensity-score.\textsuperscript{13} On the contrary, results based on the prospective American COMPLETE registry (N=119) found a superiority of ASCT for patients in CR.\textsuperscript{14} Similarly, Savage and colleagues recently reported on the outcome of patients with CD30+ PTCL in CR following 1st 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 was in favor of a significantly prolonged PFS for patients who received ASCT than for those who did not.\textsuperscript{15}
In fact, lots of irreducible statistical biases hamper proper retrospective comparisons of patient outcome 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 the comparison in retrospective studies. Usually, means to control for those statistical biases is to perform matched-population comparisons or to use multivariate analyses, to use intent-to-treat groups (ie not patients who actually receive ASCT or not; but those for whom the physician decided before any treatment to go for stem cell transplant or not, usually accessible through medical charts review), and to consider patients only in response after induction.

The present study from Garcia-Sancho et al uses most of those approaches to try avoiding usual pitfalls of retrospective comparisons when dealing with stem cell transplant procedure. Patient characteristics imbalances are “flattened” using Cox multivariate analysis, only patients in CR are considered for comparison, and most importantly the response must last at least 3 months to be considered. This is another usual caveat 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 from the local physician before any treatment, meaning that there might still exist some uncontrolled biases between the 2 treatment groups. Finally, PET-CT is now frequently used for response assessment in PTCL, especially at the end of induction, but metabolic response was not considered in the present study.
Anyway, the authors report here on one of the largest retrospective cohort of patients (N=174) in first CR from Spanish and Italian centers and show that ASCT is associated with a better outcome in multivariate analyses (both significantly prolonged PFS and OS). Of note, a sensitivity analysis is performed to show that the benefit still exists when only ALK-negative ALCL, angioimmunoblastic T-cell lymphoma (AITL) and PTCL-not otherwise specified (NOS) are taken into account, which are the usual histologies where questioning the role of ASCT has been extensively debated.

In the next months, the LYSA (Lymphoma Study Association) academic group will enroll first patients in the TRANSCRIPT (TRANSpantation 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 regimen (CHOP, CHOEP (CHOP with etoposide) or BV-CHP) followed (N=102) or not (N=102) by ASCT for those in complete metabolic response. Only ALK-negative ALCL, T follicular helper (Tfh)-phenotype PTCL and PTCL-NOS subtypes will be considered. Randomization will ensure theoretical similar baseline characteristics, ASCT allocation before induction will ensure intent-to-treat decision, and PET-CT evaluation will ensure robust response assessment. The primary endpoint will be PFS. Will the study finally put an end to this endless story in hematology? Will new therapeutic developments in first-line PTCL make the question obsolete at time of final analysis? Time will tell.
References


