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Lymphoma

Autotransplantation for advanced lymphoma and Hodgkin's disease followed by post-transplant rituxan/GM-CSF or radiotherapy and consolidation chemotherapy

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Summary:

Disease relapse occurs in 50% or more of patients who are autografted for relapsed or refractory lymphoma (NHL) or Hodgkin's disease (HD). The administration of non-cross-resistant therapies during the post-transplant phase could possibly control residual disease and delay or prevent its progression. To test this approach, 55 patients with relapsed/refractory or high-risk NHL or relapsed/refractory HD were enrolled in the following protocol: stem cell mobilization: cyclophosphamide (4.5 g/m^2) + etoposide (2.0 g/m^2) followed by GM-CSF or G-CSF; high-dose therapy: gemcitabine (1.0 g/m^2) on day −5, BCNU (300 mg/m^2) + gemcitabine (1.0 g/m^2) on day −2, melphalan (140 mg/m^2) on day −1, blood stem cell infusion on day 0; post-transplant immunotherapy (B cell NHL): rituxan (375 mg/m^2) weekly for 4 weeks + GM-CSF (250 μg thrice weekly) (weeks 4–8); post-transplant involved-field radiotherapy (HD): 30–40 Gy to pre-transplant areas of disease (weeks 4–8); post-transplant consolidation chemotherapy (all patients): dexamethasone (40 mg daily)/cyclophosphamide (300 mg/m^2/day)/etoposide (30 mg/m^2/day)/cisplatin (15 mg/m^2/day) by continuous intravenous infusion for 4 days + gemcitabine (1.0 g/m^2, day 3) (months 3 + 9) alternating with dexamethasone/paclitaxel (135 mg/m^2)/cisplatin (75 mg/m^2) (months 6 + 12). Of the 33 patients with B cell lymphoma, 14 had primary refractory disease (42%), 12 had relapsed disease (36%) and seven had high-risk disease in first CR (21%). For the entire group, the 2-year Kaplan–Meier event-free survival (EFS) and overall survival (OS) were 30% and 35%, respectively, while six of 33 patients (18%) died before day 100 from transplant-related complications. The rituxan/GM-CSF phase was well-tolerated by the 26 patients who were treated and led to radiographic responses in seven patients; an eighth patient with a blastic variant of mantle-cell lymphoma had clearance of marrow involvement after rituxan/GM-CSF. Of the 22 patients with relapsed/refractory HD (21 patients) or high-risk T cell lymphoblastic lymphoma (one patient), the 2-year Kaplan–Meier EFS and OS were 70% and 85%, respectively, while two of 22 patients (9%) died before day 100 from transplant-related complications. Eight patients received involved field radiation and seven had radiographic responses within the treatment fields. A total of 72 courses of post-transplant consolidation chemotherapy were administered to 26 of the 55 total patients. Transient grade 3–4 myelosuppression was common and one patient died from neutropenic sepsis, but no patients required an infusion of backup stem cells. After adjustment for known prognostic factors, the EFS for the cohort of HD patients was significantly better than the EFS for an historical cohort of HD patients autografted after BEAC (BCNU/etoposide/cytarabine/cyclophosphamide) without consolidation chemotherapy (P = 0.015). In conclusion, post-transplant consolidation therapy is feasible and well-tolerated for patients autografted for aggressive NHL and HD and may be associated with improved progression-free survival particularly for patients with HD.

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Although combination chemotherapy leads to cures in a substantial proportion of patients with advanced Hodgkin's disease (HD) or aggressive lymphoma (NHL), the long-term outlook for patients who do not obtain a complete remission after initial therapy or who have relapses of disease is extremely poor.[1,2] High-dose cytotoxic therapy (HDT) followed by autologous hematopoietic stem cell rescue has significantly improved the disease-free and overall survival of these patients. However, the 2–5 year event-

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or progression-free survival for patients with relapsed or refractory NHL ranged from about 31–53% in selected series with lower figures generally observed for patients with primary refractory disease, transformed lymphomas, or high-risk features prior to transplantation (high LDH, bulky disease, extranodal involvement).[3–12] Similarly, the 3–5 year actuarial disease or event-free survival for patients with relapsed or refractory HD ranged from 32 to 64% in selected series with lower figures generally observed for patients with primary refractory disease or high-risk features at the time of transplantation including 'B' symptoms, elevated LDH levels, chemotherapy resistance, bulky disease and decreased performance status.[13–19] The chief cause for treatment failure in the majority of these studies was disease progression or relapse, meaning that 50% or more of patients who received autotransplants for relapsed or refractory NHL or HD had relapses of disease.

New strategies designed to reduce the incidence of relapse after autotransplantation must take the following considerations into account: (1) the limited hematopoietic reserve during the early post-transplant period; (2) the temporal and anatomic patterns of relapse; and (3) the mechanisms responsible for lymphoma cell resistance to high-dose chemotherapy. In two representative studies, the median time to relapse or progression was 4 months for NHL patients and 5 months for HD patients. Only about 10% of relapses in both groups occurred 2 years or more after transplant.[12,13] In addition, about two-thirds of the relapses involved sites of prior disease. The precise mechanisms responsible for resistance to high-dose chemotherapy are unknown, but presumably they include those which are thought to operate in lymphomas that recur after conventional-dose regimens. These mechanisms include up-regulation of P-glycoprotein,[20,21] up-regulation of bcl-2 expression,[22–24] and mutation of the P53 genes.[22,24] The latter two mechanisms may block the induction of apoptosis by a variety of important anti-neoplastic drugs. Indeed, the induction of apoptosis by the alkylating agents typically used in high-dose regimens (eg melphalan) is highly dependent upon the presence of wild-type P53 genes.[25] These facts imply that in order to decrease relapse rates after HDT, additional treatment must be rendered early after recovery from HDT and should include the sites of prior disease. Administration of non-cross-resistant chemotherapy may be important in this effort.

With this background, two clinical protocols were developed which contained several treatment modifications designed to address some of the problems which were identified above. First, the high-dose chemotherapy regimen was modified from the standard BEAM regimen (BCNU/etoposide/cytarabine/melphalan) by the substitution of gemcitabine for cytarabine and etoposide. Compared to cytarabine, gemcitabine has equivalent anti-leukemic activity in murine and human pre-clinical leukemia models and a longer intracellular retention time while displaying a lack of cross-resistance to doxorubicin, etoposide, cyclophosphamide, melphalan, cisplatin, and methotrexate.[26–28] Gemcitabine also has single agent activity in heavily pre-treated patients with relapsed HD and NHL.[29] Additionally, etoposide was given at a higher dose level in combination with cyclophosphamide for pre-transplant cytoreduction and stem cell mobilization. Second, during the early post-transplant period (approximately weeks 4–8) when hematopoietic recovery might be incomplete, patients were scheduled to be treated with agents considered to have limited effects on marrow function: patients with B cell NHL were assigned to receive the anti-CD20 monoclonal antibody rituxan in combination with GM-CSF while patients with HD and T cell NHL were assigned to receive low-moderate dose involved-field radiation to sites of pre-transplant involvement. The rationale for adding GM-CSF to rituxan was to potentially augment antibody-dependent cellular cytotoxicity (ADCC) through enhanced effector cell recruitment and activation.[30–33] The third innovation was to utilize a series of consolidation chemotherapy treatments at 3, 6, 9 and 12 months post transplant when hematopoietic recovery might be more complete. The regimen for months 3 and 9 was dexamethasone-cyclophosphamide-etoposide-cisplatin-gemcitabine (DCEP-G) and the regimen for months 6 and 12 was dexamethasone-paclitaxel-cisplatin (DPP). The DCEP-G regimen was modified from DCEP which was originally developed for the treatment of patients with relapses of myeloma after autotransplantation.[34] This regimen produced major responses (>75% reductions in paraprotein levels) in 41% of patients with relapsed myeloma. In addition, equivalent responses were observed for patients with both plasmacytic and plasmablastic histologies, suggesting that this regimen might also be active for patients with other aggressive lymphoid neoplasms. To permit inclusion of gemcitabine, a novel agent with single agent activity against advanced NHL and especially HD,[35] the doses of cyclophosphamide, etoposide, and cisplatin were attenuated from the original DCEP. Paclitaxel was utilized because responses to tubulin-active agents do not appear to depend on the presence of wild-type p53,[25] and paclitaxel is a potent inducer of bcl-2 phosphorylation which leads to inactivation of this anti-apoptotic oncogene.[36] Furthermore, the administration of paclitaxel alone to patients with relapsed or refractory NHL resulted in overall response rates of 17% (140 mg/m^2) or 25% (200 mg/m^2) and an overall response rate of 44% when combined with moderately high-dose cyclophosphamide.[37–39] Therefore, it was anticipated that the DPP regimen might be active against residual alkylator-resistant lymphoma cells which remained after high-dose therapy. In this paper, we describe the outcomes of 55 patients with advanced aggressive NHL and HD who were offered the series of post-transplant consolidation treatments outlined above.

Materials and methods

Patients

A total of 55 patients with advanced HD or NHL received autotransplants between April 1998 and April 2001. The characteristics of the 22 HD/T cell lymphoma and 33 B cell NHL patients are shown in Table 1. Patients were defined as having relapsed disease if they were considered to be in complete remission for any length of time after induction therapy. Patients with primary refractory disease

Table 1 Patient characteristics

A. HD/T cell lymphoma	
Total number	22
HD	21
T cell lymphoma	1
Gender	
Male	13
Female	9
Age	
Median	36
Range	19–54
Disease status (pre-transplant)	
Minimal	7
Bulky	15
Remission status	
Relapsed	15
Primary refractory	6
High-risk	1
Post-transplant XRT	
Yes	8
No	14
B. B cell NHL	
Total number	33
Gender	
Male	27
Female	6
Age	
Median	55
Range	22–69
Remission status	
Relapsed	12 (36%)
Primary refractory	14 (42%)
High-risk	7 (21%)
Histology	
Diffuse large cell	22
Diffuse mixed	3
Diffuse small cleaved	3
Other	5

had radiographic or histologic evidence of residual disease after completion of induction therapy or disease progression during induction therapy. In fact all 20 of the patients in this category (14 patients with NHL and six patients with HD) had bulky residual lymphadenopathy ($\geqslant$4.0 cm) or extensive residual extranodal disease (eg $\geqslant$25% residual marrow involvement) or progressive disease prior to stem cell mobilization. None of these patients were considered to have very good partial or near-complete responses to induction chemotherapy. Patients with 'high risk' lymphoma in first complete remission were eligible for HDT if they met three or more of the following criteria at diagnosis: stage III, IV disease; $\geqslant$2 extranodal sites; LDH $\geqslant$1.2$\times$ upper limit of normal; performance status 2–4; largest tumor $\geqslant$10 cm. Patients with transformed lymphomas were eligible without regard to remission status. Patients with high risk HD in first apparent complete remission were not enrolled.

Pre-transplant mobilization chemotherapy consisted mainly of cyclophosphamide 4.5 g/m^2 over 12 h with mesna for urothelial protection followed by etoposide 2.0 g/m^2 over 4–6 h. Alternative mobilization regimens were used for five of the 55 patients: two patients received etoposide 10 mg/kg and cytarabine 2 g/m^2 for 4 consecutive days; two patients received cyclophosphamide 3.0 g/m^2 and etoposide 1.0 g/m^2 due to compromised cardiopulmonary function; and one patient received cyclophosphamide at a dose of 4.5 g/m^2 with mesna alone. In addition, one patient received rituxan at a dose of 375 mg/m^2 on days 1, 8 and 15 of the mobilization regimen in combination with cyclophosphamide and etoposide. This patient was the only one to receive pre-transplant rituxan. Hematopoietic growth factor support was primarily GM-CSF for the patients with B cell NHL and G-CSF for the patients with HD/T cell NHL. Thirty liter apheresis procedures were performed through indwelling catheters in order to collect a minimum of 4 $\times$ 10^6 CD34$^+$ progenitors per kg body weight. The higher minimal collection standard was selected based on the protocol requirement to retain a backup stem cell product for infusion in the event of delayed marrow recovery after consolidation chemotherapy. After completion of mobilization therapy, patients were restaged prior to HDT with CT scans, gallium scans, and if necessary, marrow biopsies. Based on these results, patients were defined as having minimal disease if all foci were $\leqslant$2 cm in maximal diameter and extranodal involvement was limited to one location; otherwise patients were defined as having bulky disease. All patients gave written informed consent for participation in one of the two IRB-approved protocols.

High-dose therapy and supportive care

Of the 55 total patients who received autografts, 51 received the GBM regimen, consisting of gemcitabine (1.0 g/m^2) on day $-$5, BCNU (300 mg/m^2) followed 6 h later by gemcitabine (1.0 g/m^2) on day $-$2, and melphalan (140 mg/m^2) on day $-$1. Four patients with compromised pulmonary function (DLCO $\leqslant$50% predicted) received high-dose melphalan alone (100 mg/m^2 daily $\times$ 2 days) to avoid the risk of additional pulmonary toxicity from BCNU. All four of these patients had HD.

On day 0, autologous stem cells were thawed and infused according to standard procedures. Post-infusion hematopoietic growth factor support commenced on day +4 and consisted of GM-CSF (250 or 500 μg) (B cell NHL) or G-CSF (300 or 480 μg) (HD and T cell NHL). Patients received care in individual HEPA-filtered rooms. Antibiotic prophylaxis varied during the course of the study, depending on hospital epidemiologic considerations, but generally included HSV prophylaxis with famciclovir or acyclovir and anti-fungal prophylaxis with oral troches or oral fluconazole.

Post-transplant immunotherapy (B cell NHL)

After completion of week 4 post-transplant restaging studies, the patients with B cell NHL were started on GM-CSF at a dose of 250 μg subcutaneously on a Monday–Wednesday–Friday schedule. At weeks 5, 6, 7 and 8 the patients received chimeric anti-CD20 monoclonal antibody (rituxan) at a dose of 375 mg/m^2 while the GM-CSF was continued to week 8. Restaging studies were again performed after completion of the antibody treatments to assess the response to this phase.

Post-transplant involved-field radiation (HD/T cell NHL)

Involved-field radiotherapy was administered post transplant to patients with HD or T cell NHL who entered transplant with bulky lymphadenopathy or extranodal masses. Bulky disease was defined as any tumor mass that exceeded 2 cm in maximal diameter. The plan was for radiation therapy to be completed within 12 weeks of transplant but the major requirement was that radiotherapy should not begin until the neutrophil count exceeded 1000/μl without hematopoietic growth factor support and red cell and platelet transfusion support was no longer required. The dose of radiation was graduated as follows: patients in complete remission (CR) after transplant were scheduled to receive 20 Gy to sites of disease present prior to transplant, based on normal tissue tolerance. In addition, patients who were in CR before transplant but had >5 cm tumor masses initially were also scheduled to receive 20 Gy of post-transplant radiation to those sites. Patients with residual tumor masses post transplant were scheduled to receive 30 Gy. If additional tumor shrinkage was observed after completion of the 30 Gy, then an additional 6–10 Gy was recommended based on normal tissue tolerance.

Consolidation chemotherapy

At 3 months and 9 months post transplant, patients with a neutrophil count $\geqslant$1500/μl, a platelet count $\geqslant$100 000/μl, and a serum creatinine $\leqslant$2 mg/dl were eligible to receive DCEP-G. This regimen consisted of dexamethasone 40 mg orally for 4 consecutive days, cyclophosphamide 300 mg/m^2 daily by continuous infusion (CI) for 4 days, etoposide 30 mg/m^2/day by CI for 4 days, cisplatin 15 mg/m^2/day by CI for 4 days, and gemcitabine 1 g/m^2 over 100 min on day 3 of the regimen. If the platelet count was 50–100 000/μl or the neutrophil count was 1000–1500/μl, then the gemcitabine was eliminated. If the platelet count was $<$50 000/μl, or the neutrophil count was $<$1000/μl, consolidation chemotherapy was not given. At 6 and 12 months post transplant, the patients were eligible to receive DPP, consisting of dexamethasone 40 mg orally daily for 4 days, paclitaxel 135 mg/m^2 over 6 h on day 2, and cisplatin 75 mg/m^2 over 24 h on day 3. Post-treatment supportive care included GM-CSF for patients with B cell NHL and G-CSF for patients with HD and T cell NHL. At least 2×10^6 CD34$^+$ cells/kg body weight were available for infusion following consolidation chemotherapy for delayed neutrophil recovery (neutrophil count $<$100/μl at 14 days or $<$500/μl at 21 days) or if a life-threatening infection developed. The use of a back-up stem cell product precluded further consolidation chemotherapy.

Statistical methods

For the event-free survival, an event was either relapse or death from any cause. For the overall survival, an event was death from any cause. The survival curves were generated according to the Kaplan–Meier product-limit method.[40] The comparison of event-free survival between the two cohorts of HD patients with adjustment of known prognostic factors was based on the Cox-regression model.[41]

Results

Survival

As shown in Figure 1 the 2-year Kaplan–Meier EFS for the cohort of 22 patients with HD (21 patients) or T cell NHL (one patient) was 70% (53–94%, 95% confidence interval CI) while the 2-year overall survival was 85% (71–100%, 95% CI). Of the 22 total patients, 16 were surviving event-free at a median follow-up of 1 year. Six patients had events including four patients who had relapses at 2, 3, 8 and 9 months after transplant and two patients who died from treatment-related complications. Three of the four patients who had relapses were alive at last follow-up including one patient who was in complete remission almost 1 year after a syngeneic transplant. The two patients who died of treatment-related complications included one patient who died 2 months after autotransplant from respiratory failure possibly due to a viral pneumonitis and one patient with a history of anthracycline-induced cardiomyopathy who died on day 18 from heart failure and gastrointestinal hemorrhage.

As shown in Figure 2, the 2-year Kaplan–Meier EFS for the cohort of 33 patients with B cell NHL, was 30% (18–53%, 95% CI) while the 2-year OS was 35% (21–58%,

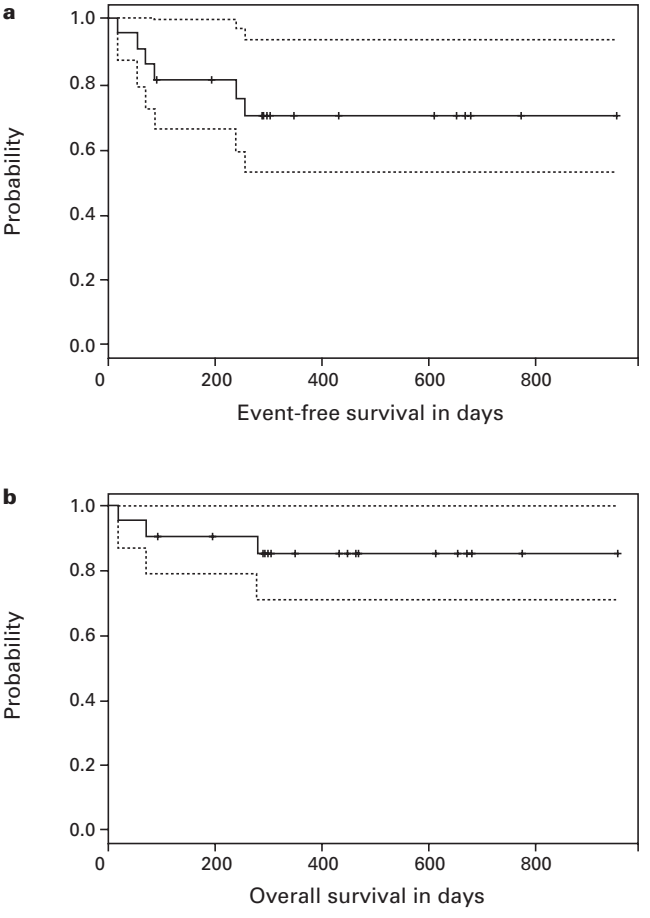

Figure 1 Event-free survival (**a**) and overall survival (**b**) for the cohort of 22 HD/T cell NHL patients. The dotted lines show the 95% confidence intervals.

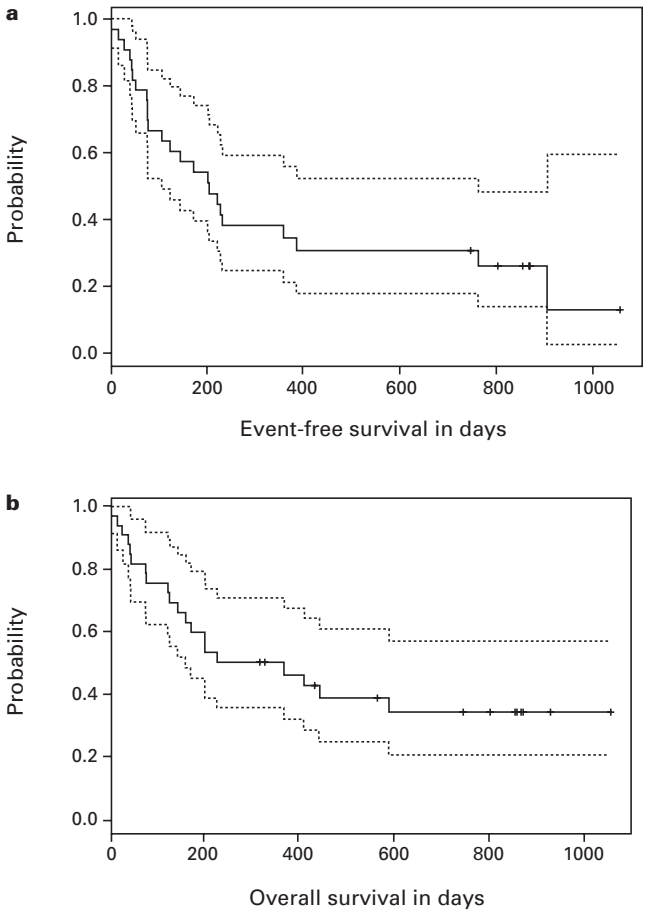

Figure 2 Event-free survival (**a**) and overall survival (**b**) for the cohort of 33 B cell NHL patients. The dotted lines show the 95% confidence intervals.

95% CI). Of the 33 total patients, nine were surviving event-free at a median follow-up at 2.2 years. Twenty-four patients had events including 14 patients who had relapses of lymphoma and 10 patients who died from causes other than disease relapse. The median time to relapse was 7 months (range 1.5–30 months). Of the 14 patients who had relapses, 10 have died (6: <1 year after transplant and 4: $\geqslant 1$ year after transplant) and four were surviving after further treatment. One noteworthy patient was progression-free and gallium-negative for about 1 year after receiving involved-field radiation to retroperitoneal adenopathy which responded minimally to rituxan plus EPOCH (infusional etoposide/vincristine/doxorubicin plus prednisone and cyclophosphamide).

Of the 10 patients with non-relapse events, six patients died before day 100 from CMV pneumonitis (2), stenotrophomonas maltophilia sepsis (1), idiopathic pneumonitis and hepatic failure (1), sepsis syndrome (1), and a fatal stem cell infusion reaction (1). Four patients died after day 100 (range 123–172 days) from bowel obstruction secondary to prior surgery (1 patient), neutropenic sepsis culminating in ARDS and renal failure following the first course of consolidation chemotherapy (1 patient), bronchiolitis obliterans (1 patient), and a demyelinating encephalopathy consistent with progressive multifocal leuko-encephalopathy (PML) (1 patient). The patient who died from the demyelinating encephalopathy had primary CNS lymphoma but had not received cranial radiation. *In situ* hybridization for JC virus, the etiologic agent for PML was negative in this patient. None of the patients who died from non-relapse events before day 100 received any post-transplant consolidation therapy, while all four of the patients who had non-relapse events after day 100 had received rituxan/GM-CSF immunotherapy and two also received one course each of consolidation chemotherapy.

Effect of post-transplant antibody therapy

Of the 33 total B cell NHL patients, six died too early to receive rituxan/GM-CSF post-transplant immunotherapy and one patient declined further treatment. Of the 26 patients who received rituxan/GM-CSF, all completed the four scheduled infusions, except one patient who relapsed and died after the third infusion. Treatment was well-tolerated and no serious infusion reactions were observed. Four of the 26 patients (15%) had about a 50–60% decrease in their platelet counts during the rituxan/GM-CSF phase accompanied by a 30–70% decrease in their white blood counts. An additional four patients (15%) had isolated reductions of 25–50% in their platelet counts. Thorough restaging studies performed just before and about 4 weeks after the rituxan/GM-CSF phase revealed that seven patients had measurable radiographic responses in sites of known involvement. Table 2 shows the CT scan measurements of index sites before and after rituxan/GM-CSF treatment for these seven patients. Figure 3 shows the CT scans of one representative patient demonstrating the radiographic response which followed rituxan/GM-CSF. As depicted in Figure 4, an eighth patient with residual marrow involvement (post transplant) of a blastic variant of mantle cell lymphoma had a complete histologic response directly following the rituxan/GM-CSF phase of therapy. Furthermore, a marrow aspirate from this patient which was positive for a clonal JH rearrangement by Southern analysis post transplant, became negative for this rearrangement after the rituxan/GM-CSF phase.

Table 2 Radiographic responses to rituxan/GM-CSF for seven (of 26) patients who received this phase of treatment

Patient	*Location*	*Post transplant*	*Post rituxan/ GM-CSF*
9740-2	Spleen	3 hypodense lesions	1 hypodense lesion
9740-7	Portahepatis	2.0 cm	1.0 cm
9740-11	Mesenteric node	3.3 cm	2.5 cm
9740-12	Liver lesion	8.7 cm × 4.3 cm	8.0 cm × 3.7 cm
9740-23	Splenic lesion	1.4 cm lesion	$<$1.0 cm
9740-30	Retroperitoneal nodes	2.0 cm × 2.3 cm (gallium +)	1.0 cm × 1.3 cm (gallium −)
9740-33	Inguinal nodes	2.3 cm × 2.9 cm	1.7 cm × 2.3 cm

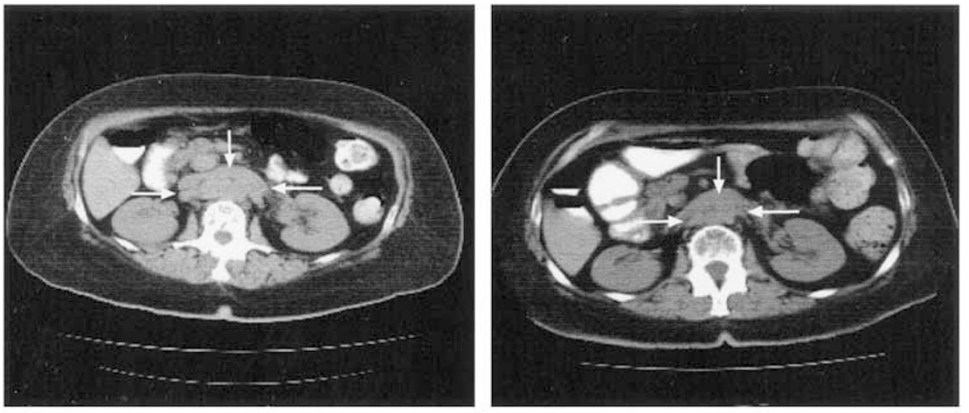

Figure 3 CT scans which demonstrate a decrease in the size of a retroperitoneal nodal mass (delineated by arrows) following the rituxan/GM-CSF phase. This response was accompanied by resolution of gallium avidity.

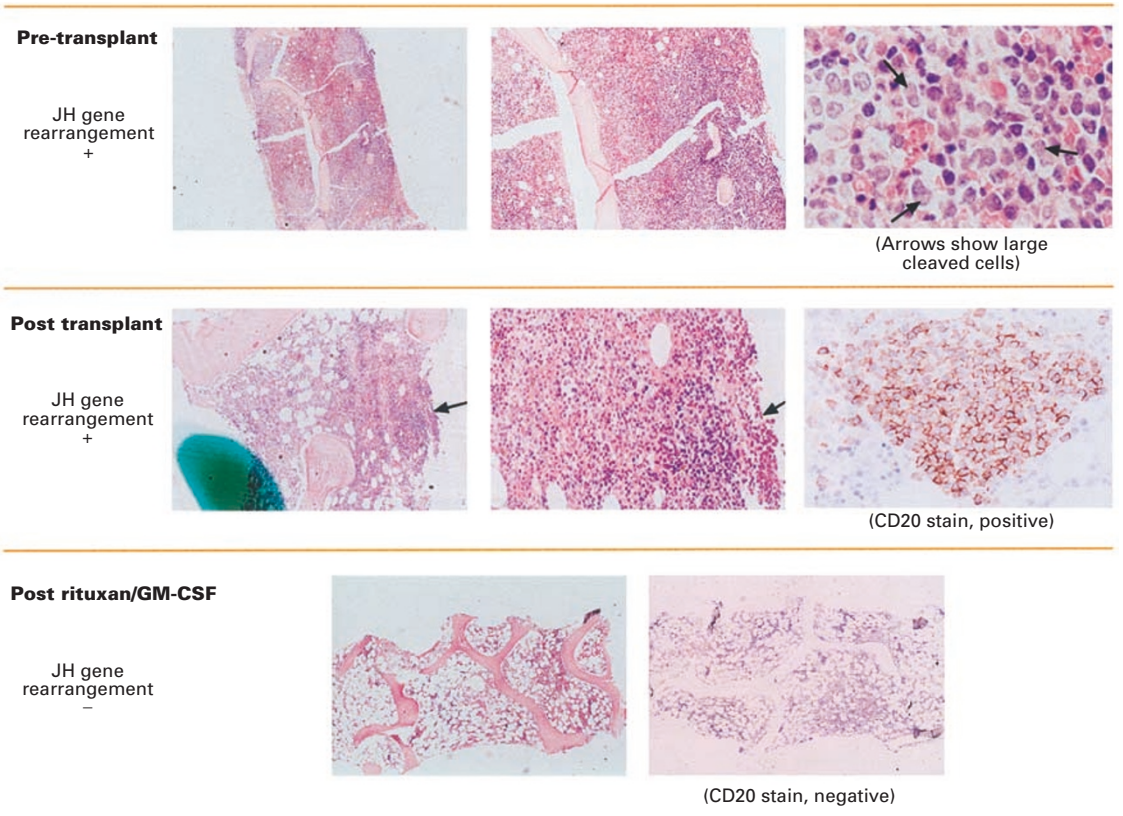

Figure 4 Serial marrow biopsy sections which demonstrate residual mantle cell lymphoma (blastic variant) post transplant (identified by black arrows) and its clearance after rituxan/GM-CSF. This histologic response was accompanied by disappearance of the clonal JH rearrangement which was detected in the pre- and post-transplant marrow samples by Southern analysis.

Effect of post-transplant radiotherapy

Of the 22 patients with HD or T cell NHL who received autotransplants, 14 met the criteria to receive post-transplant involved-field radiation. Four of the 14 patients could not be treated due to early treatment-related mortality (2), compromised pulmonary function (1), or prior radiation treatment of the involved field (1). Two additional patients refused radiotherapy. Eight patients were ultimately treated, seven of whom had incremental radiographic responses of index nodes located in the treatment fields as shown in Table 3. An additional patient who received involved-field radiation for early post-transplant disease progression also had a significant radiographic response but later developed progression in the abdomen. Radiotherapy was well-tolerated by seven patients; however, one patient who had primary refractory disease and an 8 cm mediastinal mass both pre-and post transplant developed symptoms of restrictive lung disease about 1 month after post-transplant mediastinal radiation. Currently, this patient has stable

Table 3 In-field radiographic responses which followed involved-field radiation treatment

Patient	*Treatment field*	*Post transplant*	*Post radiation*
9812-2	Mantle	6 cm × 2.0 cm	4.6 cm × 1.7 cm
9812-4	Mediastinum	7.9 cm × 2.0 cm	5.5 cm × 0.9 cm
9812-5	Pelvis	3.3 cm × 3.4 cm	2.2 cm × 2.2 cm
9812-10	Mantle	2.2 cm	1.4 cm
9812-11[a]	Mantle	5 cm × 2 cm	3.1 cm × 1.4 cm
9812-12	Mantle	5.2 cm × 3.1 cm	2.4 cm × 2.1 cm
9812-14	Inguinal	1.6 cm	0.8 cm
9812-16	Pelvic	2.4 cm	<1.0 cm

Seven patients received involved-field radiation as consolidation treatment while one patient (9812-11) was treated for early progression post transplant.
[a]Treated for early progression.

exertional dyspnea and a Karnofsky performance score of 90%.

Consolidation chemotherapy

Of the 55 total patients, 26 (15 B cell NHL patients + 11 HD/T cell NHL patients) received at least one course of consolidation chemotherapy, 19 patients received at least two courses of consolidation chemotherapy, and 17 received at least three or four courses. The reasons that 29 patients did not start consolidation chemotherapy included early relapse or treatment-related mortality (16), patient refusal (8), delayed marrow recovery (3), and severe comorbid conditions (2). A total of 72 courses of post-transplant consolidation chemotherapy were administered to the 26 patients. The treatments were generally well-tolerated, although transient grade 3–4 myelosuppression was common as shown in Table 4. The frequency of moderate to severe myelosuppression was somewhat lower after DPP (courses 2 and 4) than after DCEP-G (courses 1 and 3). One patient died from neutropenic sepsis which developed after administration of the first consolidation chemotherapy course. No patients met criteria for infusion of back-up stem cells. Of the 15 NHL patients who received at least one course of post-transplant chemotherapy, six had relapses, one died from complications of aplasia, and eight were surviving event-free. Of the 11 HD/T cell NHL patients who received at least one course of post-transplant chemotherapy, one patient had a relapse and 10 were surviving event-free. It should be noted that to date, no patients have developed post-transplant myelodysplasia or acute myelogenous leukemia.

Table 4 Percentages of patients who had (CALGB) grade 3/4 hematologic toxicity following each consolidation chemotherapy treatment

	Consolidation course			
	1	*2*	*3*	*4*
% Grade 3/4 neutropenia	100	44	83	57
% Grade 3/4 thrombocytopenia	90	50	91	29

In an attempt to evaluate what impact, if any, the consolidation chemotherapy treatments had on event-free survival, the cohort of 21 patients who were autografted for HD was compared to a similar historical cohort of 70 HD patients who received BEAC (BCNU/etoposide/cytarabine/cyclophosphamide) conditioning and post-transplant involved field radiation without consolidation chemotherapy.[13] After adjustment for known prognostic factors including disease burden prior to autotransplantation (minimal *vs* bulky), remission status (primary refractory *vs* relapsed), and receipt of post-transplant radiotherapy, the cohort of 21 HD patients described in this study had a significantly better EFS than the historical cohort ($P = 0.015$). The EFS curves for these two cohorts are depicted in Figure 5.

Discussion

To address the problem of high relapse rates after autotransplantation for relapsed or refractory NHL or HD, we attempted to introduce a series of post-transplant consolidation treatments. Early after transplantation, relatively non-myelotoxic treatments were administered: rituxan combined with GM-CSF for patients with B cell NHL and involved-field radiation for patients with HD or T cell NHL. Later after transplantation, patients were eligible to receive DCEP-G alternating with DPP at 3, 6, 9 and 12 months. Several conclusions can be drawn for this experience. First, post-transplant consolidation treatments are feasible and generally well-tolerated. Twenty-five of the 26 patients with B cell NHL who survived long enough to receive rituxan + GM-CSF, completed all four infusions and none had serious infusion-related toxicities. In addition, myelosuppression was mild and infrequent. However, two of the patients who received the rituxan infusions, later

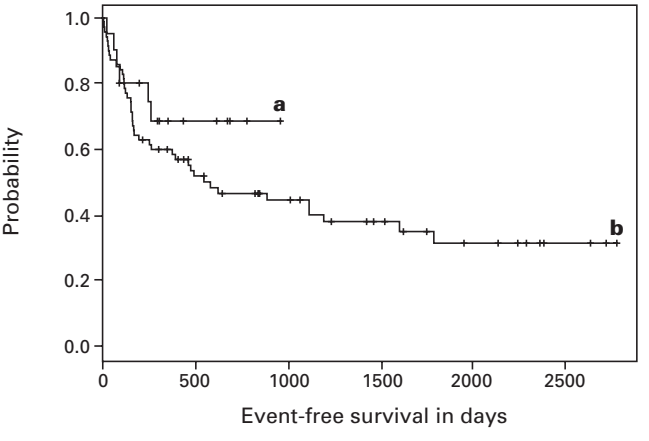

Figure 5 Comparison of event-free survivals for the cohort of 21 HD patients included in this report (upper curve, **a**) and an historical cohort of 70 HD patients (lower curve, **b**). After adjustment for known prognostic factors including disease burden prior to transplant, remission status, and administration of post-transplant radiation, these curves were significantly different ($P = 0.015$).

developed complications: bronchiolitis obliterans (1 patient) and a demyelinating encephalopathy (1 patient) which was consistent with progressive multifocal leukoencephalopathy although JC virus DNA was not detected by *in situ* hybridization. The occurrence of these unusual complications of HDT, which may be linked to infections, highlights the need for close monitoring of patients who receive post-transplant therapies with immunosuppressive potential. Indeed, another study of adjuvant rituxan after autotransplantation revealed delayed immune recovery but no apparent increase in post-transplantation infections.[42] None of the eight patients who received post-transplant involved-field radiation had late-stage infections but one patient developed restrictive lung disease, highlighting the need for close monitoring of pulmonary function in those patients who receive post-transplant radiation to the chest.

The 72 courses of post-transplant consolidation chemotherapy were also generally well-tolerated by the 26 patients who were treated, although a single patient died from ARDS and renal failure during aplasia following the first course of consolidation chemotherapy. As expected, moderate to severe marrow suppression was common, although transient, as none of the patients required an infusion of back-up stem cells. The frequency of grade 3 or 4 hematologic toxicity was lower after dexamethasone-paclitaxel-cisplatin (DPP) than after dexamethasone-cyclophosphamide-etoposide-cisplatin + gemcitabine (DCEP-G).

Second, incremental radiographic responses were noted after both the rituxan/GM-CSF phase for the patients with B cell NHL and after involved-field radiation for the patients with HD. About one-third of the patients who received post-transplant rituxan/GM-CSF (8 of 26) had measurable responses while the majority of radiotherapy recipients (7 of 8) responded. While it could be argued that the observed changes might represent delayed responses to high-dose chemotherapy, the complete marrow response which occurred in one patient directly following rituxan/GM-CSF and the resolution of gallium avidity in association with decreased adenopathy in another patient, indicate that at least some of the incremental responses observed were due to the post-transplant antibody administration.

Third, the contribution of post-transplant therapy and particularly post-transplant consolidation chemotherapy to event-free and overall survival remains to be determined. The event-free and overall survival figures for the cohort of patients with B cell NHL were no better than published results due to the relatively high rates of relapse and treatment-related mortality in this series. These causes of treatment failure may be due in part to patient selection given the relatively high proportion of patients (42%) who were transplanted with primary refractory disease. Nonetheless, the apparent failure of post-transplant consolidation therapy to delay or prevent relapse in this cohort of challenging patients with advanced B cell NHL may indicate that the post-transplant chemotherapy regimens were largely ineffective or that re-growth of lymphoma was too rapid for the treatments to be completed. Indeed, six of the 15 patients (40%) who received post-transplant chemotherapy had relapses and of the 15 patients treated, only nine (60%) were able to receive three or more courses of consolidation chemotherapy.

In contrast, the 2-year event-free and overall survival figures for the cohort of HD patients was relatively high considering that all enrolled HD patients had relapsed or refractory disease. Of the 10 patients (9 HD, 1 T cell lymphoblastic lymphoma) who received at least one course of consolidation chemotherapy, nine were surviving event-free. Eight of the 10 patients (80%) received three or more courses of consolidation chemotherapy. The event-free survival for the cohort of 21 patients autotransplanted for relapsed/refractory HD was compared to an historical cohort of 70 patients who received BEAC conditioning. The 2-year EFS for the current cohort was significantly better than the historical cohort after adjustment for previously identified independent prognostic factors.[13] These factors included disease status at transplant (minimal *vs* bulky), remission status (refractory *vs* relapsed), and administration of post-transplant involved-field radiation. However, the possibility remains that the observed difference could be due to other factors such as the use of gemcitabine in the GBM conditioning. In addition, the effect of post-transplant consolidation chemotherapy may have been to delay rather than to prevent relapse of disease. Longer follow-up of a larger number of patients will be needed to address this possibility.

Other possible strategies for augmenting lymphoma responses after autotransplantation include the sequential use of non-myeloablative allogeneic stem cell transplantation or the adoptive transfer of *ex vivo* costimulated autologous T cells.[43,44] The first strategy which is limited to patients with histocompatible donors was associated with favorable outcomes in 10 of 15 patients with relapsed or refractory HD or NHL. While feasible, the ability of *ex vivo* costimulated autologous T cells to mount an effective immune and/or clinical response post transplant in patients with aggressive lymphoma is unknown. Post-transplant administration of dendritic cell vaccines can induce anti-myeloma immune responses in patients with myeloma.[45–47] In addition, tumor-specific idiotype vaccines have been shown to induce immune responses in patients with follicular lymphoma and may be associated with superior clinical responses.[48,49] However, the applicability of these approaches to patients with aggressive B cell lymphoma is uncertain.

In this study, we have demonstrated that post-transplant consolidation therapy using rituxan/GM-CSF or involved-field radiotherapy followed by four courses of non-cross resistant chemotherapy is feasible and well tolerated for patients with aggressive NHL and HD. Furthermore, this approach may be associated with further cytoreduction in select patients with B cell NHL and improved event-free survival in patients with HD. Additional studies will be needed to validate this initial experience with post-transplant consolidation therapy.

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