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Cytoreduction regimens

A novel preparative regimen for autologous transplant in non-Hodgkin's lymphoma: long-term experience with etoposide and thiotepa

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Summary:

The purpose of this study was to evaluate the efficacy and toxicity of the preparative regimen of thiotepa and etoposide in patients undergoing autologous transplantation for relapsed non-Hodgkin's lymphoma. The study involved 65 consecutive patients who underwent autologous transplantation using the thiotepa/etoposide regimen for relapsed intermediate-grade NHL at the University of Wisconsin Hospital and Clinics (UWHC) between 1987 and 2001. The regimen consisted of thiotepa 300 mg/m^2/day and etoposide 700 mg/m^2/day on days –6, −5, and –4. The median age at the time of transplant was 49 years. A total of 50 patients (76%) had diffuse large-cell lymphoma. A total of 50 (77%) patients had chemosensitive disease, and 15 (23%) were chemoresistant. With a median follow-up of 34 months (range, 3–163), 28 patients (43%) remain in CR and 33 (51%) have developed recurrent or progressive disease. The overall survival and event-free survival at 3 years are 40% (95% CI 26–53%) and 32% (95% CI 20–45%), respectively. There was one death attributed to regimen-related toxicity (RRT). Reversible gastrointestinal toxicity was the major RRT, and there was minimal pulmonary and cardiac toxicity. We conclude that the combination of thiotepa and etoposide is an effective preparative regimen with acceptable RRT.

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For patients with relapsed, aggressive non-Hodgkin's lymphoma (NHL), high-dose chemotherapy (HDCT) followed by autologous bone marrow (BM) or peripheral blood progenitor cell (PBPC) rescue has improved overall and event-free survival (EFS) compared with conventional therapy for those with chemosensitive disease.[1] There are no randomized trials comparing different preparative regimens for relapsed NHL, and it is unknown if any preparative regimen is superior. The ideal preparative regimen would have little regimen-related toxicity (RRT) while still producing overall survival (OS) and EFS that are better than with salvage chemotherapy alone.

Despite improved supportive care, significant regimen-related morbidity and mortality may occur with the commonly used regimens containing assorted combinations of BCNU, cyclophosphamide, etoposide, busulfan, and melphalan. Various single institution studies have shown the incidence of pulmonary toxicity in BCNU-containing regimens to be anywhere from one to 17%.[2–5] Van Besien *et al*[2] reported 13% of patients receiving BEAC prior to autologous transplant for NHL developed cardiac toxicity.

Etoposide has long been used in HDCT regimens for NHL because of its excellent activity against this disease, its lack of significant extramedullary toxicity, and its favorable pharmacokinetics.[6] Thiotepa has been used most frequently in transplant preparative regimens for nonhematologic malignancies, particularly breast cancer. In 1986, Finlay *et al*[7] began studying the use of high-dose thiotepa and etoposide followed by autologous BM transplantation in children with high-grade CNS tumors. As this preparative regimen was well tolerated in the pediatric population with little RRT, a protocol using thiotepa and etoposide was developed in 1987 at the University of Wisconsin Hospital and Clinics (UWHC) as a preparative regimen for autologous BM transplantation in adults with relapsed NHL. Herein, we describe our experience with this novel HDCT regimen.

Patients and methods

Patient characteristics

Between 1987 and May 2001, 65 consecutive patients with relapsed NHL underwent HDCT followed by autologous hematopoietic stem cell transplantation at the UWHC. All patients had intermediate-grade NHL as defined by the Working Formulation. Informed consent was obtained from patients under a study protocol approved by the UWHC institutional review board. Eligibility criteria were age between 18 and 65 years; adequate renal, cardiac, pulmonary, and hepatic function, and the absence of BM involvement with lymphoma at the time of marrow harvest

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Table 1 Patient characteristics, *N* (%)

Total number of patients	65
Male	41 (63)
Female	24 (37)
Median age at transplant (years)	49
Range	19–64
Diagnosis	
Follicular large cell	6 (9)
Diffuse small cleaved	1 (2)
Diffuse mixed cleaved	3 (5)
Diffuse large cell	50 (76)
Large T cell	2 (3)
Anaplastic large cell	3 (5)
Stage I/II	23 (35)
Stage III/IV	42 (65)
Duration of response to initial therapy	
$\leqslant$12 months	29 (74)
$>$12 months	10 (26)
Status at transplant	
CR1	3 (5)
CR2	17 (26)
PR (includes 12 with PIF)	30 (46)
$<$PR (includes eight with PIF)	15 (23)
Number of pretransplant regimens	
Median	2
Range	1–6

or PBPC mobilization. In total, 61 patients received a variety of salvage regimens for relapsed or progressive disease after induction therapy. Four patients went directly to transplant after induction because of high-risk features, such as minimal initial response or bulky disease.

Table 1 outlines patient characteristics and histology at the time of diagnosis. Patients were referred for HDCT from a variety of institutions and induction and salvage regimens therefore varied.

Methods and definitions

Data from the 65 patients in the UWHC BMT database were reviewed. Complete response (CR) was defined as the resolution of all disease by imaging and biopsy (when appropriate). Lymph nodes were deemed insignificant if measured as less than 1 cm by computed tomography. Partial response (PR) was defined as a reduction of tumor burden by at least 50%. If there was less than 50% reduction, disease was considered stable. A patient was considered to have progressive disease if there was evidence of enlarging tumor by imaging or physical examination.

Disease status at the time of transplant was determined by response to the initial salvage regimen. CR and PR were defined as above. Patients achieving a CR or PR were considered to have chemosensitive disease. If there was less than 50% reduction or progression after the first salvage regimen, that patient was defined as having chemoresistant ($<$PR) disease, no matter how they responded to subsequent salvage regimens.[4]

RRT was graded according to the NCI Common Toxicity Criteria, version 2.0.

Disease status was assessed 100 days after transplant with imaging and BM biopsy (when appropriate). Response criteria used for day $+100$ and date of last contact were the same as defined for disease status at the time of transplant. The cause of death was recorded according to IBMTR definitions.

The overall survival was calculated from the date of transplant to date of last contact, or death from any cause. EFS was calculated from the date of transplant to date of disease relapse. OS and EFS rates at various post transplant time points were estimated using the Kaplan–Meier method. OS and EFS rates for 95% confidence intervals were calculated using the log–log-transformed scale. The lower confidence limit was adjusted using an 'effective *n*' argument to account for the impacts of losses-to-follow-up.

Stem cell collection

A BM biopsy without morphological evidence of lymphoma within 4 weeks of harvest or PBPC collection was required, and cells were collected a minimum of 4 weeks after the last cytotoxic therapy. From 1987 to 1995, all patients underwent BM harvest to collect hematopoietic stem cells, and a minimum marrow dose of 1×10^8 nucleated cells per kilogram of actual body weight was necessary. From 1995 to May 2001, all patients underwent PBPC mobilization with either 4.5 g/m^2 of cyclophosphamide in three divided doses followed by 10 μg/kg/day of granulocyte colony-stimulating factor (GCSF), or GCSF alone. If the PBPC yield did not meet the threshold of 3×10^6 CD34$^+$ cells/kg of recipient body weight, additional cells were collected by autologous BM harvest. Both BM and PBPC were cryopreserved in a final concentration of 10% dimethylsulfoxide.

High-dose chemotherapy

Patients were admitted to the BM Transplant Unit at the UWHC on day -7. Intravenous hydration was started 12–18 h prior to the start of HDCT. On days -6, -5, and -4, thiotepa 300 mg/m^2/day was infused over 3 h, immediately followed by etoposide 700 mg/m^2/day, infused over 8 h. In all, 15 mg of intrathecal thiotepa was given on day -6 until 1991 when pharmacodistribution studies of thiotepa showed excellent CNS penetration; thereafter, 12 mg of intrathecal methotrexate was used for CNS prophylaxis on day -7.[8]

Supportive care

All patients were nursed in HEPA-filtered rooms. Antimicrobial, antifungal, and antiviral prophylaxis was given to all patients according to the institution protocol. Empiric treatment of neutropenic fever (oral temperature $\geqslant$38.2°C) and transfusion support followed the institutional standard of practice.

Results

Response and survival

The overall response rate at day $+100$ was 62%. A total of 28 patients (43%) remain in CR a median of 43 (range, 3–163) months post transplant.

OS at 3 years was 40% (95% CI 26–53%) as shown in Figure 1. The median follow-up was 34 months (range, 3–163). EFS at 3 years was 32% (95% CI 20–45%) (Figure 1).

Table 2 details the outcomes according to disease status at transplant. Of the 50 chemosensitive patients, 24 are in continuous CR. In total, 15 patients were transplanted despite being resistant to salvage therapy (<PR). Of these 15 patients, 10 developed progressive disease after transplant. Four of the 15 remain in a CR 4, 90, 91, and 162 months after transplant. One patient had stable disease at day +100 and then achieved a CR without further therapy.

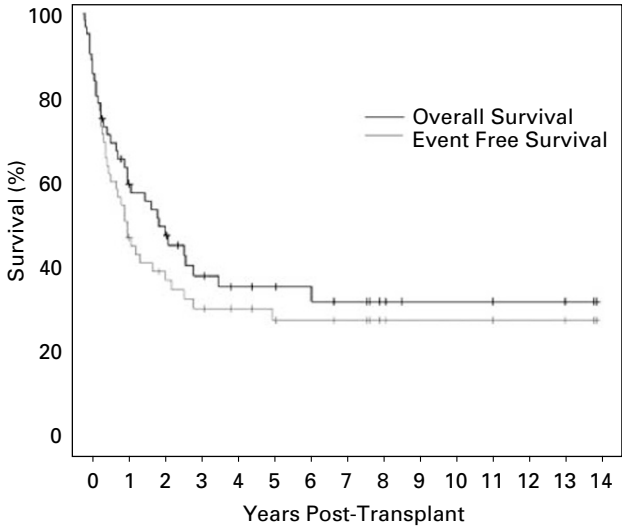

Figure 1 OS and EFS curves.

Mortality

In total, 35 (54%) patients died after transplant. In all, 30 died from relapsed or progressive disease a median of 10.8 (range, 0.6–72.5) months after transplant.

Five deaths were related to nonrelapse causes. A smoker, who was in CR, died of pulmonary failure from COPD 35 months post transplant. Another patient failed to engraft and died of a fungal infection at day +132. One patient with hepatitis C died at day +85 of severe hepatic necrosis and had evidence of active viral replication with a rising viral load. One patient was diagnosed with acute myeloid leukemia (AML) by BM biopsy on day +29 and died 109 days after transplant. This patient had been treated with four therapeutic regimens prior to transplant and had resistant lymphoma before HDCT.

There was one death directly attributable to regimen-related organ toxicity. The patient was >55 years old, a primary induction failure, and came to transplant in PR after salvage chemotherapy and radiation. Severe stomatitis developed on day +1, and eventually tracheostomy was required. The patient subsequently died of multiorgan failure on day +12.

Morbidity

Grade III and IV RRTs are listed in Table 3. All patients had the expected hematologic toxicities associated with HDCT. The predominant nonhematologic adverse effects of the preparative regimen were gastrointestinal toxicity and infection. The majority of patients (73%) had grade III or IV stomatitis/mucositis requiring intravenous hydration or total parenteral nutrition and pain control with opioids via a patient-controlled analgesia system. Episodes of mucositis typically lasted 3–5 days. Only one patient with

Table 2 Results by disease status

Disease status at transplant	*N (%)*	*CR1*	*CR2*	*PR*	*<PR*
Number of patients	65	3	17	30	15
Disease status at day +100					
CR	38 (58)	3 (100)	14 (82)	19 (63)	2 (13)
PR	2 (3)	0	0	1 (3)	1 (7)
Stable	1 (2)	0	0	0	1 (7)
Progressive	15 (23)	0	2 (18)	7 (23)	6 (40)
Disease status at date of last contact					
CR	28 (43)	2 (67)	9 (53)	13 (43)	4 (26)
PR	0	0	0	0	0
Progressive/recurrent	3 (51)	1 (33)	7 (41)	15 (50)	10 (67)
Not evaluable	4 (6)	0	1 (6)	2 (7)	1 (7)
Cause of death					
Progressive/recurrent (<day +100)	7 (10)	0	1 (6)	2 (7)	4 (26)
Progressive/recurrent (>day +100)	23 (35)	1 (33)	4 (24)	13 (43)	5 (33)
Pulmonary failure	1 (2)	0	0	1 (3)	0
Multiorgan failure	1 (2)	0	0	1 (3)	0
Fungal infection	1 (2)	0	0	1 (3)	0
Other organ failure	1 (2)	0	1 (6)[a]	0	0
Secondary malignancy	1 (2)	0	0	0	1 (7)[b]

[a]Liver failure.
[b]Acute leukemia.

Table 3 Grade III and IV RRTs

	N (%)
Cardiovascular (arrythmia)	7 (11)
Cardiovascular (general)	6 (9.5)
Gastrointestinal	
Nausea	21 (33)
Vomiting	5 (8)
Stomatitis/mucositis	46 (73)
Diarrhea (w/o colostomy)	4 (6)
Hemorrhage	
CNS	3 (5)
Hepatic	
Bilirubin	8 (13)
Alkaline phosphatase	3 (5)
GGT	5 (8)
AST	6 (9.5)
Infection	
Febrile neutropenia or Infection with grade 3/4 neutropenia	64 (98)
Neurology	5 (8)
Pulmonary	
Pneumonitis	2 (3)
BMT specific	
VOD	2 (3)
Failure to engraft	2 (3)
Secondary malignancy	
MDS/AML	2 (3)
Bladder	1 (1.5)

grade IV stomatitis required intubation (as described above). Grade III or IV nausea was quite common (33%) overall, but the incidence decreased over time as better antiemetics emerged. The vast majority of patients (98%) had neutropenic fever and 39 (62%) had documented infection associated with grade III or IV neutropenia.

Cardiac toxicity was minimal. Seven patients had supraventricular arrhythmia requiring treatment with medication for rate control. One of these patients developed rate-related myocardial ischemia with left ventricular dysfunction.

In all, 21 patients (33%) developed a rash (two grade III, no grade IV) thought to be due to etoposide.

Eight episodes of confusion were observed, all of which were grade I or II. Seven of these were thought to be due to thiotepa, the eighth was due to benzodiazepines.

Two patients with no previous radiotherapy developed interstitial pneumonitis (IP) prior to day +100 and required intensive care. One eventually needed mechanical ventilation, but both recovered without pulmonary sequelae. The patient requiring intubation came to transplant with primary refractory disease and eventually died of progressive disease 78 days after transplant. The other patient had relapsed anaplastic large-cell NHL with pulmonary and CNS involvement. This patient continues in complete remission 133 days after transplant.

Two patients were diagnosed clinically with veno-occlusive disease that subsequently resolved.

There were three secondary malignancies. At 7 months after transplant, one patient was diagnosed with transitional cell carcinoma of the bladder, but remains free of lymphoma after 82 months of follow-up. One patient who received four pretransplant therapeutic regimens and one cycle of fludarabine for relapse 5 years post transplant was diagnosed with myelodysplastic syndrome (MDS) 6 years after transplant. This patient died of progressive lymphoma 72.5 months after transplant. A third patient was diagnosed with AML on day +29, as described above.

Hematologic reconstitution

For patients receiving autologous BM, the median time to an ANC $>500/\mu$l was 23.5. days (range, 12–61), and the median time to an unsupported platelet count $>25\,000/\mu$l was 32.5 days (range, 11–300). The majority of these patients underwent transplantation prior to 1995. For the 27 patients receiving PBPC, the median time to an ANC $>500/\mu$l was 17 days (range, 8–42), and the median time to an unsupported platelet count $>25\,000/\mu$l was 42 days (range, 14–119). For the four patients who received both BM and PBPC, the median time to ANC $>500/\mu$l was 14.5 days (range, 12–35), and median time to an unsupported platelet count $>25\,000/\mu$l was 36 days (range, 24–71). Two patients failed to engraft secondary to problems with stem cell collection and cryopreservation. One of these died of a fungal infection 4 months after transplant, and the other patient died of progressive lymphoma 11 months after transplant.

Discussion

HDCT with autologous BM or PBPC transplantation is now a well-established treatment for relapsed aggressive lymphoma. Over time, advances in supportive care have led to a transplant-related mortality of less than 10%;[9] however, RRT still causes significant morbidity. A retrospective review of pulmonary toxicity within 12 months following BCNU-containing regimens in patients transplanted for NHL, Hodgkin's disease, or multiple myeloma found noninfectious pulmonary complications in 26%.[10] In an attempt to reduce RRT while maintaining or improving the efficacy of HDCT for relapsed NHL, we adopted a preparative regimen containing thiotepa and etoposide originally used in children with CNS tumors. Etoposide is an established agent in commonly used preparative regimens, including BEAM, BEAC, and CBV. It has a steep dose–response curve, little immunosuppressive potential, and extramedullary toxicity limited to the skin and gastrointestinal tract.[6,11] These qualities, in addition to the activity against lymphoma, favored the use of etoposide in the HDCT setting.

Thiotepa is an alkylating agent that has been in clinical use for over four decades, and since it is rarely used in treating NHL, resistance in the HDCT setting is not likely to be an issue. The pharmacokinetics of thiotepa are well understood, including excellent CNS penetration. Cerebrospinal fluid concentrations are equivalent to those in plasma 3–4 h after intravenous administration.[8] As with

etoposide, thiotepa's dose-limiting toxicity is gastrointestinal. At high doses, it can also be neurotoxic.

As expected, the combination of thiotepa and etoposide resulted in significant grade III/IV gastrointestinal toxicity for the majority of patients. Over the 14 years of this study, improved antiemetic therapy correlated with a decrease in severe nausea and vomiting; however, the degree and duration of oropharyngeal mucositis has persisted. Neutropenic fever was almost universal among our patient population, presumably secondary to the high rate of mucositis. There was one regimen-related death due to grade IV mucositis with subsequent multiorgan failure in an older patient with primary induction failure in PR. Since this death occurred (over 10 years ago), oropharyngeal care and analgesic use have improved, and no further episodes of grade IV mucositis have occurred. In fact, since this study has been completed, several recent patients have been hospitalized only for the administration of the preparative regimen. Neutropenic fever remains a significant risk, but with close follow-up and a strict oral care regimen some patients can remain out of the hospital for the majority of the peritransplant period. This demonstrates that with improved supportive care, the gastrointestinal toxicity with this regimen is manageable.

Acute and delayed pulmonary toxicity has been recognized as a complication related to the use of BCNU-containing regimens. Carmustine (BCNU) has been implicated as one of the main causes, particularly when combined with cyclophosphamide, as in the CBV regimen, or when given after radiotherapy. With the CBV regimen, Stiff *et al*[4] and Patti *et al*[3] reported incidences of IP of 11 and 16%, respectively. Even when BCNU is used without cyclophosphamide, as in the BEAM regimen, IP can still be a major source of morbidity. Mills *et al*[5] reported a 17% incidence of IP using BEAM without TBI. Using BEAC, van Besien *et al*[2] reported four (8.3%) cases of pulmonary toxicity, two of which occurred after day +100. When using only cyclophosphamide and busulfan as a preparative regimen in 20 patients with HD or NHL, deMagalhaes-Silverman *et al*[12] reported one case of IP.

With our regimen, cardiac and pulmonary toxicities were minimal and less than those reported with standard non-TBI preparative regimens.[2–5,10,12] No late pulmonary toxicity was seen with this regimen in contrast to that seen with regimens containing BCNU. Two (3%) patients in our cohort developed IP. The first had the T-cell-rich B-cell variant of DLCL and had received bleomycin as part of induction therapy (m-BACOD). The second patient had relapsed with pulmonary nodules after induction. Since neither thiotepa nor etoposide are known to cause pulmonary toxicity, it can be argued that previous bleomycin in the first patient and residual pulmonary lymphoma in the second may have contributed to these patients' pulmonary toxicities.

Secondary MDS and AML are well-recognized complications after autologous transplant for NHL. Preparative regimens, particularly those containing TBI, were initially blamed for these complications. However, recent data suggest that the type and intensity of pretransplant chemotherapy are the major contributing factors. In a multicenter case–control study, Metayer *et al*[13] found higher relative risks for developing post transplant MDS/AML with increasing total dosage and duration of pretransplant therapy with alkylating agents. A TBI dose of 13.2 Gy also appeared to be a risk factor, but lower doses were not. In our cohort of 65 patients, we have so far observed two (3%) cases of MDS or AML. One MDS was diagnosed 6 years post transplant. At the time of the MDS diagnosis, this patient had relapsed lymphoma and had received further chemotherapy. One patient developed AML on day +29. This is very early in the transplant course to be considered as a secondary malignancy, and it could be argued that the preparative regimen had no role in the development of AML, but that the HDCT created a permissive environment for the pre-existing leukemic clone to expand.

It is known that patients in chemosensitive relapse have better OS and disease-free survival after HDCT.[4,5,14] In our study, in which 77% of patients had chemosensitive disease, the OS and EFS times of 40% and 32% at 3 years, respectively, are comparable to those in other studies of autologous transplantation in patients with similar characteristics.[2,5] When using BEAM as the preparative regimen, Mills *et al* reported an OS of 41% and PFS of 35% at 5 years in 107 patients with a mixture of high- and intermediate-grade relapsed or refractory NHL, 52% of whom had sensitive disease. Van Besien *et al* reported a series of 48 patients with intermediate and immunoblastic NHL who underwent autologous transplantation with the BEAC regimen. In that study, 77% of patients had chemosensitive disease, and the 3-year OS was 41% with a failure-free survival of 30%. Both of these studies encompassed similar time periods as did our study.

In contrast, the Parma trial had an excellent OS of 53% and an EFS of 46% when using the BEAC regimen in 55 patients with chemosensitive disease.[1] Caballero *et al*[15] used the BEAM regimen in 68 patients with intermediate-grade NHL. OS at 3 years was 56% and disease-free survival was 71%. These impressive numbers were achieved with 37% of the patients being in first CR, 51% with chemosensitive disease, and only 12% with resistant relapse.

Our review includes a heterogeneous group of patients treated over 14 years during which time there was improvement in autologous transplantation methods and supportive care. Despite including primary induction failures and 15 (23%) patients with resistant disease, patients treated with this regimen had OS and EFS that appear similar to previously published studies of HDCT in NHL. In contrast to commonly used preparative regimens, the combination of thiotepa and etoposide leads to minimal pulmonary toxicity, whereas the gastrointestinal toxicity, particularly mucositis, is significant but manageable. Therefore, based on its apparently equivalent efficacy and acceptable RRT, we conclude that the etoposide and thiotepa preparative regimen is an alternative to the current non-TBI-containing regimens and deserves further study.

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