The Bottom Line

Hematopoietic Stem Cell Transplantation in Nodal T Cell Non-Hodgkin Lymphomas: Revisiting the Issues

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The management of nodal T cell non-Hodgkin lymphomas (T-NHL), whether in newly diagnosed or relapsed settings, is a formidable clinical challenge. This heterogeneous group of malignancies has both innate and acquired chemoresistance to standard regimens and, with a few notable exceptions, most subtypes have poor long-term outcomes. The current initial treatment paradigm for nodal T-NHL is, unfortunately, based on patients included in aggressive B cell lymphoma trials in the 1990s. Thus, standard-dose, anthracycline-based regimens, such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) are the default standard of care for T-NHL, despite long-term survival rates of only 20% to 40% and as low as 10% for those with high-risk features [1,2]. Furthermore, recent population-based data suggest that median overall survival (OS) after relapse is less than 6 months, particularly if hematopoietic stem cell transplantation (HCT) is not performed [3]. A number of novel agents are now approved in T cell lymphomas that may change the future treatment landscape, but for now, HCT retains an important role in the management of T-NHL. However, both the timing of HCT and the best modality, autologous versus allogeneic, are controversial topics.

In this issue of Biology of Blood and Marrow Transplantation, Beitinjanesh et al. report on a single-institution retrospective analysis of patients with nodal T-NHL undergoing HCT on institutional transplantation protocols at MD Anderson Cancer Center [4]. Although they included patients spanning almost 2 decades, the majority of transplantations were performed after the year 2000, and they excluded anaplastic lymphoma kinase—positive anaplastic large cell lymphoma (ALCL) patients, which is the only favorable subtype of nodal T-NHL. Among 134 patients with peripheral T cell lymphoma (PTCL)—not otherwise specified, angioimmunoblastic T cell lymphoma (AITL), or anaplastic lymphoma kinase (ALK)—negative ALCL, 58 underwent HCT as part of front-line therapy (47 autologous HCT [autoHCT] and 11 allogeneic HCT [alloHCT]) and 76 patients received HCT (41 autoHCT and 35 alloHCT) in the relapsed setting. Overall, the main conclusions of their analysis are consistent with other reports that indicate that HCT is most effective when performed as part of initial therapy, chemosensitivity is the most important predictor of outcome, and, reflecting greater nonrelapse mortality, alloHCT does not have superior outcomes compared with autoHCT. Although this report confirms published data, it also raises a number of important considerations regarding the timing and type of HCT utilized.

Confirming a growing number of retrospective and prospective publications [5], the current report finds that consolidative autoHCT in the front-line setting has promising outcomes. Specifically, with a median follow-up of 35 months, the 4-year progression-free (PFS) and OS are 56% and 75%, respectively. For patients in first complete remission, the 4-year PFS and OS were 64% and 84%, respectively. Although these are impressive numbers, this study shares the caveat with many others: patients who are unable to undergo transplantation are not included. For example, the prospective Nordic NLG-T-01 trial of dose-dense cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone (CHOP-E) plus autoHCT consolidation found that only three of patients were unable to undergo planned transplantation because of progression or other treatment failure [6]; similarly, a prospective German trial reported that only 66% of patients initially enrolled could undergo planned autoHCT [7]. The current paper by Beitinjanesh et al., by design, only included patients referred to a tertiary care center and able to undergo HCT; thus, the denominator of potential patients unable to be considered for HCT is unknown, and these excellent outcomes must be tempered as they reflect a relatively selected patient population.

The most important confirmatory findings in this paper are the favorable significance of chemosensitive disease and that earlier transplantation (of either modality) may be very helpful in improving outcomes. These are similar to the major conclusions in a Center for International Blood and Marrow Transplant Research (CIBMTR) analysis of autoHCT
and alloHCT in T-NHL [8]. Despite important patient- and disease-based differences in autoHCT and alloHCT recipients, a unifying observation was that transplantation was often offered late in the disease course, with 50% of alloHCT and 30% of autoHCT patients receiving more than 2 prior treatment regimens. This translated to worse outcomes: patients receiving more than 2 lines of therapy had a 3-fold increased risk of relapse, 5-fold increased risk of overall mortality, and 7-fold increased risk of nonrelapse mortality. Similarly, patients with chemotherapy-resistant disease had a 2-fold increased risk of relapse, treatment failure, and overall mortality. The current study similarly found that patients with primary induction failure, an incomplete response to induction treatment (ie, partial response), or multiple lines of treatment were associated with inferior outcomes. The main conclusion of the authors is that transplantation is most beneficial when offered as part of first- or second-line therapy, particularly if there is chemosensitivity.

An additional confirmatory finding is the description of graft-versus-lymphoma (GVL). A potent GVL effect in T-NHL has been previously reported [9-12]. At least 1 group has shown inferior outcomes and increased relapse after non-myeloablative regimens, suggesting that it is the combined impact of the preparative regimen as well as allogeneic stem cell source that affects outcomes. The current paper supports a GVL effect via 4 patients responding to donor lymphocyte infusion and 4 of 8 patients who relapsed after autoHCT enjoying long-term survival after a salvage alloHCT. Although there are controversies over the relative value of myeloablative versus reduced-intensity regimens, the current paper found no statistically significant differences based on regimen intensity.

Two highly controversial topics elicited by the current manuscript are whether or not alloHCT should be considered as first-line treatment in any T-NHL patient, and second, whether or not autoHCT can be successful in the relapsed setting. When should alloHCT be considered as a front-line consolidation? The current study does not define why patients were chosen for auto versus alloHCT modality, but others have shown that high International Prognostic Index (IPI) and non-ALCL histologies do not benefit as much from consolidation autoHCT [6,7]. For example, in the Nordic trial, 5-year OS was over 70% for ALCL versus approximately 50% for PTCL-not otherwise specified andAITL. Similarly, a high prognostic index for peripheral T cell lymphoma, unspecified (PTCL-U) score reduces long-term outcomes from approximately 50% to less than 20% [7]. Accordingly, a recent prospective trial of consolidative alloHCT in initial management enrolled 23 patients; in contrast to the prognostic factors identified in autoHCT settings, neither the histology nor the prognostic index for PTCL-U affected outcomes and 16 of 23 patients remain in a continuous remission with a median follow-up of 40 months [11]. Although these are small numbers, the combined finding that autoHCT is not as effective in high-risk patients and that alloHCT is feasible is provocative and suggests that alloHCT as first-line therapy may be reasonable for some patients. Only 11 patients underwent alloHCT as front-line consolidation in the current report. Although not statistically significant because of the small number of patients, patients undergoing alloHCT as part of initial treatment were numerically more likely to have bone marrow involvement (27% versus 4%), receive more lines of treatment before HCT (median 2 versus 1 prior regimen), and have primary induction failure (45% versus 19%). Despite these adverse features, outcomes are similar to those for patients who received autoHCT consolidation with 4-year PFS and OS of 34% and 54%, respectively.

The second controversial issue raised by the current paper is the role of autoHCT in relapsed settings. To date, there are no prospective data evaluating the feasibility and efficacy of autoHCT in relapsed T-NHL. Most reports are retrospective, small, and from a single institution, and they collectively show poor outcomes, particularly when compared with front-line datasets. For example, a Stanford analysis found only 10% long-term disease control after autoHCT at relapse [13]; similarly, an Italian study of 40 patients found the median PFS after autoHCT at relapse to be only 6 months [14]. In contrast, registry trials show more optimistic findings. The CIBMTR evaluated 115 patients undergoing autoHCT; after excluding patients who underwent transplantation in first remission, the 3-year PFS and OS were 41% and 53%, respectively [8]. However, patients undergoing autoHCT at relapse in the CIBMTR analysis were also more likely to have chemosensitive disease, harbor ALC1 histology, and have fewer lines of therapy.

The current report includes 41 patients undergoing autoHCT at relapse and is 1 of the larger single-institution cohorts to be evaluated. Patients undergoing autoHCT in second or third complete remission had a 4-year OS of 59%; the majority of patients had ALC1 or PTCL histology. Although afflicted by the same caveats discussed in the front-line setting, these numbers suggest that there are some patients who will benefit from autoHCT, even if this is performed in the relapsed setting.

Finally, although the title of the current report suggests a comparative intent of autoHCT versus alloHCT, it is difficult to draw conclusions with relatively small patient numbers in each group and the comparative analysis should be viewed with caution. Most other datasets have not been able to compare autoHCT and alloHCT because of a recurring theme that patients selected for alloHCT tend to have more adverse features. For example, the initial intent of the aforementioned CIBMTR study was to compare autoHCT and alloHCT outcomes, but there were substantially differing baseline characteristics by treatment modality and a true comparative analysis could not be performed. Patients undergoing autoHCT were more likely to be in first complete remission, have chemotherapy-sensitive disease, have ALC1 subtype, and have 2 or fewer lines of prior therapy.

Overall, the MD Anderson Cancer Center experience highlights the outcomes of T-NHL patients undergoing HCT. The retrospective nature and multiple caveats mentioned above challenge the ability to make strong and definitive conclusions; nevertheless, it is clear that there is a subset of patients with T-NHL who achieve long-term disease control and survival with transplantation modalities. Prospective trials focused on identifying the best candidates, increasing the number of patients eligible for transplantation strategies, and incorporating more rational agents into the treatment paradigm earlier in the disease course are all badly needed. For now, this report supports accumulating literature that HCT remains an important tool in management of T-NHL via both autologous and allogeneic modalities.

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