Hematopoietic Stem Cell Transplantation for Non-Hodgkin’s Lymphoma

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High-dose myeloablative therapy with autologous or allogeneic stem cell rescue is an effective treatment strategy for non-Hodgkin's lymphoma (NHL), but NHL is much less likely to stay in remission after an autologous transplant than after an allogeneic transplant. The benefit of undergoing an autologous transplant earlier in the course of the disease, especially for patients who present with intermediate or high scores on the International Prognostic Index of risk factors, is still unclear. The addition of immunotherapy, biologic modifiers, and antibody therapy such as rituximab (Rituxan) or radiolabeled antibody to the autologous transplant are approaches undergoing evaluation. Historically, there has been a high regimen-related mortality rate associated with myeloablative allogeneic transplant that has made this approach a less appealing option for therapy. The use of nonmyeloablative allogeneic transplants as treatment for NHL is less well studied and remains to be defined.

For clinicians, the most practical way to approach the treatment of non-Hodgkin's lymphoma is based on the clinical behavior of the disease. Hematopoietic stem cell transplantation (HSCT) has been the backbone of the therapeutic options for treating aggressive (intermediate- and high-risk) disease that has relapsed or does not respond to initial therapy. Its role in the treatment of indolent lymphomas has been more commonly applied in patients with multiply relapsed or refractory disease. In some cases, such as chemotherapy-sensitive, relapsed aggressive NHL, HSCT results in a durable remission and is superior to conventional salvage therapy.[1,2] There may be a role, however, for an earlier HSCT in patients with poor prognostic factors at the time of initial diagnosis. In this review, we will summarize the treatment of indolent and aggressive NHL with HSCT and comment on the evolving role of new hematopoietic stem cell transplant-based therapies.

Indolent Non-Hodgkin’s Lymphoma

The role of HSCT in treating indolent lymphoma has been limited not only by the heterogeneity of the disease and its chronicity with many long-term survivors, but also by high rates of transplant-related mortality with allogeneic HSCT and high rates of relapse after autologous HSCT.

Autologous Transplants

Autologous transplants in this setting have an observed regimen-related toxicity rate that is similar to that seen with other HSCT-treated diseases. In most cases, the regimen-related mortality rate is about 5% to 10%. However, most published studies report a continual relapse rate with no obvious plateau in the survival curves. Thus, autologous HSCT is not curative therapy for the majority of indolent lymphomas treated with current regimens.[3,4] Relapses are thought to be due to both the inability to eradicate the tumor cells and tumor contamination of the infused stem cell product.

In Vitro Purging in Autologous Transplantation

Numerous groups, including Freedman et al,[5] have reported that patients who receive autologous grafts that are not contaminated with lymphoma cells by polymerase chain reaction (PCR) analysis have a statistically higher initial disease-free survival rate, compared to patients with PCR-contaminated stem cells. As a result, considerable effort has gone into studying the best way to purge grafts of tumor contaminant cells. The earliest such studies centered on positive selection of CD34 cells. Other approaches have focused on tumor elimination by antitumor antibodies and complement or chemotherapy exposure with drugs such as 4-hydroperoxycyclophosphamide or mafosfamide. Initially, improved disease-free survival was reported in patients who underwent autologous bone marrow purging with a cocktail of anti-B cell monoclonal antibodies.[6] Greater than a 3 log depletion of follicular lymphoma cells was achieved, and no lymphoma cells could be detected in 50% of treated patients. Patients who had PCR-detected residual lymphoma cells in their stem cell product were initially more likely to relapse posttransplant, with a relapse rate of 39% (vs 5% in PCR-negative patients) after a median follow-up of 23 months (P In Vivo Purging in Autologous Transplantation

Recently, interest has focused on in vivo purging. Antibodies such as rituximab (Rituxan), given prior to high-dose chemotherapy, appear to increase the sensitivity of lymphoma cells to chemotherapy. Rituximab has been studied by numerous investigators, in many cases administered with[4]
mobilization regimens for collecting peripheral blood stem cells (PBSC) in mantle cell and indolent NHL patients.[10-12] In a small pilot study, Magini et al[11] showed that 93% of patients receiving rituximab with chemotherapy had a PCR-negative stem cell graft, compared to 40% of control cases. When granulocyte colonystimulating factor (G-CSF, Neupogen) alone is used for mobilization of PBSC with rituximab, two more doses of rituximab should be given before PBSC collection to get the least contaminated product. Thus, several groups have shown that rituximab can render a stem cell product free of contaminating tumor cells by PCR while having no adverse effects on the collection of an adequate number of stem cells or on engraftment posttransplant. Rituximab has also been administered post-HSCT. Brugger et al[13] treated patients with follicular and mantle cell NHL with four weekly doses of rituximab after autologous HSCT. Following total-body irradiation and high-dose chemotherapy, the complete response rate was 44%, and after the addition of rituximab to the transplant regimen, this rate initially increased to 57% and continued to improve over time. By 1 year, it was 88%, and by 2 years, all follicular NHL patients and 90% of mantle cell lymphoma patients were in complete remission. Following high-dose therapy, 48% of evaluable patients had no evidence of disease by PCR. Immediately after rituximab therapy, this parameter improved to 80%, and at 6 months posttransplant, it was 100%. Leukopenia and infections were reported. Horwitz et al[14] studied the administration of rituximab alone posttransplant in more aggressive NHL or transformed B cell NHL, reporting grade 3/4 neutropenia in 9 of 20 patients. Flinn et al[10] also reported late infection problems, with three deaths in the first year posttransplant as well as neutropenia, disseminated herpes zoster, and atypical mycobacterial infections. Thus, rituximab therapy appears to be deliverable with good results in this setting. However, increasing evidence suggests that some patients (at least 25% to 45%)[10,13,14] also develop transient neutropenia after transplant, and there may be an increased risk of infection. Randomized controlled studies of rituximab use in an autologous transplant setting are lacking. In the future, other antibodies such as CD22 and CD40 will be similarly studied. It may be that the most effective therapy will involve a combination of antibodies, similar to what has been reported for in vitro purging. **Targeted Therapy in Autologous Transplants**

Another area of active research has been to give targeted therapy, ie, using radiolabeled antibody, combined with chemotherapy and followed by autologous stem cell rescue. This targeted radiotherapy is based on the fact that hematologic malignancies are sensitive to radiation. In addition, the antibody is not internalized, nor does it need to activate an immune response to generate an antitumor effect. Based on the isotope tagged to the antibody and its penetration, the radiolabeled antibody does not need to reach every malignant cell for it to be effective. Different radiolabeled antibodies to anti-CD20 have been used in an autologous transplant setting.[15-19] In a phase I/II study of iodine-131 tositumomab (anti-CD20, Bexxar), etoposide, and cyclophosphamide (Cytoxan, Neosar), Press et al[17] reported that the maximum tolerated dose of the anti-CD20 monoclonal antibody was 25 Gy, with etoposide, 60 mg/kg, and cyclophosphamide, 100 mg/kg. The reported time to engraftment and toxicity data were similar to historical results with total-body radiation, etoposide, and cyclophosphamide therapy. Overall survival at 2 years was 83%, and the progression-free survival rate at 2 years was 68%. Approximately 21% developed a human antimurine antibody. The results have been encouraging, but which radioisotope and regimen will prove to be the most effective and practical to deliver remains unknown. Many of the radiolabeled antibody studies published to date have been restrictive in their eligibility requirements, for example, requiring no evidence of enlarged spleen and low tumor burden of no more than 500 cc. Randomized studies are needed to show an increased benefit in patients, for example, with increased survival and disease-free survival associated with the radiolabeled antibody-containing regimens. Longterm follow-up is also needed to address the issue of whether secondary malignancies are more likely to occur with intensified radiolabeled targeted therapy. **Unique Problems With Autologous Transplant**

Unique issues arise with respect to transplanting low-grade lymphoma. Fludarabine (Fludara) is commonly used as conventional therapy to treat the disease, and its use may affect the ability to mobilize stem cells.[20] Autologous transplants are also problematic in this setting, given the high rate of secondary cancers reported, including myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML), for which incidence rates are as high as 20%.[9,21] **Timing of Autologous Transplant**

Recently, investigators have placed much emphasis on moving autologous HSCT up earlier in patients with poor prognostic factors. Colombat et al[22] treated 29 patients, with 7 in first complete remission at a median follow-up of 6 years. The overall survival was 64%, and the actuarial event-free survival was 55%. Tarella et al[23] treated 46 patients with advanced low-grade NHL;
had small lymphocytic lymphoma, 29 had follicular lymphoma, and 10 also had histologic transformation. Patients received tumor debulking by two courses of APO (doxorubicin [Adriamycin], prednisone, vincristine [Oncovin], methotrexate, asparaginase [Elspar], mercaptopurine [Purinethol]) and two courses of DHAP (dexamethasone, high-dose cytarabine [Ara-C], cisplatin [Platinol]), sequential administration of highdose etopoide, methotrexate, and cyclophosphamide with stem cell harvest, and high-dose mitoxantrone (Novantrone) and melphalan (Alkeran) with PBSC infusion. Ten follicular lymphoma patients had ex vivo purging of stem cells. At a median follow-up of 4.3 years, the estimated 9-year overall survival was 84% and progression-free survival was 45%. Follicular lymphoma patients had longer survival without evidence of disease-59% vs 17% for small lymphocytic lymphoma patients. These results indicate that there may be longer progression-free survival after autologous transplant if it is part of the up-front therapy. Thus, we need to address the issue of whether a randomized study should be conducted in patients with intermediate and high scores on the International Prognostic Index (IPI) of risk factors, comparing the addition of a front-line autologous HSCT after conventional therapy. Indeed, front-line autologous transplant may be very relevant for the long-term benefit of patients. As oncologists, we tend to treat patients with multiple cycles of different therapeutic regimens and have in the past relied heavily on alkylating agents. As we treat patients more intensely for longer periods of time, we can expect to see more secondary cancers-especially MDS/AML. The use of autologous transplant upfront and the decreasing use of multiple regimens of therapy initially may prolong the time to the development of MDS. If we conduct such studies in the future, we need to use molecular correlating studies (eg, microarray assays) to help identify patients that do benefit from upfront transplants.

**Immunotherapy and Biologic Modifier Therapy After Autologous Transplant**

Indolent NHL may be a better target for immunotherapy approaches, in both autologous and allogeneic settings. Several different approaches are being used to study the addition of immunotherapy to an autologous transplant to reduce relapse rates. These strategies include treatment with immune stimulators such as dose-intensive interleukin-2 (IL-2, Proleukin) therapy,[24] IL-2-incubated stem cells with sequential IL-2,[25,26] and low-dose IL-2 with or without rituximab.[27] In indolent lymphoma, vaccination with idiotypespecific vaccines after transplant is an alternative approach to be further studied. Again, no randomized studies have shown evidence of efficacy with immunotherapy in this setting, but the randomized Southwest Oncology Group study of dose-intense IL-2 after an autologous transplant is still ongoing. Other biologic modifiers such as bcl-2 antisense for maintenance therapy after autologous transplant also need to be investigated.

**Myeloablative and Nonmyeloablative Allogeneic Transplants**

Allogeneic transplants offer the advantage of a "clean" stem cell product and a graft-vs-lymphoma effect. With a myeloablative allogeneic transplant, there is the risk of developing graft-vs-host disease (GVHD) and a high regimen-related mortality rate. International Bone Marrow Transplant Registry data for myeloablative regimens shows a transplantrelated mortality rate of 40% to 50%, with an event-free survival rate of 49%. The high regimen-related mortality rate has limited the use of myeloablative allogeneic transplants. It should be noted, however, that there is a plateau in survival in these allogeneic transplant recipients. Because of the high associated upfront mortality rate, myeloablative allogeneic transplants have never shown a survival advantage. In particular, patients with a history of multiple therapeutic regimens also seem to have an increased risk of complications. T-cell depletion or antithymocyte globulin (Thymoglobulin) therapy is being used by many centers to cut down on GVHD incidence, but these approaches usually result in higher relapse rates and may not be the answer unless further manipulations of the stem cell infusion allow us to safely and effectively separate the cells that cause GVHD from those that provide the graft-vs-lymphoma effect. The intent of myeloablative allogeneic transplant is to use high-dose therapy to help eradicate the underlying disease, prevent graft rejection, and produce a graft-vs-lymphoma response to maintain disease control. In indolent NHL, a graft-vs-lymphoma effect is documented by lower relapse rates after an allogeneic transplant and by the evidence of tumor control by infusion of donor lymphocyte cells following a myeloablative transplant. Thus, if the risk associated with a myeloablative allogeneic transplant can be lowered, the lower risk for disease progression may eventually lead to a superior outcome. The source of donor stem cells appears to make a difference in initial mortality rates, with PBSC being superior to bone marrow.[28]

Alternatively, nonmyeloablative transplants have been studied based on the theory that the most important part of an allogeneic transplant is the donor cell graft-vs-lymphoma effect. Khouri et al[29] treated 15 patients, 11 of whom had engraftment of donor cells and 8 of the 11 who achieved a complete remission. Five of six patients (83.3%) with chemotherapysensitive disease have survived, compared with two of nine (22.2%) with refractory or untested disease ($P = .04$). Thus, patients with...
lower tumor burden and chemotherapy-sensitive disease may be more effectively treated with a nonmyeloablative approach and have the longest duration of responses. However, caution is needed in selecting patients for nonmyeloablative therapy. In many diseases, higher doses of radiation and chemotherapy have been associated with a reduced risk of relapse.[30] Nonmyeloablative therapy probably needs to be considered mainly in patients with a diagnosis that is very sensitive to the graft-vs-lymphoma effect, older patients, and patients with comorbid medical problems. Indolent NHL may be a good target for reduced-intensity nonmyeloablative allogeneic stem cell transplant.[31] Tandem transplants with autologous transplant followed by nonmyeloablative allogeneic transplant has also been studied.[32] In one trial, 11 of 13 patients achieved a complete response postallograft, including 9 patients with a partial response after the autograft. Seven also received additional donor lymphocytes. Seven patients developed acute GVHD (grade 2-4) and two developed chronic extensive disease. Between 210 and 340 days postallografting, 2 patients have relapsed, 10 are alive, and 5 are in complete remission. Five have died-two from GVHD and progressive disease, two from GVHD and infection, and one from disease progression. Chronic Graft-vs-Host Disease Chronic GVHD will remain a problem after a nonmyeloablative transplant. It therefore behooves us to remember that in a myeloablative setting, significant chronic GVHD is associated with a 50% nonrelapse mortality rate.[33] The pathophysiology of GVHD is poorly understood and needs to be further studied. The identity of the antigenic targets for the immune reactive cells have not been well clarified; nor is it clear which populations of cells mediate the ongoing immune responses seen in chronic GVHD. In a coisogenic murine model, T cells from donor mice transplanted into mice with only a three-amino acid difference in their Dr molecule developed chronic GVHD.[34] Some investigators believe that recipient alloantigens provide the stimulus for the graft-derived T cells that have already undergone selection and maturation in the donor thymus environment, causing GVHD. Alternative explanations have included flawed T-cell reconstitution, dominant autoantigens driving the system, and improper thymic selection of de novo donor cells undergoing maturation in the new host that does not result in tolerance. Many of our therapies for chronic GVHD, though, only control disease but do not delete the pathogenic clone. The incidence of GVHD appears to be similar between nonmyeloablative and myeloablative transplant recipients, although long-term follow-up is lacking.[35] Older patients have decreased thymus function, and thus, as we age we generate an environment more conducive to the development of chronic GVHD. The preferred source for nonmyeloablative transplants studies are PBSCs, which are associated with a higher risk of developing chronic GVHD, a longer disease duration, and a greater amount of therapy required to treat GVHD.[36] Also, many nonmyeloablative transplants depend on additional donor lymphocyte infusions for disease control. In general, 80% of patients who receive donor lymphocytes and respond develop GVHD. Better understanding of graft selection and the mechanism of chronic GVHD, as well as alternative approaches to treating GVHD that do not affect lymphoma control, are needed. Optimizing Allogeneic Transplant Therapy Interest is also beginning to focus on optimizing immune responses against lymphoma cells in an allogeneic transplant. Numerous laboratories are studying the generation of minor histocompatible antigen-specific clones to treat residual disease after allogeneic transplant for a hematologic malignancy. However, the concept of using restricted antigenspecific T-cell clones as effective treatment after transplant may be flawed. The reason that the graft-vs-tumor effect is so prominent in an allogeneic setting most likely is due to its polyclonal recognition of tumor cells that results in disease control. Limited recognition of tumor cells by antigen-specific clones will most likely lead to escape of recognition of the tumor cells by various mechanisms, and will not result in effective long-term disease control. Further investigation of the ability to amplify the polyclonal tumor response after an allogeneic transplant, to prevent relapse and to determine which patients require this intervention, needs to be undertaken. In addition, what is lacking in humans is the ability to separate the cells that cause GVHD from the cells that cause a graft-vs-tumor effect, and we need to study the differences in the antigen recognition repertoire of these cells. Summary The optimal therapy for indolent lymphoma and the timing of various transplant entities remains unclear. It is conceivable that early autologous transplant for patients with intermediate and poor IPI risk factors may maximize survival and quality of life, with nonmyeloablative allogeneic transplants being left to later, when disease recours. Quality of life in patients with chronic GVHD is poorly studied in the setting of nonmyeloablative transplants, and for patients with indolent NHL, quality of life is more of an issue early in the disease than disease eradication, thus making this type of approach an interesting one for investigation in future randomized trials. Indolent disease is more likely to be a good target for nonmyeloablative immunotherapy than aggressive disease that will quickly outgrow the ability of the immune system to control it. How much bulky low-grade NHL tumor burden patients
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It is well established that in chemotherapy-sensitive relapsed aggressive NHL, autologous HSCT results in durable remissions and is superior to conventional salvage therapy.[1,2] Mantle cell NHL, although considered an aggressive form of the disease, could probably be categorized as both indolent and aggressive. In general, it is well accepted that an autologous transplant is reasonable consolidation therapy for mantle cell patients in first complete remission. In meta-analysis, the addition of rituximab has also been shown to increase overall and disease-free survival with limited follow-up, and thus, has become the standard of therapy to incorporate with an autologous transplant in mantle cell patients. The addition of radiolabeled anti-CD20 to a cyclophosphamide and etoposide conditioning regimen has resulted in encouraging initial response rates for patients with persistent mantle cell disease.[37] Non-Mantle Cell NHL

Upfront autologous transplant, as outlined by Cabellero et al,[38] has been studied in diffuse large cell NHL. In this study, 42% of patients received stem cell transplants in first complete response, 19% in second complete response, and 47% with active disease. Moreover, 35% had disease sensitive to chemotherapy, and 12% had chemotherapy-refractory disease. The estimated overall and disease-free survival rates at 5 years were 53% and 43%, respectively, and the transplant-associated mortality rate was 11%. By multivariate analysis, the following variables significantly affected overall and diseasefree survival rates: the number of regimens to reach first complete remission and disease status at transplant. Total-body irradiation in conditioning regimens had an adverse effect on survival and age-adjusted IPI scores also affected disease-free survival. However, in terms of transplanting non-mantle cell, aggressive NHL patients in first complete remission, the role of autologous HSCT remains controversial. Several recently published randomized studies and prospective trials have compared upfront HSCT to standard therapy in poor-prognosis patients in first complete or partial remission.[39-43] These studies differed in their design and conclusions. Gianni et al[39] reported much early toxicity in the transplant arm. Although differences could not be accurately measured due to the study's crossover design, event-free survival in the initial transplant arm was 76% compared with 49% in the nontransplant arm (P = .004). Haoiun et al[40] did not at first show any differences in overall or disease-free survival, but their retrospective analysis showed that patients with an IPI score of 2 or 3 who underwent HSCT had a better outcome, with a disease-free survival rate of 55% vs 39%, and an overall survival rate of 64% vs 49% (P = .4) at 8 years. Kluin-Nelemans et al[42] compared eight cycles of CHOP (cyclophosphamide, doxorubicin HCl, vincristine, prednisone) to six cycles of CHOP plus BEAC (carmustine [BCNU], etoposide, cytarabine, cyclophosphamide) and found no difference in outcome. Most patients in the study by the European Organization for Research and Treatment of Cancer had favorable IPI scores. Other studies that contained a shortened induction regimen before transplant have failed to show an advantage. Taken together, these results would seem to suggest that patients need to receive standard induction chemotherapy for diffuse large cell NHL before an autologous transplant. Patients with poor IPI risk factors at initial diagnosis of diffuse large cell NHL may benefit from front-line HSCT. On the other hand, patients who present with favorable IPI factors should not undergo an upfront autologous HSCT, but rather, should wait until first relapse. With respect specifically to adult Burkitt's and Burkitt's-like NHL, a retrospective analysis of 117 patients in Europe showed that 70 patients received an autologous transplant in first complete remission.[44] The major factor predicting for outcome after transplant was disease status at time of transplant. The 3-year actuarial survival was 72% for patients in first complete remission, compared to 36% for patients transplanted with chemosensitive relapse and 7% for chemorefractory disease. As more dose-intense therapy has become the norm for treating newly diagnosed adult Burkitt's and Burkitt's-like NHL, a randomized study comparing outcome after transplant in first complete remission to these newer dose-intense regimens is needed. Other Autologous Transplant Strategies

Tandem autologous transplants have also been assessed to see if they will increase response rates.[45] The addition of radiolabeled antibody,[17-19] immunotherapy (eg, dose-intense IL-2, IL-2-incubated PBSC, IL-2 and rituximab, and rituximab alone), and antigen-specific therapy (eg, Epstein-Barr virus-driven T-cells clones) to conditioning regimens are also being studied. Biologic modifiers such as bcl-2 antisense will also be studied for maintenance therapy after an autologous transplant. Myeloablative and Nonmyeloablative Allogeneic Transplants

The role of myeloablative allogeneic transplant in aggressive NHL has limitations similar to those discussed in the indolent NHL section. The lower relapse rates but still high mortality rates
associated with myeloablative regimens have limited their use to patients whose stem cells cannot be collected for an autologous transplant and patients with chemorefractory disease. Many physicians believe that a total-body irradiation-containing allogeneic myeloablative regimen for chemorefractory disease may be more effective than a chemotherapy-only regimen. The use of nonmyeloablative transplants in this setting has been less studied. Aggressive non-mantle cell NHL may not be the best candidate for nonmyeloablative therapy. Intermediate-grade NHL historically has been thought to be only moderately sensitive to an allogeneic graft-vs-lymphoma effect. Allogeneic transplants have resulted in fewer relapses than an autologous or syngeneic transplant, but response to donor lymphocytes is less common and more transient in intermediate NHL. Highgrade lymphomas such as Burkitt’s, Burkitt’s like, and immunoblastic NHL appear to be more insensitive to a graft-vs-lymphoma effect, as they grow rapidly and may lack adequate ability to cause an immune response. Thus, high-grade NHL patients will benefit more from a myeloablative allogeneic transplant than a nonmyeloablative approach and, if medically stable, should not be offered the nonmyeloablative therapy. **Diffuse NHL**

Diffuse NHL patients may be an appropriate group in which to study the tandem transplant approach, with an autologous transplant first for tumor control followed by a nonmyeloablative allogeneic transplant. The problem remains, however, that at least 35% of diffuse NHL patients in first relapse with chemotherapy-sensitive disease are cured with an autologous transplant. To commit these patients to the risk of developing GVHD does not seem reasonable. What is needed is a better way to determine which patients will remain in the cured group with an autologous transplant. Certain indicators are inherently useful. For example, patients who relapse and then respond to salvage therapy with a complete response are more likely to stay in remission after an autologous transplant then patients with refractory disease. Thus, a better understanding of tumor markers is needed. It is hoped that this will emerge from the many ongoing molecular studies (eg, involving microarray assays), so that we can differentiate the various diffuse NHL patients and determine who is most likely to remain in remission after an autologous transplant alone. Until then, it is more reasonable to study a strategy of offering all patients with chemotherapy-sensitive diffuse NHL a standard autologous transplant and offering patients with persistent disease after the autologous transplant (who have an HLA-matched donor) a nonmyeloablative transplant.

Positron-emission tomography (PET) evaluation post-autologous transplant and PCR evaluation of bone marrow may help us determine which patients have persistent minimal disease that would benefit from a nonmyeloablative allogeneic transplant. We need to study whether the use of natural killer cells, donor lymphocytes sensitized to minor HLA tumor-associated antigens, amplification of the polyclonal tumor response after an allogeneic transplant, or vaccination strategies can improve the nonmyeloablative approach. Patients who are in complete remission after an autologous transplant should be followed and offered allogeneic therapy only at the time of disease progression. Until then, we need to explore how to decrease the toxicity of allogeneic transplants, to better control chronic GVHD, to determine which patients will benefit from a nonmyeloablative approach, and to maximize the allogeneic graft-vs-lymphoma effect.

**Conclusions**
The role of HSCT in the treatment of NHL is still evolving. Basic questions about when to incorporate HSCT early in the course of the disease remain unanswered. How to increase the benefit of autologous therapy through the addition of therapies such as immunotherapy, targeted radiolabeled antibody, antibody therapy, and biologic modifiers has yet to be established. Moreover, we need to explore how to decrease the toxicity of allogeneic transplants, to better control chronic GVHD, to determine which patients will benefit from a nonmyeloablative approach, and to maximize the allogeneic graft-vs-lymphoma effect.

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