Allogeneic stem cell transplant in non-Hodgkin lymphomas: Still an indication?

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Abstract
Allogeneic hematopoietic cell transplantation (alloHCT) used to play a defined role in the treatment of non-Hodgkin lymphoma (NHL). With the advent of modern targeted molecular therapies and immunotherapies, treatment standards at least for B-cell lymphoma have undergone significant changes, thereby questioning the traditional role of alloHCT in these diseases. This paper attempts to describe the current place and the perspectives of alloHCT in the rapidly evolving treatment landscape of NHL.

KEYWORDS
allogeneic transplantation, CAR-T cells, lymphoma, NHL

1 | INTRODUCTION

Entering the clinical stage more than 50 years ago, allogeneic hematopoietic cell transplantation (alloHCT) was the first immunotherapy successfully applied to patients, and can be considered as the ancestor of modern cellular immunotherapy. Despite its inherent drawbacks of significant non-relapse mortality and morbidity due to graft-versus-host disease, until recently, alloHCT has been playing a defined role in the management algorithms of the main NHL subtypes (i.e., diffuse large B-cell lymphoma [DLBCL]; follicular lymphoma [FL]; mantle cell lymphoma [MCL]; and peripheral T-cell lymphoma [PTCL]), mostly in the salvage setting. With the advent of modern targeted molecular therapies and immunotherapies, treatment standards at least for B-cell lymphoma have undergone substantial changes, thereby questioning the traditional role of alloHCT in these diseases. This paper attempts to describe the current place and the perspectives of alloHCT in the rapidly evolving treatment landscapes of DLBCL, FL, MCL, and PTCL.

2 | DIFFUSE LARGE B-CELL LYMPHOMA

As in almost all neoplastic indications where it is effective, the basis of alloHCT in DLBCL is graft-versus-lymphoma activity (GVL). Circumstantial evidence for GVL efficacy in DLBCL can be derived from the effectiveness of immunomodulation for preventing or treating post-transplant relapse, and from observations showing that non-myeloablative alloHCT can provide long-term disease control in patients having failed autologous hematopoietic cell transplantation (autoHCT). However, compared to the other main NHL entities, DLBCL appears to be less GVL-sensitive resulting in long-term progression-free survival rates of 30%-40%, and even less if calculated by intent-to-treat. While the standard indication for alloHCT in DLBCL used to be chemosensitive disease following failure of autoHCT, chimeric antigen receptor-engineered T-cells (CARTs) have become the preferred cellular immunotherapy in this setting. A preliminary intent-to-treat comparison of alloHCT versus CARTs in large B-cell lymphoma (LBCL) suggested that in patients having failed at least two lines of systemic therapy, survival tended to be better with the CART versus the alloHCT approach. One limitation of this study was the short follow-up of 10 months in the CART group. Figure 1 shows an update of this comparison with a median follow-up of 15 (9–24) months, suggesting that the favorable trend for CARTs was maintained, both measured from treatment indication and start of cellular therapy.

In conclusion, for the time being, alloHCT remains an indication for advanced DLBCL when CARTs have failed or are not feasible.
However, it is clear that emerging innovations, such as bispecific antibodies and moving CARTs to the second line, have the potential for further modifying the importance of alloHCT for rescuing patients with relapsed/refractory DLBCL.

3 | FOLLICULAR LYMPHOMA

Although FL appears to be the most GVL-sensitive disease among all alloHCT indications currently considered as standard, with a 5-year relapse risk less than 20% in all major studies published, the number of allogeneic transplantsations for this subtype is decreasing since several years, making FL the least frequent allo indication of the four entities discussed in this review. In 2018, the numbers of allo-transplants registered with the European Society for Blood and Marrow Transplantation (EBMT) for PTCL, DLBCL, MCL, and FL were 401, 320, 161, and 144, respectively (EBMT data on file, PROMISE download 19 February 2020). This has to do with the indolent course of the disease, the high efficacy of standard first-line treatment with chemoimmunotherapies and CD20 antibody maintenance, and the availability of a broad effective toolkit for salvage treatment, including relvlimab, targeted therapies, and also autoHCT. Even in high-risk disease, defined by failure of first-line treatment within 2 years (“POD24”), there is no proven benefit of alloHCT over autoHCT.7

In contrast to DLBCL and MCL, there is no CART therapy approved for FL available to date, and due to the indolent character of the disease the benefit of CART approaches in terms of durable lymphoma control will be more difficult to assess. Nevertheless, the development of CD19-directed CARTs and other immunotherapies for indolent lymphoma is already quite advanced, suggesting that the alloHCT indication will further narrow in the near future.

For today, alloHCT is still a potentially curative option for those patients with FL who are resistant to less aggressive approaches, that is, who relapse early after salvage autoHCT or a similarly intensive regimen, and for patients with emerging exhaustion of hematopoiesis, or incipient myelodysplasia.

4 | MANTLE CELL LYMPHOMA

Efficacy of donor lymphocyte infusions (DLI) and plateaus in the relapse curves after reduced intensity conditioning (RIC) suggest that there is a biologically relevant contribution of GVL also in MCL.8,9

Given the poor prognosis of MCL recurring after state-of-the-art intensive first-line treatment with consolidating autoHCT and rituximab maintenance, the traditional place of (RIC) alloHCT has been consolidation of second-line responses. With the introduction of Bruton’s tyrosine kinase inhibitors (BTKi) as standard of care salvage therapy in MCL, and the recent approval of the CART product brexucabtagene autoleucel for relapsed/refractory MCL, the place of alloHCT in the MCL management algorithm needs to be re-evaluated. A recent international consensus project recommended considering alloHCT in MCL only if CARTs have failed or are not feasible (Hamadani et al., manuscript in preparation). This would mean that alloHCT comes into play only on the fourth place after standard induction, BTKi, and CARTs. However, in areas where CARTs are not available, considering alloHCT already for consolidation of second-line responses to BTKi might be worthwhile in high-risk patients, such as those without a complete response to BTKi or early failure after standard induction.10 Again, the expected advent of novel molecular agents and immunotherapeutics in the clinical routine of MCL management, such as venetoclax, enhanced CD19-directed antibodies, and next-generation phosphatidylinositol 3-kinase delta inhibitors has the potential to further differentiate the alloHCT indication in MCL in the near future.

5 | PERIPHERAL T-CELL LYMPHOMA

In contrast to B-cell lymphoma, there have been no major therapeutic improvements for PTCL in the last decades, with the exception of anaplastic large cell lymphoma (ALCL). Although the value of autoHCT consolidation is ambiguous, accepted standard treatment for the three predominant nodal PTCL subsets (i.e., ALK-negative ALCL, PTCL not otherwise specified [PTCL-NOS], and angioimmunoblastic T-cell lymphoma
Abbreviations: alloHCT, allogeneic hematopoietic cell transplantation; autoHCT, autologous hematopoietic cell transplantation; BTKi, Bruton’s tyrosine kinase inhibitors; CAR T-cell therapy, chimeric antigen receptor-engineered T-cell therapy.

[AITL] consists in CHOP-like induction followed by high-dose intensification. With this strategy, 5-years progression-free survival rates of 35%–45% can be expected. Of particular concern in PTCL is the high rate of primary refractoriness which can affect up to one third of the patients.

Similar to FL and MCL, PTCL appears to be quite susceptible to GVL effects as illustrated by survival plateaus around 50% after alloHCT across numerous studies and efficacy of DLI, prompting the exploration of allotransplantation as first-line consolidation. A large randomized trial comparing alloHCT with autoHCT in the first-line setting, however, failed to show a benefit for the alloHCT strategy, largely because the lower relapse risk associated with alloHCT was neutralized by excess non-relapse mortality. Thus, except for selected orphan PTCL subsets such as hepatosplenic T-cell lymphoma, first-line alloHCT should not be performed outside of clinical trials.

In contrast, alloHCT is the preferred option in relapsed/refractory PTCL, ideally after having achieved a state of controlled disease prior to transplant. This is because of the lack of therapeutic alternatives with curative perspective. In patients not having undergone autoHCT during first-line treatment, also auto-transplantation may be considered though appearing inferior to alloHCT in intent-to-treat comparisons. Similar to the other lymphoma subsets described in this paper, reduced intensity conditioning provides outcomes in PTCL that are at least similar to that observed after myeloablative conditioning, and haplo-identical donors seem to be a valuable alternative if matched related or unrelated donors are not available.

6 | CONCLUSIONS

Table 1

| Lymphoma Type                        | Indications                                                                 |
|--------------------------------------|-----------------------------------------------------------------------------|
| Large B-cell lymphoma                | 4th line after failure of induction, autoHCT attempt, and CAR T-cell therapy |
| Follicular lymphoma                  | early relapse after salvage autoHCT or a similarly intensive regimen, and emerging exhaustion of hematopoiesis/incipient myelodysplasia. |
| Mantle cell lymphoma                 | 4th line after failure of induction, BTKi, and CAR T-cell therapy.           |
| Peripheral T-cell lymphoma           | relapsed/refractory disease.                                                |

Although substantial therapeutic innovations in particular for B-cell lymphoma have entered the clinical stage recently, or are at the doorstep, immunotherapy by alloHCT remains an effective and potentially curative option for settings where the medical need unmet by traditional chemotherapy can also not be covered by novel therapeutics. This gap might be bigger than believed as some promises of novel agents given in phase-2 studies have not been fully kept in the real world. Suggestions for current indications for alloHCT are summarized in Table 1. If alloHCT is taken into account according to these suggestions, it has to be kept in mind that the window of opportunity for a successful outcome of transplantation is largest before tumor refractoriness and performance status deterioration have developed through serial palliative or experimental treatment attempts.

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