Chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) has been standard treatment for aggressive non-Hodgkin’s lymphoma (NHL) since the early 1990s when it was shown that CHOP conferred long-term survival rates that were equivalent to those achieved with second- and third-generation regimens but with less toxicity.\(^1,2\) However, only 40 to 45 percent of patients with aggressive NHL are cured with CHOP, and the majority of patients either fail to attain a complete remission (CR) or relapse after a CR. Second-line (salvage) chemotherapy is curative in fewer than 15 percent of these patients.\(^3\)–\(^8\)

The dose-dependent sensitivity of leukemia and lymphoma cells to both radiotherapy\(^9,10\) and to certain chemotherapeutic agents,\(^11,12\) and the demonstration in animals that autologous bone marrow can restore hematopoiesis after lethal irradiation,\(^13\)–\(^15\) paved the way for the use of myeloablative or high-dose therapy (HDT) in patients with lymphoma that was resistant to standard doses of chemotherapy. Appelbaum and colleagues were the first to demonstrate that HDT could, in fact, confer long-term disease-free survival (DFS) to patients with lymphoma in whom standard-dose chemotherapy failed and that autologous bone marrow successfully restored hematopoiesis after such myeloablative therapy.\(^16\)–\(^17\)

High-dose therapy with autologous stem cell transplantation (ASCT) has been shown in a randomized trial to result in better overall survival (OS) and event-free survival (EFS) rates for patients with chemosensitive relapsed aggressive NHL when compared with standard-dose second-line chemotherapy.\(^18\) This has led to the widespread acceptance of HDT-ASCT as the treatment of choice for patients with relapsed or primary refractory chemosensitive aggressive NHL.\(^19\) Its use as up-front treatment for patients with poor-risk aggressive NHL is currently under investigation.

For patients with relapsed or primary refractory aggressive NHL, allogeneic transplantation confers higher remission rates than does autologous transplantation, but this benefit is offset by significant therapy-associated mortality, such that the overall outcome is similar to that following autologous transplantation.\(^20\) Autologous transplantation therefore remains the preferred strategy for the management of patients with relapsed or primary refractory aggressive NHL. Nonmyeloablative allogeneic transplantation may be associated with significantly less toxicity than is conventional allogeneic transplantation, but its efficacy and role have yet to be established.

This chapter reviews the theoretic and historical basis for both autologous and allogeneic transplantation, focusing on the pivotal clinical trials that have led to their current applications for the treatment of aggressive NHL. Issues concerning conditioning regimens, prognostic factors, and long-term toxicity as they relate to autologous transplantation are also reviewed. For the purposes of this discussion, we
restrict the use of the term “aggressive NHL” to mean diffuse large B-cell lymphoma; peripheral T-cell lymphoma, unspecified; and systemic anaplastic large cell lymphoma, as defined by the World Health Organization classification scheme. These entities include categories F through H in the Working Formulation classification, and categories D, E, I, and J are specifically excluded.

AUTOLOGOUS STEM CELL TRANSPLANTATION FOR AGGRESSIVE NON-HODGKIN’S LYMPHOMA

A seminal contribution of the early trials of HDT-ASCT for relapsed or primary refractory aggressive NHL was the observation that chemosensitivity to second-line therapy appeared to be the primary determinant of outcome. Patients with chemosensitive disease had a long-term DFS rate after HDT-ASCT of approximately 40 to 45 percent compared with approximately 10 to 15 percent for patients with disease that was resistant to second-line therapy (Figure 13–1). As a result, patients with disease resistant to second-line therapy generally are not offered HDT since their outcome is similar to that expected with standard-dose second-line therapy.

Relapsed Disease

A retrospective analysis performed by the Groupe d’Etudes des Lymphomes de l’Adulte (GELA) showed that patients with chemosensitive relapsed or primary refractory aggressive NHL had a better outcome if treated with HDT-ASCT than if treated with salvage chemotherapy alone. To overcome the biases implicit in retrospective studies or nonrandomized trials, the Parma study was designed to assess the true benefit of HDT-ASCT by randomizing patients with chemosensitive relapsed disease to either HDT or standard-dose second-line therapy. Two hundred fifteen patients with Working Formulation intermediate-grade (163 patients) or high-grade (52 patients) NHL in first or second relapse, without bone marrow involvement at relapse, underwent cytoreductive chemotherapy with two cycles of DHAP (dexamethasone, cytarabine, and cisplatin) to assess for chemosensitivity. One hundred twenty-five patients (58%) had chemosensitive disease and 109 of them were then randomized to either four additional courses of DHAP (54 patients) or to HDT-ASCT (55 patients). In both arms, involved-field radiotherapy (IFRT) was administered to sites of bulky disease. High-dose therapy consisted of BEAC (carmustine, etoposide, cytarabine, and cyclophosphamide), and the source of stem cells was bone marrow in all patients. With a median follow-up of 63 months, the EFS rates at 5 years were 12 percent and 46 percent for the conventional therapy and the HDT arms, respectively (p = .001) (Figure 13–2). The respective OS rates were 32 percent and 53 percent (p = .038). Thus, with a planned course of treatment consisting of second-line therapy followed by HDT-ASCT for only those patients with chemosensitive disease, approximately 25 percent of patients with relapsed aggressive NHL are expected to be cured.

Having confirmed the superiority of HDT over conventional salvage chemotherapy, the Parma study established HDT-ASCT as the standard of care for patients with chemosensitive relapsed aggressive NHL. It is important to note that all of the 109 patients randomized in this trial had attained a CR with prior anthracycline-based chemotherapy, and, therefore, none had primary refractory disease.
Primary Refractory Disease

Primary refractory disease has been variably defined as anything from a partial remission (PR) after a full course of primary (induction) therapy to stable or progressive disease after induction therapy. With respect to the response to second-line therapy, patients who achieve a PR with induction therapy appear to be indistinguishable from those whose disease is stable or progressing with induction therapy. As such, we consider primary refractory disease to mean the failure of a full course of induction chemotherapy to induce a CR, thereby including disease for which the response to induction therapy is partial, stable, or progressive.

In one of the earliest studies of HDT-ASCT to distinguish patients with primary refractory disease from those with relapsed disease, Philip and colleagues reported that no patient with primary refractory disease was disease-free beyond 1 year (see Figure 13–1). Consequently, patients with primary refractory aggressive NHL were long regarded as having a poor prognosis that could not be altered by HDT-ASCT. However, it is important to note that no patient with primary refractory disease in the aforementioned trial was sensitive to second-line chemotherapy, and in several subsequent trials, chemosensitivity was not routinely assessed.

Data from the American Bone Marrow Transplant Registry (ABMTR) and the Southwest Oncology Group suggest that patients with primary refractory disease do, in fact, benefit from HDT-ASCT, provided that their disease is sensitive to second-line therapy. In the ABMTR analysis, sensitivity to second-line therapy was the only variable that correlated with outcome; patients with chemosensitive primary refractory disease had a 3-year survival rate of 48 percent compared to 19 percent for patients with chemoresistant disease (p = .0002).

In addition to the lack of chemosensitivity determination, several other factors have confounded the interpretation of the results of HDT-ASCT trials for patients with primary refractory aggressive NHL. These have included inconsistent definitions of “primary refractory,” the inclusion of patients with various histologies and the grouping together of patients with relapsed and primary refractory disease for the purpose of survival analyses.

Investigators at the University of Toronto and our own group have both reported on the outcome of patients with chemosensitive primary refractory aggressive NHL. The response rate to second-line therapy in both studies was approximately 50 percent. For the patients who underwent transplantation, that is, those with chemosensitive disease, the 3-year EFS rate was 39 percent in the study by Prince and colleagues and 44.2 percent in our study, with respective 3-year OS rates of 51 percent and 52.5 percent. The results from these studies suggest that if chemosensitive disease can be demonstrated, then patients with primary refractory aggressive NHL derive equivalent benefit from HDT-ASCT as do patients with chemosensitive relapsed disease. As such, even in the absence of data from randomized trials, HDT-ASCT appears justified for these patients.

A lower response rate to second-line chemotherapy is one factor that distinguishes patients with primary refractory disease from those with relapsed disease. Among patients treated with ICE chemotherapy (ifosfamide, carboplatin, and etoposide), the relative risk for chemoresistance among patients with primary refractory disease, compared with patients with relapsed disease, was 2.7 (p = .001). In the series reported by Prince and colleagues, where most patients received DHAP or mini-BEAM (carmustine, etoposide, cytarabine, and melphalan)
as second-line therapy, 45.6 percent of patients had chemosensitive disease. This is in contrast to the 58 percent response rate observed among the patients with relapsed disease in the Parma study.18 Among patients with “primary progressive” aggressive NHL, which included patients with disease that relapsed within 90 days of achieving a CR to induction therapy, who were treated with a variety of second-line regimens, Josting and colleagues reported a response rate of only 15 percent.44 The reasons for this particularly poor response rate are not clear. Given these observations, it would be erroneous to conclude that the overall outcome of patients with primary refractory disease is similar to that of patients with disease that relapsed after a CR to induction therapy. It is only once chemosensitivity is attained that the two groups may be equated.

**Up-front HDT-ASCT for Patients with Poor-Risk Disease**

A natural consequence of the success of HDT-ASCT for relapsed or primary refractory disease was its evaluation as a part of the primary therapy for patients with poor-prognosis aggressive NHL. Central to the issue of up-front HDT-ASCT is the ability to reliably identify those patients in whom standard therapy is likely to fail. Prior to the advent of the international prognostic index (IPI) and its correlate, the age-adjusted IPI (AAIPI),45 a number of prognostic models comprised of patient-specific and disease-related factors had been developed to identify those patients with aggressive NHL who were destined to do poorly with standard therapy.46 Using such criteria to identify poor-prognosis individuals, Gulati and colleagues were the first to suggest that DFS could be improved significantly if HDT-ASCT was performed in first CR or PR.47 Similar encouraging results were obtained in a number of other pilot studies that used various criteria to identify poor-risk individuals for autologous transplantation in first CR or PR48,49 or after abbreviated chemotherapy.50,51

The promising results of these pilot studies formed the basis of several randomized trials that investigated the benefit of up-front HDT-ASCT for poor-risk individuals (Table 13–1).52–58 Having identified patients with poor-risk disease by criteria other than the IPI or AAIPI, these trials investigated various paradigms for up-front HDT-ASCT, namely, following a CR after a full-course of induction chemotherapy;52,53 following a full course of induction therapy, regardless of response;54 following a CR or PR after abbreviated standard-dose chemotherapy55 or abbreviated dose-intense chemotherapy;56,57 and following a “slow” response to induction chemotherapy.58 Although most of these trials did not demonstrate an advantage for up-front HDT-ASCT, subgroup analyses demonstrated that patients with high-intermediate or high-risk disease by the AAIPI (ie, those with two or three risk factors, respectively) did appear to benefit from up-front HDT-ASCT when it was administered after a full course of standard chemotherapy.53,54 Similarly, an advantage in EFS was observed in the trials by Gianni and colleagues56 and the GOELAMS (Groupe Ouest Est d’Etude des Lucenies et Autres Maladies du Sang),57 in which HDT-ASCT followed abbreviated dose-intense therapy. In both of these trials the majority of patients had two or three adverse factors of the AAIPI (83 and 55%, respectively).

The apparent benefit of HDT-ASCT for patients with high-intermediate and high-risk disease, whose long-term survival rate with standard chemotherapy is expected to be between 25 percent and 45 percent,45 prompted the use of HDT as part of the up-front treatment for these patients. Encouraging results have been obtained in phase II trials, wherein HDT was incorporated into the primary therapy of poor-risk patients as defined by the IPI (Table 13–2).59,60 Although both of these trials evaluated up-front HDT-ASCT, there were important differences in trial design. In the trial by Pettengel and colleagues,59 high-intermediate- and high-risk patients received HDT following an abbreviated course of V APEC-B intensified with ifosfamide and cytarabine. Nademanee and colleagues60 offered HDT to high-risk patients who achieved a CR or PR with conventional therapy and to high-intermediate-risk patients who achieved a PR with conventional therapy. Both trials demonstrated a marked improvement in both OS and DFS/EFS rates compared to historic controls, although the relative improvement appeared to be more pronounced in the trial by Nademanee and colleagues, in which patients underwent HDT after a full course of conventional therapy.60
The GELA LNH93-3 study is the only reported trial of patients randomized to HDT-ASCT based on poor risk as defined by the IPI. Patients with two or three risk factors of the AAIPI received either standard chemotherapy or an experimental investigative regimen over 42 days, followed by HDT-ASCT. Interim analysis demonstrated an inferior outcome for the HDT arm, and the study was stopped prematurely. At a median follow-up of 30 months, the 3-year survival rates for the conventional therapy and HDT arms were 63 percent and 47 percent, respectively. The reasons for poor outcome in the HDT arm are unclear, but they may be related to the relatively short duration of the induction therapy.

The results of these trials suggest that HDT is best used as an adjunct to full-course standard-dose

<table>
<thead>
<tr>
<th>Lead Author or Group</th>
<th>Histology</th>
<th>Adverse Features</th>
<th>Trial Design/Therapy</th>
<th>Outcomes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GELA52,53</td>
<td>IGL and HGL</td>
<td>Any 1 of ECOG PS 2–4; ≥ 2 ENS; bulk ≥ 10 cm; BM or CNS involvement; Burkitt’s or lymphoblastic lymphoma without BM/CNS involvement</td>
<td>Pts with CR after ACVB or NCVB randomized to: Sequential chemotherapy: methotrexate → ifosfamide → L-asparaginase → cytarabine vs HDT: methotrexate → cyclophosphamide/ carmustine/etoposide/ASCT</td>
<td>5-year DFS All pts: p = NS AAIPI 2–3: p = .02</td>
</tr>
<tr>
<td>NHLCSG54</td>
<td>IGL, IBL</td>
<td>Stage II, III, IV without BM involvement</td>
<td>Standard therapy: VACOP-B vs HDT: VACOP-B followed by BEAM/ASCT (all pts)</td>
<td>6-year DFS All pts: p = NS AAIPI 2–3: p = .008</td>
</tr>
<tr>
<td>EORTC55</td>
<td>IGL, IBL, Burkitt’s</td>
<td>IGL—stages II–IV HGL—stages IX, II–IV</td>
<td>Standard therapy: 6 cycles CHVmP/BV vs HDT: 3 cycles CHVmP/BV followed by BEAC/ASCT for responding patients</td>
<td>5-year TTP All pts: p = NS</td>
</tr>
<tr>
<td>Gianni56</td>
<td>IGL, IBL</td>
<td>Stages I–II, III, or IV, excluding T-cell lymphoma or BM+</td>
<td>Standard therapy: MACOP-B vs HDT: abbreviated dose-intense chemotherapy followed by melphalan/TBI/ASCT or melphalan/mitoxantrone/ASCT for responding patients</td>
<td>7-year OS (by ITT) All pts: p = .004</td>
</tr>
<tr>
<td>GOELAMS57</td>
<td>IGL, HGL</td>
<td>Stages II with bulky abdominal disease, III, IV</td>
<td>Standard therapy: CHOP × 8 vs HDT: CEEP × 2 → cytarabine/high-dose methotrexate → BEAM/ASCT</td>
<td>4-year EFS (by ITT) All pts: p = .03</td>
</tr>
<tr>
<td>Verdonck58</td>
<td>IGL, IBL</td>
<td>Stages II–IV with PR after 3 cycles of CHOP and BM–</td>
<td>Pts in PR after 3 cycles of CHOP randomized to: Standard therapy: CHOP × 5 vs HDT: CHOP × 1 → cyclophosphamide/ TBI/ASCT</td>
<td>4-year OS (by ITT) All pts: p = .12 AAIPI 2: p = .01 CR rates: p = NS 4-year EFS: p = NS 4-year OS: p = NS</td>
</tr>
</tbody>
</table>

HDT-ASCT = high-dose therapy with autologous stem cell transplantation; IPI = international prognostic index; IGL = intermediate-grade lymphoma; HGL = high-grade lymphoma; PS = performance status; ENS = extranodal sites; BM = bone marrow; CNS = central nervous system; Pts = patients; CR = complete remission; ACVB = doxorubicin, cyclophosphamide, vindesine, bleomycin; NCVB = mitoxantrone, cyclophosphamide, vindesine, bleomycin; DFS = disease-free survival; NS = not significant; AAIPI = age-adjusted IPI; IBL = immunoblastic lymphoma; VACOP-B = etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; BEAM = carmustine, etoposide, cytarabine, melphalan; OS = overall survival; CHVmP/BV = cyclophosphamide, doxorubicin, teniposide, prednisone, bleomycin, vincristine; BEAC = carmustine, etoposide, cytarabine, cyclophosphamide; TTP = time to progression; MACOP-B = methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; TBI = total-body irradiation; EFS = event-free survival; ITT = intention-to-treat; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CEEP = cyclophosphamide, epirubicin, vindesine, prednisone; PR = partial remission.

*Results for outcomes are presented in terms of survival benefit for patients who received HDT-ASCT.

†Adverse factors of the AAIPI: serum lactate dehydrogenase level greater than normal, ECOG PS greater than or equal to 2, and stage III/IV disease.
therapy and not as a substitute for the terminal portion of a standard regimen. A recently initiated intergroup trial is evaluating the utility of up-front transplantation for patients with aggressive NHL with two or three factors of the AAIPI (Figure 13–3).

Patients who achieve a CR or PR after five cycles of CHOP are randomly assigned to receive either three more cycles of CHOP or one more cycle of CHOP followed by HDT-ASCT. This trial should determine whether up-front transplantation for poor-prognosis patients confers a benefit when used to “consolidate” a response achieved with primary therapy.

### Conditioning Regimens

Transplantation of autologous or allogeneic stem cells rescues patients from the potentially lethal marrow aplasia induced by high-dose chemotherapy and/or radiotherapy, and it is therefore the extramedullary toxicity that limits continued dose escalation. The choice of conditioning regimen is dependent on the antitumor effects of its individual components and their combined dose-limiting organ toxicities. A complete review of high-dose regimens is beyond the scope of this chapter, and the reader is referred instead to an excellent review of the topic.63

Table 13–3 lists the conditioning regimens commonly used for aggressive NHL, although the doses and schedules may vary depending on institutional preferences.18,35,38,48,52,60,64–68 Given their significant antilymphoma activity and their ability to overcome resistance with dose escalation, alkylating agents form the cornerstone of most conditioning regimens. Other regimens less commonly used include melphalan/etoposide42 and melphalan/mitoxantrone.56 Conditioning regimens comprised of high-dose ifosfamide and carboplatin also are being investigated.69,70

The use of total-body irradiation (TBI) is controversial as there are no prospective randomized trials comparing TBI-based conditioning regimens to

### Table 13–2. PHASE II TRIALS OF UP-FRONT HDT FOR PATIENTS WITH POOR-RISK DISEASE AS DEFINED BY THE IPI OR AAIPI*

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<tr>
<th>Lead Author</th>
<th>Histology</th>
<th>Adverse Factors</th>
<th>Trial Design/Therapy</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Pettengel69</td>
<td>HGL</td>
<td>2 or 3 factors of the AAIPI</td>
<td>VAPEC-B × 7 cycles → ifosfamide/cytarabine × 3 cycles → busulphan/cyclophosphamide/ASCT</td>
<td>2-year EFS: Historic control: 35% (p = .01)</td>
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<td>(Kiel classification53)</td>
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<tr>
<td>Nademanee60</td>
<td>IGL/IBL</td>
<td>4 factors of the IPI with CR/PR after 1st therapy; 3 factors of the IPI with PR after 1st therapy</td>
<td>Conventional therapy → cyclophosphamide/etoposide/(TBI or carmustine)/ASCT</td>
<td>3-year OS: 91%</td>
</tr>
</tbody>
</table>

HDT = high-dose therapy; IPI = international prognostic index; AAIPI = age-adjusted IPI; HGL = high-grade lymphoma; VAPEC-B = vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, and bleomycin; ASCT = autologous stem cell transplantation; EFS = event-free survival; OS = overall survival; IGL = intermediate-grade lymphoma; IBL = immunoblastic lymphoma; CR = complete remission; PR = partial remission; TBI = total-body irradiation; DFS = disease-free survival.*Adverse factors for the IPI include: age > 60, ECOG PS ≥ 2, serum lactate dehydrogenase level > normal, involvement of more than 1 extranodal site, and stage III/IV disease; adverse factors for the AAIPI include serum lactate dehydrogenase level > normal, ECOG PS ≥ 2, and stage III/IV disease.

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**Figure 13–3.** Schema of the current cooperative group randomized trial of up-front HDT-ASCT (high-dose therapy with autologous stem cell transplantation) versus standard therapy for patients with aggressive non-Hodgkin’s lymphoma and 2 or 3 factors of the age-adjusted international prognostic index. CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; PR = partial remission; CR = complete remission.
chemotherapy-only regimens. The group from Stanford University retrospectively assessed the influence of preparatory regimens on the outcome of 221 consecutive patients who underwent HDT-ASCT for relapsed or refractory disease or for poor-risk lymphoma as part of up-front treatment. Patients received TBI-based conditioning (134 patients) unless they had or were to receive IFRT, or if TBI was felt to significantly increase morbidity due to advanced age or poor performance status. There were no differences in relapse rates or EFS rates between the two groups. An improved OS was noted for the group receiving TBI, although subgroup analysis demonstrated this benefit to be restricted only to the patients who received bone marrow and not to the patients who received peripheral blood progenitor cells (PBPCs). In a univariate analysis of 369 patients with relapsed or poor-risk NHL who underwent autologous transplantation, Nademanee and colleagues found that OS and DFS rates were better for patients who were treated with a TBI-based conditioning regimen. However, a multivariate analysis failed to demonstrate any prognostic significance. Other studies also have suggested that TBI-based regimens do not confer any significant benefit over chemotherapy-based regimens. Although commonly used, TBI is avoided in patients who have received prior radiotherapy as toxicity, particularly pneumonitis in patients who have received prior chest radiotherapy, can be significant.

In the absence of randomized trials comparing the various regimens, none can be recommended over another. The associated extramedullary toxicities and the patient’s ability to tolerate such insults should determine the choice of conditioning regimen.

### Involved-Field Radiotherapy

The use of IFRT in conjunction with HDT was prompted by the observation that relapse after autologous transplantation frequently occurs at sites of prior disease and the demonstration in several studies that disease bulk prior to HDT is an adverse prognostic factor. However, the utility of IFRT in the setting of HDT is unclear. Although some studies have shown that relapse rates at irradiated sites are significantly lower than those at sites not irradiated, overall relapse rates and survival are not improved by IFRT because of relapses at sites not irradiated or previously uninvolved. Irradiation of all involved sites with doses conventionally used for IFRT (18 to 36 Gy) is precluded by the toxicity that would be incurred by normal adjacent tissue.

Friedberg and colleagues assessed the role of IFRT as a part of the conditioning regimens among 152 patients who underwent HDT-ASCT, 93 of

<table>
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<tr>
<th>Table 13–3. COMMON CONDITIONING REGIMENS FOR AGGRESSIVE NHL</th>
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<td><strong>Regimen</strong></td>
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<td>CBV</td>
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<td>Augmented CBV</td>
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<td>BEAC</td>
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<tr>
<td>Cy/VP-16/total-body irradiation (TBI)</td>
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*Based on ideal body weight or adjusted ideal body weight.
CNS = central nervous system; VOD = veno-occlusive disease of the liver.
Stem Cell Transplantation for Aggressive Non-Hodgkin’s Lymphoma

whom had aggressive NHL. When compared to a group of 400 patients who did not receive IFRT, there was no difference in DFS. However, the group who received IFRT had a significantly worse OS (median 94 months versus 109+ months, \( p = .005 \)), primarily because of secondary myelodysplasia and other radiation-related toxicities. Despite the absence of conclusive data regarding the use of IFRT, many centers routinely use it as a component of the conditioning regimen or following transplantation, particularly to sites of bulky disease.

**Stem Cell Mobilization**

Since the mid-1990s, mobilized PBPCs have all but replaced the use of bone marrow for hematopoietic reconstitution after myeloablative therapy. Compared to bone marrow, the use of PBPCs results in faster hematopoietic recovery, shorter hospital stays, and lower costs. Although the transplantation of autologous bone marrow that has been harvested after priming with filgrastim has been shown to result in neutrophil and platelet engraftment that is comparable to that achieved with transplantation of filgrastim-mobilized PBPCs, the ease and low morbidity of procurement favors the use of PBPCs.

Progenitor cells may be mobilized into the peripheral blood from the bone marrow using chemotherapy, cytokines such as granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF), or chemotherapy in combination with cytokines. Mobilization of PBPCs with chemotherapy and G-CSF or GM-CSF is considered standard on the basis of nonrandomized and randomized studies that demonstrated better stem cell yields with the use of the combination compared to either chemotherapy or cytokines alone. Since chemosensitivity is a prerequisite for patients with relapsed or refractory aggressive NHL to undergo HDT, PBPC mobilization with growth factor and second-line chemotherapy together is convenient and is being used increasingly.

Prior radiotherapy, mobilization with growth factor or chemotherapy alone, and the amount and kind of prior chemotherapy are factors associated with low PBPC yields. Previous exposure to drugs such as nitrogen mustard, melphalan, procarbazine, and cytarabine (> 7.5 g) or salvage therapy with dexamethasone- BEAM has been implicated as being responsible for poor PBPC mobilization. The use of stem cell factor may improve PBPC mobilization in patients with such adverse features.

**Contamination of the Stem Cell Product and Purging**

The incidence of morphologic bone marrow involvement at the time of the diagnosis of relapsed or refractory aggressive NHL has been reported infrequently but appears to be between 10 and 35 percent. However, using more sensitive molecular techniques for detection, the frequency of bone marrow involvement is significantly higher. Even when there is no histologic evidence of bone marrow involvement, occult involvement is frequent, and second-line chemotherapy often does not eradicate disease from the bone marrow. In one study involving patients with a t(14;18) translocation who underwent HDT-ASCT, 100 percent of those with chemosensitive aggressive NHL had disease detectable in the bone marrow by the polymerase chain reaction.

Despite the apparent high incidence of occult contamination of the bone marrow among patients with relapsed or primary refractory aggressive NHL, there have been only a few reports of its impact on stem cell harvests. Results from small studies using molecular techniques for detection of malignant cells suggest that approximately 30 to 50 percent of bone marrow and/or peripheral blood stem cell harvests are contaminated with lymphoma cells. The predictive value of bone marrow histology on the likelihood of graft contamination is poor, and the stem cell product frequently is contaminated, even when the bone marrow and the peripheral blood have no morphologic evidence of lymphoma. Conversely, contaminant-free PBPCs often can be harvested from patients with overt bone marrow involvement. There appears to be no significant difference in the degree of contamination of mobilized PBPCs versus bone marrow harvests.

Unlike the case for acute myelogenous leukemia (AML) or solid tumors, in which re-infused tumor cells have been shown to be responsible for relapse, the contribution to relapse by contami-
nating lymphoma cells in the stem cell product is less clear. Several studies have suggested that occult contamination of the graft is highly correlated with relapse\textsuperscript{110,111,113} and that eradication of lymphoma from the graft is associated with lower relapse rates.\textsuperscript{111} In a study involving patients with either indolent or aggressive NHL, transplantation of stem cell grafts that had residual detectable contaminating cells after immunologic purging was associated with a 10-fold increase in the risk of relapse compared with the transplantation of grafts that were rendered lymphoma-free after purging.\textsuperscript{111} However, since a significant proportion of patients with contaminated grafts relapse at sites of prior disease,\textsuperscript{110} and since the presence of tumor cells in the harvest does not invariably result in relapse,\textsuperscript{111,113,118} it is unclear whether it is the contaminated graft per se that contributes to relapse or whether a contaminated graft serves as a marker of greater disease bulk or chemoresistance.

Limited data exist on the efficacy and utility of ex vivo purging of stem cell grafts for patients with aggressive NHL. Available reports suggest that between 20 and 50 percent of contaminated bone marrow grafts can be rendered lymphoma free by ex vivo purging,\textsuperscript{111,119} but there are no reports on the purging of PBPC harvests of patients with aggressive NHL. Also, the clinical benefit of purging is unknown as large-scale studies evaluating the role of purging among patients with aggressive NHL with detectable molecular markers are lacking. Data from the European Blood and Marrow Transplant (EBMT) Lymphoma Registry suggest that purging of bone marrow harvests had no effect on either progression-free survival (PFS) or OS.\textsuperscript{120} However, the purging efficacy was not reported, and data from the Dana-Farber Cancer Institute (DFCI) suggest that purging is beneficial only if contaminating lymphoma cells are completely eliminated.\textsuperscript{111} Again, the DFCI data are derived largely from patients with indolent NHL.

**Prognostic Factors for HDT-ASCT**

As discussed, chemosensitivity to second-line therapy is the most important determinant of the outcome of HDT-ASCT for both relapsed and primary refractory aggressive NHL. However, analyses of prognostic factors limited to patients with chemosensitive disease have been performed infrequently. Prince and colleagues\textsuperscript{121} and we\textsuperscript{43} have shown that the remission status at the time of HDT is predictive of outcome, such that patients in CR have a 4-year OS rate of approximately 60 to 70 percent compared with 25 to 30 percent for patients in PR. In a multivariable analysis that accounted for chemosensitivity, Vose and colleagues showed that three or more prior chemotherapy regimens and an elevated serum lactate dehydrogenase level also predicted for a poorer outcome.\textsuperscript{29} In the Parma study, the time to relapse was predictive of chemosensitivity, such that patients whose disease relapsed within 12 months from their initial diagnosis had a lower response rate to second-line therapy.\textsuperscript{122} However, among patients with chemosensitive disease who underwent HDT, time to relapse did not have any predictive value. Despite having chemosensitive disease, patients with histologic evidence of bone marrow involvement after second-line therapy are often excluded from HDT. However, limited data suggest that the failure to eradicate disease from the bone marrow prior to HDT may not adversely affect survival.\textsuperscript{123}

The ability to identify poor-risk patients even before the determination of chemosensitivity may enable the selection of patients for other novel curative approaches. In an intention-to-treat analysis, we have shown that the second-line IPI (sIPI, ie, the IPI at the time of diagnosis of relapsed or refractory disease) is predictive of failure-free survival (FFS) and OS (Figure 13–4).\textsuperscript{124} Patients with an sIPI of 1 or 2 had a 2.5-year FFS of 45 percent compared with 9 percent for patients with an sIPI of 3 or 4. The sIPI appears to retain its predictive value even if one considers homogeneous populations with respect to relapsed\textsuperscript{125} or primary refractory\textsuperscript{31} disease. Patients with primary refractory disease and a second-line age-adjusted IPI (sAAIPI) of 3 or 4 have a particularly poor outcome, with few long-term survivors.\textsuperscript{31} In contrast to these results, the sAAIPI was not predictive of outcome among the patients who underwent HDT-ASCT in the Parma trial.\textsuperscript{126} However, only 16 patients had two or three adverse factors of the sAAIPI, and the lack of predictive value may have been due to the small number of patients and inadequate power to detect a significant difference.
Stem Cell Transplantation for Aggressive Non-Hodgkin’s Lymphoma

Reported rates for the development of so-called therapy-related MDS (t-MDS) or AML (t-AML) after HDT-ASCT have varied wildly (Table 13–4), with median latency periods ranging from 2.5 to 4 years. Most reports have included patients with either Hodgkin’s disease (HD) or NHL, and the incidence and characteristics of t-MDS/t-AML among patients who underwent HDT-ASCT specifically for aggressive NHL has not been reported.

The incidence rates and latency periods for the development of t-MDS or t-AML following HDT-ASCT correlate well with those expected as a result of standard alkylator-based therapy for HD or indolent lymphoma. In two large studies of secondary leukemia associated with the treatment of NHL, the vast majority of t-AML occurred among patients with indolent lymphoma, and in the EBMT Lymphoma Registry database, t-MDS/t-AML was more frequent among patients with indolent lymphoma. Among patients who have undergone HDT-ASCT for multiple myeloma, the incidence of t-MDS is significantly increased among those patients who have had more extensive prior treatment with alkylating agents. These observations suggest that it is not the transplant procedure per se but, rather, prior therapy that is responsible for t-MDS/t-AML. The high frequency of abnormalities of chromosomes 5 and 7 among patients with t-MDS or t-AML lends further support to the theory that prior therapy, particularly alkylating agents, rather than the conditioning regimen is responsible for t-MDS/t-AML noted after HDT-ASCT.

Nevertheless, some assert that it is the conditioning regimen that is responsible for the development of t-MDS/t-AML. This would require that the observed disordered hematopoiesis be derived from stem cells that survive the conditioning regimen. Indeed, that stem cells may survive “myeloablative” therapy is supported by studies demonstrating hematopoietic reconstitution among recipients of HDT without stem cell support and studies showing long-term mixed chimerism among patients who have undergone T-cell-depleted allogeneic bone marrow transplantation. The association of low-dose TBI with the development of MDS and AML among patients with low-grade lymphoma lends support to the observed associations of TBI-based...
preparative regimens with t-MDS/t-AML.\textsuperscript{130,135} Although the follow-up period has been short, investigators at St. Bartholomew’s Hospital in London have observed no t-MDS/t-AML after eliminating TBI from the conditioning regimen.\textsuperscript{144} In other studies, TBI has not been associated independently with t-MDS/t-AML,\textsuperscript{138} and clear evidence implicating TBI as the etiology of t-MDS/t-AML is lacking. The low incidence of t-MDS/t-AML among patients who have undergone allogeneic transplantation with TBI-based conditioning\textsuperscript{148} and among patients who have undergone HDT-ASCT for breast cancer\textsuperscript{149–151} is evidence against the conditioning regimen being responsible for its development.

Some investigators have advocated routine cytogenetic evaluation of the bone marrow prior to HDT to assess for the presence of cytogenetic abnormalities that may indicate or herald the development of MDS.\textsuperscript{152,153} However, cytogenetic abnormalities following autologous transplantation are frequent and often are not associated with the development of t-MDS/t-AML.\textsuperscript{154,155} Although the abnormal clone that is responsible for t-MDS/t-AML may be present prior to HDT-ASCT,\textsuperscript{156,157} the predictive value of bone marrow cytogenetics prior to HDT-ASCT has not been established.\textsuperscript{129,136}

### ALLOGENEIC STEM CELL TRANSPLANTATION FOR AGGRESSIVE NON-HODGKIN’S LYMPHOMA

Allogeneic bone marrow transplantation initially was conceived of as a means by which to rescue patients from the marrow aplasia induced by potentially therapeutic but myeloablative therapy.\textsuperscript{158,159} The antitumor effects of high-dose chemotherapy and radiotherapy notwithstanding, it became apparent from observations of patients with acute leukemia who underwent allogeneic transplantation that the risk of relapse after allogeneic transplantation was inversely correlated with the development and severity of graft-versus-host disease.\textsuperscript{160,161} Evi-

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>Number of Patients with t-MDS or t-AML</th>
<th>Actuarial Incidence of t-MDS or t-AML*</th>
<th>Median Latency Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>From Primary Dx</td>
<td>From ASCT</td>
<td>Risk Factors</td>
</tr>
<tr>
<td>Traweek\textsuperscript{129}</td>
<td>HD: 4/108</td>
<td>NHL: 6/167</td>
<td>9% (\pm 4.7)% at 3 yr</td>
</tr>
<tr>
<td>Darrington\textsuperscript{130}</td>
<td>HD: 6/249</td>
<td>NHL: 6/262</td>
<td>4% at 5 yr</td>
</tr>
<tr>
<td>Stone\textsuperscript{131}</td>
<td>NHL: 20/262</td>
<td>18% &amp; 9% at 6 yr</td>
<td>69 mo (25–144)</td>
</tr>
<tr>
<td>Bhatia\textsuperscript{132}</td>
<td>HD or NHL: 10/258</td>
<td>13.5% &amp; 4.8% at 6 yr</td>
<td>5.4 yr (1.5–12)\textsuperscript{‡}</td>
</tr>
<tr>
<td>Wheeler\textsuperscript{134}</td>
<td>HD: 5/150</td>
<td>NHL: 1/150</td>
<td>4.2% (0.6–7.7) at 5 yr</td>
</tr>
<tr>
<td>Milligan\textsuperscript{135}</td>
<td>NHL: 37/3168</td>
<td>3% (2–4.3) at 5 yr</td>
<td>5.7% (3.4–9.4) at 10 yr</td>
</tr>
<tr>
<td>Friedberg\textsuperscript{136}</td>
<td>Indolent NHL: 22/311 Aggressive NHL: 17/241</td>
<td>14.7% (10.6–18.9) at 8 yr</td>
<td>19.8% (13.7–25.9) at 10 yr</td>
</tr>
<tr>
<td>Krishnan\textsuperscript{137}</td>
<td>HD: 11/218</td>
<td>NHL: 11/394</td>
<td>HD: 8.1% &amp; 2.5% at 6 yr</td>
</tr>
<tr>
<td>Califaretti\textsuperscript{138}</td>
<td>HD: 8/148</td>
<td>NHL: 8/156</td>
<td>5.4% at 5 yr</td>
</tr>
</tbody>
</table>

MDS = myelodysplasia; AML = acute myelogenous leukemia; HDT-ASCT = high-dose therapy with autologous stem cell transplantation; t-MDS = therapy-related MDS; Dx = diagnosis; HD = Hodgkin’s disease; NHL = non-Hodgkin’s lymphoma; TBI = total-body irradiation; PBPCs = peripheral blood progenitor cells.

*From time of ASCT.

\[1\] The latency period represents the mean instead of the median.

\[2\] Latency periods listed from an earlier publication in which nine patients were reported.\textsuperscript{133}
idence that a graft-versus-tumor effect was a consequence of allogeneic transplantation, and that it was mediated by mature T cells, comes from the following observations, primarily among patients with either acute leukemia or chronic myelogenous leukemia (CML): (1) the risk of relapse was higher among patients with T-cell-depleted grafts or syngeneic grafts or (2) the infusion of donor lymphocytes induced remission among patients with CML or other malignancies whose disease relapsed after allogeneic transplantation; and (3) donor in vitro–selected leukemia-reactive cytotoxic T cells can induce a remission of CML that relapses after allogeneic transplantation. 

Evidence for a graft-versus-lymphoma effect is largely indirect and is inferred from lower relapse rates among recipients of allogeneic transplants compared with recipients of autologous transplants and from observations of tumor regression with donor lymphocyte infusions. Animal models also support the existence of a true graft-versus-lymphoma effect and suggest that it is mediated by mature T lymphocytes.

The role of allogeneic transplantation in the management of patients with relapsed or primary refractory aggressive NHL has been difficult to discern from earlier studies because of the small number of patients, the inclusion of patients with various histologies, and the lack of homogeneity with respect to chemosensitivity. Whereas some studies have suggested that patients with indolent NHL have a better outcome after allogeneic transplantation compared with patients with an aggressive histology, other studies suggest that the reverse is true. Several studies have demonstrated that chemosensitive disease predicts for a better outcome.

In a retrospective analysis, the Société Française de Greffe de Moelle reported the outcome of 73 patients with aggressive NHL, including those with transformed histology or with follicular large cell lymphoma, who underwent allogeneic transplantation. Fourteen of these patients underwent transplantation in first remission. With a median follow-up of 90 months, the 5-year PFS rate was 40 percent. The only factors predictive of OS were having received fewer than three pretransplant regimens and having achieved a CR at transplant. Patients in CR at transplant had a long-term survival rate of 76 percent compared with 23 percent for patients not in CR. Interestingly, among 22 patients with chemosensitive disease, 16 percent of whom also had bone marrow involvement, the PFS rate was 60 percent. This compares favorably with the EFS rate of 46 percent among patients with relapsed chemosensitive disease without bone marrow involvement in the Parma trial.

There have been few studies that have compared the outcome of allogeneic transplantation with that of autologous transplantation for NHL, none of which have been prospective randomized trials. A retrospective review from the Fred Hutchinson Cancer Center compared the outcome of patients with HD or Working Formulation intermediate-grade or high-grade NHL who underwent autologous transplantation to the outcome of those who underwent allogeneic transplantation if an HLA-matched sibling was available. The type of transplant did not influence the relapse rate or the DFS rate. The EBMT Lymphoma Registry reported similar results in a case-controlled analysis of 101 patients with low-, intermediate-, or high-grade NHL who underwent allogeneic transplantation. The results were upheld when the group with intermediate-grade lymphoma was analyzed separately. However, in a more recent report involving 272 patients with intermediate-grade NHL, the EBMT Lymphoma Registry reported that allogeneic transplantation was associated with a lower relapse rate compared to autologous transplantation, although the OS rate was lower due to transplant-related mortality, which was estimated at 30 percent at 2 years. In a series of consecutive patients with chemosensitive relapsed or refractory HD or intermediate- or high-grade NHL treated at the Johns Hopkins University, patients who underwent allogeneic transplantation had a lower 4-year relapse rate compared to those who underwent autologous transplantation (18% versus 46%, respectively; \( p = .02 \)). There was no difference in relapse rates by histology. However, the EFS rates were equivalent, due to a high transplant-related mortality rate for patients who underwent allogeneic transplantation (47% versus 21%; \( p = .007 \)). Matching for age, histology, chemosensitivity, and year of transplant, the Ontario Blood and Marrow Transplant network compared 44 patients with NHL, most of whom had chemosensitive disease and an aggressive histology,
who underwent allogeneic transplantation with patients who underwent autologous transplantation.\textsuperscript{173} Patients who underwent allogeneic transplantation had a lower relapse rate (relative risk, 0.190; 95% CI, 0.043 to 0.834), but the OS rate was not different in the two groups.

The group from Wayne State University\textsuperscript{171} reported the only prospective comparison of allogeneic versus autologous transplantation for NHL. Patients underwent allogeneic transplantation (31 patients) if they were younger than 55 years and if they had an HLA-identical or 1-antigen-disparate sibling donor. All others (35 patients) underwent autologous transplantation. Patients with all histologic grades were eligible, but only 12 and 19 patients with intermediate-grade histology underwent allogeneic and autologous transplantation, respectively. The 4-year probabilities of disease progression were 69 percent and 20 percent for the autologous and allogeneic groups, respectively ($p = .001$). There was no difference in PFS. If only patients with chemosensitive disease were considered, the probabilities of disease progression were 60 percent and 18 percent in the autologous and allogeneic transplantation groups, respectively.

Despite the apparent superior DFS rates conferred by allogeneic transplantation, OS rates appear comparable to or even inferior to those achieved with autologous transplantation.\textsuperscript{172} The lack of a survival benefit is due to the high procedure-related mortality associated with allogeneic transplantation, which can range from 30 to 40 percent for patients with aggressive NHL.\textsuperscript{172,188} Nonmyeloablative allogeneic transplantation is being explored currently as a means to harness the potentially powerful graft-versus-lymphoma effect, while minimizing the mortality associated with traditional allogeneic transplantation. Its role in the treatment of patients with relapsed or primary refractory aggressive NHL remains to be determined.

### ALLOGENEIC STEM CELL TRANSPLANTATION AFTER THE FAILURE OF AUTOLOGOUS TRANSPLANTATION

Few data exist on the outcome of patients in whom HDT-ASCT fails. Vose and colleagues reported a median survival of 3 months for patients with aggressive NHL who had progressive disease after HDT-ASCT.\textsuperscript{190} However, most patients in this series did not have chemosensitive disease. At our institution, patients with chemosensitive relapsed or primary refractory aggressive NHL in whom HDT-ASCT failed had a median survival of 6.2 months.\textsuperscript{191} Although a minority of patients can achieve subsequent long-term cure, there are no established curative options for patients who have failed HDT-ASCT, and survival appears to be inversely proportional to the time to failure.\textsuperscript{190,191}

Allogeneic transplantation as “salvage” therapy for patients in whom HDT-ASCT has failed is rarely curative. Tsai and colleagues reported that of 14 patients with either NHL or HD who underwent salvage allogeneic transplantation, only 2 were alive and disease free at the time of the report.\textsuperscript{192} In a report by de Lima and colleagues, 8 patients with NHL underwent allogeneic transplantation after a failed autologous transplant. Three patients were alive and disease free at 25, 22, and 7 months after transplantation.\textsuperscript{193} The group from the University of Nebraska reported a 36 percent 2-year FFS rate for patients with NHL (9 patients) or HD (7 patients) who underwent allogeneic transplantation after failed autologous transplant.\textsuperscript{194} There was a suggestion that patients who underwent allogeneic transplantation more than 1 year after autologous transplantation had a better OS than did patients who underwent allogeneic transplantation sooner.

Since the failure of HDT-ASCT is often associated with rapidly progressive disease and a poor performance status, few patients are suitable candidates for allogeneic transplantation. However, it may be considered for select patients with an adequate performance status and a minimal disease burden.

### CONCLUSION

High-dose therapy with autologous stem cell transplantation is standard treatment for patients with relapsed or primary refractory aggressive NHL that is sensitive to second-line therapy. However, not all patients with chemosensitive disease derive equal benefit from HDT-ASCT, and patients with relapsed disease with an sAAIPI of 4 and those with
primary refractory disease with an sAAIPI of 3 or 4 have poor outcomes. These patients should be considered for alternative novel treatment strategies. Up-front HDT-ASCT may benefit patients with poor-prognosis aggressive NHL, but this has yet to be proven conclusively. At present, poor-risk patients are best identified by the IPI, although there is accumulating evidence that the clinical behavior of aggressive lymphoma can be profiled by the expression of certain molecular markers.\textsuperscript{195–197} Identification of such markers by complementary deoxyribonucleic acid microarrays and other methods will undoubtedly form the basis of new prognostic models that may further refine our ability to identify poor-risk patients.\textsuperscript{198} Such risk stratification should allow for tailored therapy not only for the primary treatment of aggressive NHL but also for the treatment of relapsed and refractory disease.

There are several new paradigms being explored currently that are designed to improve the results of HDT-ASCT. More effective second-line therapy and conditioning regimens and the use of highly purified stem cell grafts obtained by the positive selection of CD34+ cells\textsuperscript{199–201} and/or purging of tumor cells will hopefully improve the results of HDT-ASCT, particularly for poor-prognosis patients. Conditioning regimens using targeted radioimmunotherapy may significantly enhance eradication of these radiosensitive tumors without the attendant organ toxicities of TBI.\textsuperscript{202} Furthermore, post-transplant immunotherapeutic strategies such as the use of monoclonal antibodies,\textsuperscript{203} cytokines,\textsuperscript{204,205} and vaccines\textsuperscript{206} may play a significant role in the eradication of minimal residual disease following HDT-ASCT.

The significant toxicity associated with conventional autologous transplantation results in outcomes comparable to those achieved by autologous transplantation. However, carefully selected patients with poor-risk features, such as high sIPI scores, who are unlikely to be cured by conventional HDT-ASCT should be considered for autologous transplantation if an HLA-matched sibling donor is available. If proven to be effective, nonmyeloablative autologous transplantation may be an attractive option for treating patients with poor-risk relapsed or primary aggressive NHL.

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