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Allogeneic hematopoietic cell transplantation for indolent non-Hodgkin lymphoma: indications and outcomes

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Abstract

Purpose of review—Allogeneic hematopoietic cell transplantation (HCT) can potentially cure indolent non-Hodgkin lymphoma (NHL). However, the optimal timing and indications remain unclear. Here, we review recent published reports on the subject and summarize our approach.

Recent findings—Recent prospective clinical trials of allogeneic HCT in indolent NHL are marked by substantial variation in eligibility criteria, patient populations, and transplant approach. Nonetheless, several common themes are apparent. Indolent NHL is highly susceptible to immunologic graft-vs.-lymphoma (GVL) effects, and relapse rates after allogeneic HCT are uniformly low. Allogeneic HCT early in the disease course produces the highest overall and progression-free survival, but also increases patient exposure to potential transplant-related complications such as chronic graft-vs.-host disease (GVHD). In contrast, allogeneic HCT can be reserved as a “last resort” for patients who are refractory to conventional chemotherapy, delaying their exposure to GVHD and other transplant-associated risks. No trials have directly addressed the optimal timing of allogeneic HCT in indolent NHL nor prospectively compared different transplant approaches.

Summary—Excellent outcomes have been reported with allogeneic HCT for indolent NHL, both early and late in the disease course. The optimal timing of allogeneic HCT is unknown and depends heavily on patient preferences.

Keywords

Follicular lymphoma; allogeneic hematopoietic cell transplantation; immunotherapy

INTRODUCTION

Indolent non-Hodgkin lymphoma (NHL) is a relatively common form of cancer in the Western world. Approximately 15,000 new cases of follicular lymphoma (the most common form of indolent NHL) are diagnosed annually in the U.S., with a median age at diagnosis of 60 years [1]. Indolent NHL typically responds well to chemoimmunotherapy, and modern rituximab-containing regimens can produce lengthy remissions. However, indolent NHL is

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generally thought to be incurable with conventional chemotherapy, and patients eventually develop chemorefractory disease or histologic transformation to a more aggressive form of NHL.

While some groups have recently reported intriguing results with high-dose chemotherapy and autologous hematopoietic cell transplantation (HCT), allogeneic HCT arguably remains the only approach with curative potential in indolent NHL. However, the integration of allogeneic HCT into the treatment of indolent NHL remains controversial, as allogeneic HCT carries a significant risk of short- and long-term morbidity and its optimal timing is unclear. The curative potential of allogeneic HCT must be balanced against its higher upfront morbidity and mortality, particularly as many patients can achieve prolonged disease-free survival with chemotherapy alone. On the other hand, outcomes with allogeneic HCT are likely to be best when patients are transplanted early in their disease course, rather than at the development of chemoresistance or histologic transformation.

The benefit of allogeneic HCT derives primarily from the so-called graft-vs.-lymphoma (GVL) effect, wherein the donor immune system identifies and eradicates residual lymphoma. The existence of an immunologic GVL effect has been demonstrated conclusively, and this effect appears to be strongest against slow-growing malignancies such as indolent NHL [2–4]. However, the donor immune system may also recognize and attack normal host tissues, causing graft-vs.-host disease (GVHD). The acute and chronic forms of GVHD are major complications of allogeneic HCT and result in considerable morbidity; chronic GVHD in particular can persist for years and is the major determinant of quality of life in long-term survivors of allogeneic HCT [5]. Outcomes after allogeneic HCT have improved substantially over time [6], but the curative potential of this approach must be balanced against its unique set of complications. In this review, we summarize recent data on outcomes of allogeneic HCT in indolent NHL and offer our perspective on incorporating this approach into the treatment of this condition.

CONDITIONING INTENSITY

As initially developed, allogeneic HCT incorporated high-dose myeloablative chemoradiotherapy as pre-transplant conditioning. While myeloablative conditioning is effective in eradicating residual lymphoma, it carries significant regimen-related toxicity and mortality. The toxicity of myeloablative conditioning is particularly pronounced in diseases such as indolent NHL, where patients are often older and heavily pre-treated by the time they undergo allogeneic HCT. Registry studies have shown high rates of treatment-related mortality (TRM) in patients with indolent NHL undergoing myeloablative allogeneic HCT, ranging from 30–38% [7;8]. These high rates of TRM are even more prohibitive given that myeloablative conditioning is generally reserved for younger and healthier patients, thus excluding the majority of patients with indolent NHL. As a result of these findings, myeloablative allogeneic HCT is rarely utilized for indolent NHL, and is generally avoided outside the context of clinical trials or for individual patients with unusual clinical situations.

Reduced-intensity conditioning is currently the dominant approach to allogeneic HCT for indolent NHL. These approaches were based on the recognition that the benefit of allogeneic

HCT derives primarily from immunologic GVL effects rather than high-dose chemotherapy. Thus, reduced-intensity approaches are designed to suppress the recipient immune system sufficiently to guarantee donor hematopoietic engraftment, while avoiding regimen-related toxicity. A wide variety of reduced-intensity approaches have been described in the literature, but none have been compared directly, leaving the choice of regimen to institutional preference or expertise.

For patients who require intensive cytoreduction before allogeneic HCT, tandem autologous/allogeneic HCT is generally preferred over myeloablative allogeneic HCT. In the tandem approach, patients undergo high-dose therapy with autologous HCT, followed shortly by a reduced-intensity allogeneic HCT. This tandem approach seeks to maximize both the cytoreductive benefit of high-dose chemotherapy and the long-term disease control afforded by allogeneic HCT, while separating the toxicities of these two approaches to improve tolerability. Preliminary results with this tandem approach have been promising, with relatively low TRM and good anti-tumor efficacy [9–11].

OUTCOMES OF REDUCED-INTENSITY ALLOGENEIC HCT

Reduced-intensity conditioning regimens allow the expansion of allogeneic HCT eligibility to patients who are older (up to age 70 and beyond), more heavily pretreated (including those whose NHL has progressed after a previous autologous HCT), and those with medical comorbidities. Several large prospective clinical trials have tested various reduced-intensity allogeneic HCT regimens in patients with indolent NHL. These studies differed in their eligibility criteria and patient populations, making it challenging to compare their results directly, but they illustrate several common themes.

The M.D. Anderson group has published the cohort with the longest follow-up, at a median of 107 months [12]. These patients were selected on the basis of chemosensitive disease and were conditioned with a combination of fludarabine (90 mg/m^2), cyclophosphamide (2,250 mg/m^2), and rituximab (FCR). GVHD prophylaxis consisted of tacrolimus and methotrexate, with anti-thymocyte globulin (ATG) added for patients who had unrelated donors. The exact dosage and form of ATG administered is unclear; the authors variously describe 15 mg/kg equine ATG on days −5 through −3 [13], and 1 mg/kg rabbit ATG on days −2 and −1 [12]. Virtually all patients conditioned with FCR had HLA-identical sibling donors (45 of 47). While 38% of patients were in complete remission going into allogeneic HCT, all patients achieved a complete remission after allogeneic HCT, and only 3 subsequent relapses were seen. At a median of 11 years of follow-up, the overall and progression-free survivals were 78% and 72%, respectively. Extensive chronic GVHD was seen in 40% of patients.

These results are very impressive, although they should be understood in the context of several caveats. This approach was restricted to patients with chemosensitive disease, and almost entirely to those with HLA-identical related donors, thus selecting a group of patients with a favorable prognosis at baseline. Additionally, allogeneic HCT was performed very early in the disease course, after a median of 3 prior lines of treatment. In such populations, FCR alone is a highly active regimen, producing median progression-free survivals of 4

years or more [14]. The differential contribution of allogeneic HCT in this selected good-risk patient population is undoubtedly real, but these caveats should be borne in mind when generalizing these results. Based on the impressive results of the M.D. Anderson studies, a multi-center BMT-CTN trial is ongoing to confirm these findings.

The M.D. Anderson group also studied radioisotope-based conditioning for patients with chemorefractory indolent NHL, enrolling 26 patients and conditioning them with yttrium-90 (^{90}Y)-ibritumomab tiuxetan in combination with fludarabine, cyclophosphamide, and rituximab [14]. With 3 years of median follow-up, overall and progression-free survivals were 88% and 85%, respectively. No difference in survival or relapse was seen between patients with chemosensitive vs. chemorefractory disease with this approach, suggesting that it may be a useful intensification of the conditioning regimen for patients with chemorefractory indolent NHL.

Our group at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle reported on outcomes with a non-myeloablative regimen consisting of 2 Gy total body irradiation and fludarabine 90 mg/m^2 [15]. This regimen is designed to have minimal toxicity but also carries very limited anti-tumor efficacy, relying instead on immunologic GVL for disease control. Patients in our cohort were heavily pre-treated, with a median of 6 lines of prior treatment before allogeneic HCT. Only 63% had chemosensitive disease at the time of transplant. At 3 years, overall and progression-free survivals for patients with indolent NHL were 52% and 43%, respectively, and extensive chronic GVHD was seen in 47% of patients. For the subset of patients with indolent NHL and HLA-identical related donors, overall and progression-free survivals were somewhat better at 67% and 54%, respectively. Relapse was uncommon, occurring in only 14% of patients with indolent NHL despite the presence of pre-transplant bulky disease and chemotherapy resistance in many patients. These results demonstrate that allogeneic HCT can be an effective “last resort”, salvaging approximately 50% of patients even after extensive pre-treatment and chemotherapy resistance.

Investigators at FHCRC have also described the use of radioisotope-based conditioning and allogeneic HCT to treat high-risk lymphomas. Using a regimen of ^{90}Y-ibritumomab tiuxetan followed by fludarabine and low-dose TBI, responses were seen in 15 of 18 (83%) of patients with indolent NHL [16]. Taken together with the results published by the M.D. Anderson group [12] and others [17], these findings suggest that radioisotope-based conditioning may be appropriate for patients with bulky or chemorefractory indolent NHL.

The U.K. group reported a large series of 82 patients transplanted using in vivo T-cell depletion with fludarabine 150 mg/m^2, melphalan 140 mg/m^2, and alemtuzumab [18]. Thirteen patients received post-transplant donor lymphocyte infusions (DLI) for relapsed lymphoma, while 28 received DLI for persistent mixed donor chimerism. In keeping with general observations of T-cell-depleted approaches, extensive chronic GVHD was low at 18%, but relapse was slightly higher than in other studies at 26%. Overall and progression-free survivals at 4 years were identical at 76%.

The GELTAMO group reported the results of two prospective multicenter trials testing reduced-intensity conditioning with fludarabine (125–150 mg/m^2) and melphalan (80–140

mg/m^2) followed by allogeneic HCT for follicular lymphoma [19]. This group reported a low relapse rate of 8%, in keeping with other groups' findings, but noted a relatively high rate of TRM (37%), particularly in patients with progressive disease at the time of allogeneic HCT. Overall survivals at 4 years were 71%, 48% and 29% for patients who were in complete remission, partial remission, or relapse at the time of allogeneic HCT, underscoring the importance of chemosensitivity as a prognostic factor in this setting. Extensive chronic GVHD was seen in 42% of patients.

The CALGB similarly tested a reduced-intensity conditioning regimen of cyclophosphamide (3 g/m^2) and fludarabine (125 mg/m^2) followed by allogeneic HCT in a group of patients with indolent B-cell malignancies, including follicular NHL and chronic lymphocytic leukemia [20]. Like the M.D. Anderson trial, the CALGB study enrolled favorable-risk patients: the study population was transplanted early in their disease course (after a median of 2 prior treatment regimens) and exclusively from HLA-identical sibling donors. At 3 years, TRM was low at 9%, while progression-free and overall survivals were high at 75% and 81%, respectively, in patients with follicular NHL. Extensive chronic GVHD was relatively rare, occurring in 18% of patients. These results confirm the observation by the M.D. Anderson group that reduced-intensity allogeneic HCT can produce very good disease-free survival in selected favorable-risk patients with indolent NHL. However, as with the M.D. Anderson results, the 81% overall survival at 4 years should be interpreted in the context of the expected survival with conventional chemotherapy early in the course of indolent NHL, where regimens such as FCR can consistently produce 4-year median progression-free survival without GVHD or other transplant-associated risks [14].

COMMON THEMES IN THE LITERATURE

The literature on allogeneic HCT for indolent NHL consists of a number of prospective clinical trials testing a variety of transplant approaches and enrolling varying patient populations. However, a number of common themes emerge from the literature:

1. *Reduced-intensity conditioning approaches are superior to myeloablative approaches*. Myeloablative conditioning not only excludes the majority of patients with indolent NHL by virtue of their advanced age, but carries a prohibitive risk of TRM even in selected younger and healthier patients. While myeloablative allogeneic HCT may be considered for patients with indolent NHL in the setting of clinical trials or unusual individual circumstances, most patients will be best served with reduced-intensity approaches. For patients with bulky or rapidly progressive disease who require substantial cytoreduction before allogeneic HCT, either tandem autologous/allogeneic HCT or radioisotope-based conditioning are likely to be better options than myeloablative allogeneic HCT.
2. *The relapse rate after allogeneic HCT is low*. Of all the indications for allogeneic HCT, indolent NHL appears to be the most sensitive to the immunologic GVL effect [21;22]. Reported relapse rates are typically <10% for good-risk patients undergoing allogeneic HCT, and no higher than 14% even for patients with higher risk disease. The exception is with T-cell-depleting conditioning such as alemtuzumab-based regimens, but even in this setting the relapse rate is reported to

be 26%, which compares favorably with relapse risk after allogeneic HCT for acute leukemias or aggressive NHL. Whether the low relapse rate is due to the indolent nature of the malignancy (allowing time for GVL effects to gain kinetic superiority) or because of biological factors inherent to indolent NHL, it is clear that allogeneic HCT is highly effective in controlling and eradicating even advanced and chemorefractory indolent NHL.

3. *Chemosensitivity is an important prognostic factor.* The published literature consistently indicates that patients with chemosensitive disease at the time of transplant have superior outcomes. Some trials go so far as to exclude patients with chemorefractory disease in recognition of this finding. While durable disease control can be seen after allogeneic HCT even in patients with chemorefractory disease, such patients may be best treated with more intensive investigational approaches such as radioisotope-based conditioning or tandem autologous/ allogeneic HCT.

4. *Transplant-related complications are the major cause of treatment failure*. In this population, lymphoma relapse after allogeneic HCT is uncommon, and most treatment failures stem from GVHD, infection, or other transplant-related toxicities. Thus, the most effective way to improve the utility of allogeneic HCT in indolent NHL will be to make transplantation safer by reducing these complications. Space limitations preclude a review of current investigational approaches to preventing GVHD and reducing TRM, but it is important to recognize that as transplants become safer, the role for allogeneic HCT in indolent NHL will likely expand significantly. In addition, extensive chronic GVHD is consistently reported in approximately 35–50% of patients (with the exception of lower rates with T-cell depletion), and the impact of this complication on survivors' quality of life must be considered along with the crude survival statistics.

5. *The optimal timing of allogeneic HCT is a major unresolved issue*. The published literature indicates that the best results with allogeneic HCT are obtained when patients are transplanted early in their disease course [12;20]. However, allogeneic HCT remains a viable and effective "last resort" as well [15]. As patients may obtain prolonged complete remissions with standard therapy, early allogeneic HCT is a controversial approach as it exposes patients to the risk of GVHD and other transplant-related complications. One could make the case for early allogeneic HCT on the basis of the M.D. Anderson and CALGB results, arguing that patients may wish to accept the risk of transplant-related complications in return for a higher chance of long-term cure. On the other hand, one could argue on the basis of the Seattle results that allogeneic HCT should be reserved for a "last resort", as this approach delays exposing patients to chronic GVHD and other transplant-associated risks. Complicating the picture is the specter of histologic transformation; with a "last resort" approach to allogeneic HCT, patients run the risk of transforming to an aggressive NHL, which carries a poor prognosis even with allogeneic HCT [15]. Finally, the impact of novel, highly effective targeted therapies for indolent NHL such as ibrutinib on the timing and outcomes of allogeneic HCT remains to be seen.

CONCLUSION

Given the above published literature, we believe that patients with indolent NHL should be referred to a transplant center early in their disease course for a discussion of the risks and benefits of allogeneic HCT. It should be emphasized that of all malignant indications for allogeneic HCT, indolent NHL is the condition which responds best to this approach. Allogeneic HCT is a highly effective treatment for indolent NHL, and in fact is arguably the only curative approach to these diseases. However, patients should be counseled that allogeneic HCT involves significant risks, particularly that of chronic GVHD, which are not attached to conventional chemotherapy.

The decision to undergo allogeneic HCT involves a trade-off between the higher short-term risk of morbidity and mortality vs. the better long-term odds of disease-free survival. We believe that there are multiple reasonable approaches to the timing of allogeneic HCT, based on available data: early transplantation is justified based on the M.D. Anderson and CALGB results, while the Seattle results justify reserving allotransplantation for the point where conventional options are exhausted. Given the uncertainties surrounding the decision, patient preferences and values should be the deciding factor in those patients with indolent NHL who are suitable candidates for allogeneic HCT. As further advances make allogeneic HCT safer by reducing GVHD and transplant-related complications, the risk-benefit ratio in indolent NHL is likely to tilt further in favor of early and widespread use of allogeneic HCT given the highly potent GVL effect in this disease setting. Additional research may help clarify the optimal way to incorporate novel targeted therapies with allogeneic HCT to further improve outcomes.

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KEY POINTS

- Reduced-intensity allogeneic hematopoietic cell transplantation is highly effective against indolent non-Hodgkin lymphoma, producing excellent long-term disease-free survival.
- Chemosensitivity is a major prognostic factor for patients undergoing allogeneic HCT for indolent NHL.
- The optimal timing of allogeneic HCT in indolent NHL is a major area of uncertainty; both early and late transplantation are arguably reasonable approaches, and informed patient preferences are often the deciding factor.