Autologous Bone Marrow Transplantation in B-Cell Non-Hodgkin's Lymphoma: Very Low Treatment-Related Mortality in 100 Patients in Sensitive Relapse

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One hundred patients with B-cell non-Hodgkin's lymphoma (NHL) in sensitive relapse or incomplete first remission underwent high-dose chemoradiotherapy and anti-B-cell monoclonal antibody (MAb)-treated autologous bone marrow transplantation (ABMT). These patients demonstrated good performance status with a Karnofsky score of 80% or greater. The majority of these patients had one or more adverse prognostic features including a failure to achieve a complete remission (CR) with conventional combination chemotherapy (37 patients), bone marrow infiltration (69 patients), a history of extranodal disease other than bone marrow infiltration (42 patients), and histologic conversion (18 patients). At the time of ABMT, only 52 patients were in CR; however, all patients achieved a minimal disease state following conventional intensive therapy. Moreover, at the time of marrow harvest, 37 of these patients had histologic evidence of lymphoma cells infiltrating the marrow. Following high-dose ablative therapy, two acute in-hospital treatment-related deaths were observed. Two late deaths were observed, not due to recurrent lymphoma. Of the remaining 96 patients, 61 are in unmaintained CR with a median follow-up of 13 months. Kaplan-Meier actuarial analysis predicts 50% probability of disease-free survival (DFS) at 37.8 months. This very low treatment-related mortality provides the rationale to apply high-dose therapy and ABMT as consolidative therapy for patients in first remission who are at high risk for relapse following conventional therapy.

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HIGH-DOSE chemoradiotherapy and autologous bone marrow transplantation (ABMT) have been shown to be the only potentially curative treatment modality for patients with relapsed non-Hodgkin's lymphoma (NHL). Retrospective analysis strongly suggests that certain subgroups of patients with NHL are more likely to benefit from this approach.[1-4] Conversely, patients whose tumors are resistant to all forms of conventional therapy, either at the time of diagnosis or relapse, demonstrate less than 15% long-term disease-free survival following ABMT.[1,2,4-6] In contrast, patients whose disease is still responsive to conventional-dose therapy are more likely to benefit from ABMT with long-term disease-free survivals (DFSs) ranging from 25% to 60%.[1-14]

More widespread use of ABMT for patients with NHL has been limited by significant fatal toxicity and infiltration of the bone marrow by lymphoma cells. Most patients thus far treated have had resistant disease and/or poor performance status. The treatment-related fatal toxicity, in these series, ranged from 20% to 30% and was usually the result of infection or interstitial pneumonitis.[1,2,4,6,15] This high level of treatment mortality has been an obstacle to the use of ABMT for NHL patients before the development of resistant disease. A second obstacle to the use of ABMT is lymphomatous infiltration of the bone marrow. Between 20% to 75% of patients have overt marrow involvement at the time of relapse[16] and as such are usually excluded from ABMT. Moreover, prior studies have shown that widespread leukemic and bone marrow relapse can occur in patients, even when following reinfusion of histologically negative marrows.[17]

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Increasing evidence, now using sensitive cell culture and molecular biologic techniques, demonstrates that histologically negative marrows are contaminated by lymphoma cells.[18-21] Although the majority of patients relapse in prior sites of disease, the issue of whether contaminating tumor cells within reinfused marrow contribute to relapse is unresolved.

In the present study, we report the results of 100 patients with NHL who had sensitive disease and good performance status at the time of high-dose chemoradiotherapy and anti-B-cell monoclonal antibody (MAb)-purged ABMT. This series includes 69 patients with a prior history of bone marrow infiltration and 37 patients with bone marrow involvement at the time of ABMT. This procedure was highly tolerable with only two acute in-hospital treatment-related deaths. Kaplan-Meier actuarial analysis indicated a 50% probability that patients will remain disease-free for 37.8 months. More importantly, this very low treatment-related mortality suggests that high-dose therapy and ABMT should now be evaluated as consolidation therapy for patients in first remission who are at high risk for relapse following conventional therapy.

METHODS

Selection of Patients and Treatment Protocol

Patients were eligible for study if they were less than 65 years of age, had relapsed NHL after standard chemotherapeutic regimens, and had lymphoma cells that expressed the CD20 (B1) antigen by indirect immunofluorescence and flow cytometric analysis or immunoperoxidase staining.[22] In addition, patients with sensitive NHL but who had failed to enter complete remission (CR) after one or more standard chemotherapeutic regimens were eligible. For all patients, a minimal disease status had to be attained through chemotherapy, radiotherapy, or both before entry. This status was defined as lymph nodal mass less than 2 cm in its greatest diameter and histologic evidence of bone marrow involvement of 20% or less of the intratrabecular space as determined by iliac crest biopsy. Additional criteria for entry included the absence of comorbid disease of the heart, kidney, lung, and liver, and a Karnofsky score above 80%. Active CNS involvement with lymphoma or any circumstance that would obviate the ability to deliver full-dose total body irradiation (TBI) excluded patients from the protocol. Informed consent was obtained from all patients.

Preparative therapy consisted of cyclophosphamide, 60 mg/kg of body weight, infused on each of 2 consecutive days before radiotherapy. TBI, 5 to 10 cGy/min, was administered either in a single dose of 850 cGy in the first four patients or in fractionated doses (200 cGy) twice daily on 3 consecutive days (total of 1,200 cGy) in all subsequent patients. Within 18 hours of the completion of radiotherapy, cryopreserved bone marrow that had been previously treated in vitro with MAbs and rabbit complement was thawed rapidly and reinfused through a central venous catheter.

Collection, Processing, and Infusion of Marrow

Bone marrow was obtained, treated in vitro with MAbs and rabbit complement, and stored within 4 weeks of its use in transplantation in all patients except one.[3,23,24] The bone marrow cells from 18 patients were treated with anti-B1 (CD20) and marrow cells from 51 patients were treated with Coulter clone anti-B1 MAb (B1-IND 2151, Coulter Immunology, Hialeah, FL). The bone marrow cells from 31 patients were treated with more than one MAb including 23 with anti-B1, anti-B5,[25] and J5 (anti-CD10),[26] and eight with combinations of anti-B1 with either anti-B5, J5, or J2 (anti-CD9)[27] depending on the tumor cell phenotype (two with anti-B1, anti-B5, J2; two with anti-B1, J5; four with anti-B1, anti-B5). After treatment, the cells were cryopreserved as previously described.[3] Before reinfusion, the cryopreserved marrow cells were rapidly thawed, and diluted in medium containing DNAase as previously described.[3] The median number of infused cells was 3.82×10^7/kg (range, 1.45 to 12.35×10^7/kg), with 85% to 95% viability as measured by trypan blue dye exclusion.

Supportive Care

Patients were treated and cared for in reverse isolation rooms until they were discharged. Discharge was permitted if the absolute granulocyte count was stable at more than 500/mm^3, and no fever had occurred in the absence of antibiotics for 48 hours. Trimethoprim-sulfamethoxazole or ciprofloxacin prophylaxis was begun in patients when chemotherapy was initiated but was stopped if broad spectrum intravenous antibiotics were required. Patients also received prophylactic acyclovir (5 mg/kg or 400 mg orally every 8 hours) for herpes simplex infections. Prophylaxis with trimethoprim-sulfamethoxizole was reinstituted at the time of discharge and continued for 6 to 12 months to prevent *Pneumocystis carinii* pneumonia. Cytomegalovirus-negative blood products were used in all patients regardless of prior exposure to the virus (frozen deglycerolized RBCs and screened platelet donors).[28] Blood products were irradiated with 2,000 cGy to obviate problems of alloreactivity.

Evaluation and Statistical Analysis

Before treatment, all patients were evaluated by physical examination, blood-chemistry profile, complete blood count, chest x-ray, abdominal-pelvic computed tomographic (CT) scanning (chest CT if indicated), bone marrow aspirate and biopsy, as well as cell-surface phenotypic studies of peripheral blood and bone marrow mononuclear cells. Other studies such as gallium scanning were done as needed to determine the extent of disease. Follow-up restaging was carried out every 6 months after transplantation or as clinically indicated.

CR was defined as the disappearance of all measurable and assessable disease. Disease-free survival (DFS) was calculated from the day of marrow transplantation (day 0). DFS

curves were estimated by the method of Kaplan and Meier and compared by the log-rank test.[29,30]

RESULTS

Patient Characteristics

One hundred patients (60 men and 40 women) with B-cell NHL who were in a minimal disease state or CR underwent ABMT between December 1982 and December 1988 (Table 1). The median age of this patient population at the time of ABMT was 43 years (range, 24 to 64). This series included a large number (43) of patients over the age of 45. All patients had no comorbid disease and had a Karnofsky score of 80% or greater. This patient population was considered to be of poor prognostic risk since 42 patients had a history of extramedullary and extranodal disease, and 69 had bone marrow infiltration at some time during the course of their disease. Although the majority of patients (64) had intermediate-grade NHL, 34 patients with low-grade lymphoma underwent ABMT. Moreover, 18 patients who are included in the intermediate-grade subgroup at ABMT had undergone histologic transformation from a previous low-grade NHL.

Table 1. Patient Characteristics

Characteristics	No. of Patients	
Age at ABMT (yrs)		
< 30	5	
30-40	52	
> 45	43	
Sex		
Male	60	
Female	40	
Histology at ABMT		
Low	34	(FSC-20, FM-13, DIL-1)
Intermediate	64	(DLC-39, DM-6, DSC-14, FLC-5)
High	2	(SNC-2)
Previous sites of extranodal disease		
Liver	11	
Lung	6	
GI	5	
Skin	5	
Pleura	4	
GU	3	
Bone	3	
Bone Marrow	69	

Abbreviations: WF, Working Formulation; FSC, follicular small-cleaved WF-A; FM, follicular mixed-small-cleaved and large-cell WF-B; DIL, diffuse intermediate lymphocytic lymphoma; DLC, diffuse large-cell WF-G; DM, diffuse mixed small-large cell WF-F; DSC, diffuse small-cleaved-cell WF-E; FLC, follicular predominant large-cell WF-D; SNC, small-noncleaved-cell WF-J; GI, gastrointestinal; GU, genitourinary.

Table 2. Prior Therapy

	No. of Patients
Prior treatment	
Chemotherapy	100 (median, 3 regimens; range, 2-8)
Local radiotherapy	27
TBI (150 cGy)	2
Prior response	
CR	63
PR	37
Status at ABMT	
CR	52
PR	48
BM involvement	37

Abbreviations: PR, partial remission; BM, bone marrow.

Prior Therapy

All patients had relapsed or failed to achieve a first CR from conventional combination chemotherapy, and most had been treated with multiple regimens (median, three; range, two to eight) (Table 2). In addition to chemotherapy, 27 patients had been treated with involved-field radiotherapy and two had been treated with TBI (150 cGy). Ten patients received chest radiotherapy. A prior CR was documented in only 63 patients with a median disease-free interval of 14 months (range, 1 to 84 months). When patients were considered potential candidates for ABMT, they were treated with conventional- or high-dose salvage regimens in an attempt to induce a remission. Following this preparative therapy, only 52 patients achieved a CR, and 48 patients achieved a minimal disease state. Of interest, 37 of these patients had some histologic evidence of residual lymphoma cells on bone marrow biopsy at the time of harvest.

Hematologic Engraftment

All patients achieved granulocyte engraftment defined as an absolute neutrophil count of 500/mm^3 in a median of 27 days (range, 10 to 99 days). There was no correlation between the number of cells infused and the time to WBC engraftment. Stable platelet engraftment defined as 40,000 platelets/mm^3 in a median of 29 days with a range of 10 to 137 days was achieved in all but three patients. Two of the latter had very extensive prior therapy, and one patient had prior TBI (150 cGy).

Acute and Chronic Toxicity

Two acute in-hospital treatment-related deaths were observed. One patient died of venoocclusive disease of the liver at day 18 and the other of thrombocytopenic cerebral hemorrhage at day 36. Two late deaths from nonlymphomatous causes were observed. One died of interstitial pneumonitis secondary to extensive prior mediastinal irradiation (5,500 cGy) at 112 days. An additional patient with a prior history of Sjogrens syndrome died with a myelodysplastic syndrome and pulmonary hemorrhage at 408 days.

The acute toxicities were similar to that observed in prior studies using cyclophosphamide and TBI. The major acute toxicity was fever associated with neutropenia. Although 90 patients developed fever, positive blood cultures were observed in only 19 patients. The majority of these were due to gram-positive organisms (13 patients) with gram-negative (three patients) and fungal sepsis (three patients) being less common. Sixty percent of patients had some level of demonstrable mucositis (National Cancer Institute [NCI], common toxicity criteria grade 1-2) with 15% having severe mucositis (NCI, CTC grade 3-4). All patients required both RBC and platelet transfusions. During hospitalization, the median number of units of RBCs and platelets transfused was 11 (range, two to 75) and 66 (range, 11 to 604), respectively. No additional significant episodes of acute bleeding were seen.

The late infectious complications have been limited. Twenty-six patients developed herpes zoster infections; all but two were localized dermatomal. Late pneumonitis was observed in 12 patients. Of these, three cases were due to *P carinii* at 10, 11, and 12 months in three patients who were not on trimethoprim-sulfamethoxazole prophylaxis. Eight additional cases of self-limited culture-negative pneumonia were observed between 2 and 24 months with six occurring in the first 6 months. Following relapse, one patient developed cytomegalovirus pneumonitis in the terminal stages of her disease.

Between 5 and 12 months following ABMT, nine patients have developed transient Coombs-negative hemolytic anemia associated with a minimal elevation of serum creatinine. These patients required RBC transfusion for several months with one patient still requiring RBC transfusions at 15 months. Two developed moderate hypertension. Although renal biopsies were not performed, this clinical picture is consistent with radiation nephritis as previously reported.[31]

Therapeutic Results

Of 100 patients, 61 remain in complete unmaintained remission. Of the 39 remaining patients, 35 have relapsed, and four have died in remission. The median follow-up of the disease-free patients was 13 months (range, 4 to 72 months). The median time to failure among the relapses was 7 months (range, 1 to 44 months). Kaplan-Meier actuarial analysis indicated a 50% probability that patients will remain disease-free for 37.8 months (Fig 1A).

Eighty percent of patients relapsed in sites of prior disease. Specifically, 23 patients relapsed in only old sites, five patients relapsed in both old and new sites, and seven patients relapsed in entirely new sites. Of the seven patients who relapsed in entirely new sites, none had evidence of bone marrow infiltration at harvest.

Twelve of the 35 relapses involved the bone marrow, and eight of these patients had a prior history of bone marrow infiltration. Of the 37 patients who had histologic evidence of bone marrow infiltration at the time of harvest, 11 relapsed, five of these in the bone marrow. Of the 63 patients who were marrow-negative at the time of harvest, 24 patients relapsed, seven in the bone marrow.

The influence of histology before ABMT upon DFS was examined. As seen in Fig 1B, there was no significant difference in the DFS for patients with either low- or intermediate/high-grade NHL at the time of ABMT. Patients with an intermediate-grade NHL who had undergone histologic transformation from a prior low-grade lymphoma had a similar DFS with the remainder of the population (data not shown). Both patients with high-grade NHL relapsed within 6 months of ABMT (2 and 5.3 months). Of interest was the observation that a prior history of bone marrow infiltration (Fig 1C) or histologically positive bone marrow at the time of harvest (Fig 1D) did not adversely influence DFS.

DISCUSSION

In the present study, we report the results of 100 patients with B-cell NHL in sensitive relapse or incomplete first remission who underwent

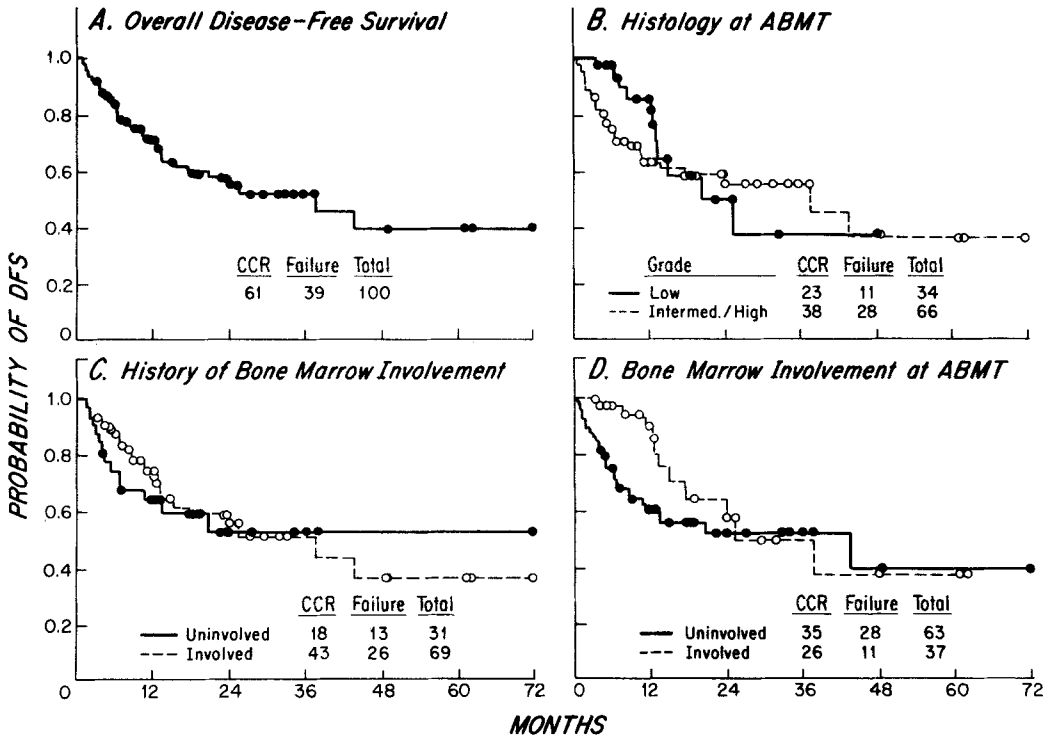

Fig 1. Kaplan-Meier estimate of DFS probability in relation to prognostic factors: (A) overall survival for the 100 patients; (B) survival in relation to histologic characteristics at the time of ABMT; (C) a history of lymphomatous bone marrow involvement; and (D) lymphomatous bone marrow involvement at the time of ABMT.

high-dose chemoradiotherapy and anti-B-cell MAb-treated ABMT. All these patients demonstrated good performance status with Karnofsky score of 80% or greater. The majority of these patients demonstrated one or more adverse prognostic features including a failure to achieve a CR with conventional combination chemotherapy (37 patients), bone marrow infiltration (69 patients), a history of extranodal disease other than bone marrow infiltration (42 patients), and histologic conversion (18 patients). At the time of ABMT, only 52 patients were in CR; however, all patients achieved a minimal disease state following conventional aggressive therapy. Moreover, at the time of marrow harvest, 37 of these patients had histologic evidence of lymphoma cells infiltrating the marrow. Following high-dose ablative therapy, two acute in-hospital treatment-related deaths were observed. Two late deaths were observed, not due to recurrent lymphoma. Of the remaining 96 patients, 61 are in unmaintained CR with a median follow-up of 13 months. There is a 50% probability of DFS at 37.8 months.

The most significant observation of this study was the low treatment-associated mortality. Four patients died without evidence of relapse. This mortality rate is comparable to that reported for combination chemotherapeutic regimens in the treatment of newly diagnosed NHL. The European Bone Marrow Transplant Group with approximately 400 relapsed NHL patients observed a 20% treatment-related mortality[15] with other large series observing approximately 20% to 30%. The principle causes of treatment-related deaths in these series were interstitial pneumonitis and infection. Although 10 of our patients had prior irradiation to the chest, only one death due to interstitial pneumonitis was observed. No infectious deaths occurred in our series. The major difference in these mortality rates is probably related to patient selection. Our patients were required to achieve a minimal disease state before ABMT and, more importantly, were transplanted with a Karnofsky performance status above 80%. The inclusion of 34 patients with low-grade NHL and only two

patients with high-grade NHL may also have contributed to these results since most other studies have included only patients with high- and intermediate-grade NHL. In those studies, which included the subpopulation of NHL patients in sensitive relapse, a 20% treatment-related mortality was still observed, although the Karnofsky status for those patients varied between 20% and 100%.[1] Additional differences between these studies included histology, disease sensitivity at time of relapse, ablative regimen, and the use of prophylactic antibiotics.

Although median follow-up is still short, our results suggest that a history of lymphomatous bone marrow infiltration does not appear to affect long-term DFS. This observation is consistent with other studies that have examined this issue.[14,15] Of our 100 patients, 69 had a history of bone marrow involvement. Moreover, 37 had biopsy-proven bone marrow infiltration at the time of harvest. In contrast to the majority of other studies, we have not excluded these patients from ABMT. The bone marrows from all 100 patients were treated ex vivo with anti-B-cell MAbs and complement with the intent of depleting lymphoma cells. Although the median follow-up is only 13 months, 45% of patients with marrow involvement at the time of harvest who have relapsed did so in the marrow. In contrast, only 29% of relapsed patients with a negative marrow at harvest, relapsed in the bone marrow. The bone marrow relapse rate in our patients appears to be higher than reported by others using untreated histologically uninvolved marrow.[1] These results may be due to the fact that the majority of our patients had a history of bone marrow infiltration, that nearly 40% had positive marrows at harvest, and that approximately 50% had a low-grade or transformed from low-grade NHL, a disease that commonly involves the marrow. These results do not address the importance of ex vivo purging. It is not possible with present technology to determine whether relapse results from endogenous residual tumor cells or from reinfused tumor cells contaminating the bone marrow. It is a fact that most patients relapse in prior sites of bulk disease, and therefore tumor cells reinfused with the bone marrow may not contribute to relapse. However, the reinfused marrow-derived tumor cells may in fact be capable of homing to sites other than the bone marrow. To address this question, either cell surface or genetic markers of marrow-derived tumor cells would be required. This would permit the detection of these tumor cells in very small numbers at the time of relapse and to determine whether they were reinfused or endogeneously derived.

Our results of DFS for patients with sensitive relapsed NHL are identical to those previously reported in other series. High-dose ablative therapy and ABMT will result in a 40% to 50% long-term DFS for responsive patients. Published studies suggest that ABMT provides little benefit for patients with primary resistant or resistant relapsed NHL, with only 10% to 15% long-term disease-free survivors at best. At the time of referral for ABMT, between 30% to 60% of relapsed patients have resistant disease.[32] Moreover, many patients are excluded from ABMT because of overt bone marrow infiltration. Generally, the exclusion of patients with low-grade NHL from ABMT is due to the high frequency of marrow involvement in patients with that histology. With the 20% to 30% acute mortality and 40% to 60% relapse rates, only 25% of patients potentially derive long-term benefit. Therefore, the impact of ABMT on the treatment of NHL is presently minimal.

Most series support the view that only patients in relapse who are sensitive to conventional therapy will benefit from high-dose ablative therapy and ABMT. Preliminary studies suggest that when high-dose therapy and ABMT are used as consolidative treatment for patients who are unlikely to be cured with conventional therapy, the long-term DFS appears to be very high.[3,4,33,34] Three limited studies have addressed this approach. Gulati et al[4] reported 14 patients with poor-prognosis diffuse large-cell lymphoma transplanted in first remission. Eleven patients remained disease-free from 31 to 71 months. Seventeen patients with intermediate- and high-grade NHL in incomplete first remission were reported by Philip et al.[33] Thirteen of these patients were reported to be disease-free from 8 to 72 months. Finally, we have also taken 15 patients with poor-prognosis NHL in first remission. Only one patient has relapsed with follow-up from 2 to 48 months. It is important to note that in these 46 patients transplanted in first remission, only three early deaths were observed.

Several major issues concerning the role of high-dose therapy and ABMT in the treatment of B-cell NHL include improving high-dose ablative therapy, hastening engraftment, decreasing toxicity, examining the role of marrow purging, and determining the efficacy of this modality in the primary treatment of incurable NHL. Although each of these are important, the use of high-dose therapy and ABMT as a consolidation treatment regimen for patients in first remission may significantly affect the natural history of incurable NHL. The rationale for treating patients earlier is based on the present study's low mortality in relapsed patients and the high efficacy thus far observed in other studies for patients transplanted in first remission as well as the prompt engraftment observed in that patient population. Although controversial, several studies suggest that subgroups of patients with intermediate NHL can be identified who are at high risk for relapse. These include pretreatment clinical parameters as well as early assessment of responsiveness to therapy.[35-37] Moreover, we and others are beginning to undertake ABMT in first remission for subgroups of patients with incurable NHL including advanced-stage diffuse small-cleaved and follicular small-cleaved-cell and mixed NHL. Considering that more recently developed conventional-dose treatment regimens have had limited impact on the cure rate for NHL, it is now important to determine whether high-dose consolidation with bone marrow rescue will result in long-term DFS with tolerable mortality and morbidity.

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