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Autologous Hematopoietic Stem Cell Transplantation for Mantle Cell Lymphoma

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ABSTRACT

This study evaluated the outcomes of patients who underwent high-dose chemotherapy (HDC) and autologous hematopoietic stem cell transplantation (autoHSCT) for mantle cell non-Hodgkin's lymphoma and the effect of clinical and treatment characteristics. The clinical outcome and prognostic factors in 40 patients who underwent HDC and autoHSCT for mantle cell lymphoma between June 1991 and August 1998 were analyzed. With a median follow-up of 24 months for the surviving patients (range, 4-68 months), the 2-year overall survival was 65% and the 2-year event-free survival (EFS) was 36%. In univariate analysis, characteristics predictive of a poor EFS were blastic morphology ($P = .019$) and the patient having received 3 or more prior chemotherapy regimens ($P = .004$). In a multivariate analysis, the only factor associated with a poor EFS was the number of prior chemotherapy regimens. Those patients who received 3 or more prior therapies had a 2-year EFS of 0%, and those who received <3 therapies had a 2-year EFS of 45% ($P = .004$). Patients with mantle cell lymphoma can obtain prolonged EFS with HDC and autoHSCT; however, this strategy for prolonged EFS appears to work optimally in patients who are less heavily pretreated. Whether this therapy will increase the overall survival or EFS in patients receiving transplants in first complete remission will need to be tested in prospective randomized clinical trials.

KEY WORDS

Mantle cell lymphoma • Non-Hodgkin's lymphoma • High-dose chemotherapy • Autologous hematopoietic stem cell transplantation

INTRODUCTION

Mantle cell lymphoma is a clinicopathologic entity that is now recognized as a distinct subtype of non-Hodgkin's lymphoma (NHL). This entity has been previously called diffuse poorly differentiated lymphocytic lymphoma, diffuse small cleaved-cell lymphoma, intermediate lymphocytic lymphoma, and mantle-zone lymphoma [1-4]. Based on uniform histologic, immunophenotypic, and genotypic features, hematopathologists now diagnose mantle cell lymphoma in approximately 6% to 9% of NHL cases [5-7]. Patients with mantle cell lymphoma typically present with advanced-stage disease which frequently includes bone marrow, blood, and splenic involvement [8]. Although mantle cell lymphoma was previously thought to represent a form of indolent lymphoma, it has more recently been recognized that the median survival of patients with this type of lymphoma is only 3 years versus 7 to 9 years with typical "indolent" NHL [8,9].

Unlike other aggressive NHLs, however, patients with mantle cell lymphoma have a poorer complete response rate with standard anthracycline-based or non–anthracycline-based chemotherapy [10,11]. Progression of this lymphoma typically occurs within the first 12 to 18 months after the initial diagnosis despite conventional chemotherapy [12]. Standard salvage regimens have not appeared to have much success in producing second long-term remissions in this disease [13]. Because high-dose chemotherapy (HDC) and autologous transplantation have been superior to conventional salvage therapy in other types of aggressive NHL, this treatment has now been applied to patients with mantle cell lymphoma who were otherwise transplantation candidates.

This study evaluates the results of HDC and autologous hematopoietic stem cell transplantation (autoHSCT) in patients with mantle cell lymphoma referred to the University of Nebraska Medical Center (Omaha, NE) at various points in their disease course.

PATIENTS AND METHODS

Between June 1991 and August 1998, 40 patients with mantle cell lymphoma were treated with HDC and autoHSCT at the University of Nebraska Medical Center. Patients included in this study had lymph node biopsies reviewed and classified according to the Revised European American Lymphoma (REAL) classification by 1 of 3 hematopathologists (D.D.W., W.C.C., T.C.G.) [14]. Bone marrow, blood smears, and other pathologic specimens were also reviewed as appropriate for the patient's clinical circumstance.

Patients were eligible for transplantation before 1996 if they had failed to achieve an initial remission or had relapsed after attaining a remission with conventional therapy. Starting in 1996, patients in first complete remission were also offered transplantation. Transplantation protocols were approved by the Institutional Review Board (IRB), and informed consent was obtained from all patients before transplantation. Entry criteria required a cardiac ejection fraction ≥50% and a carbon monoxide diffusion capacity ≥50% of predicted normal value. Normal hepatic and renal function were required unless dysfunction could be attributed to the presence of lymphoma. During the latter period of patient accrual, a negative human immunodeficiency virus antibody test result was required before transplantation.

During the early period of patient accrual, patients received transplants of autologous unpurged bone marrow. A bone marrow biopsy within 1 month of harvest was required to be morphologically free of lymphoma, although patients may have had previous bone marrow involvement. During the latter period of patient accrual, patients received transplants of mobilized autologous peripheral blood progenitors. The upper age limit for transplantation was 60 years until March 1992, when the limit was removed as long as the patient met other physiological entry criteria.

Those patients receiving autologous bone marrow were given general anesthesia while it was harvested. Marrow was collected for a minimum nucleated cell count of 2.0×10^8/kg and frozen at a controlled rate and preserved in 10% dimethylsulfoxide (DMSO). In those patients receiving peripheral blood progenitors, the cells were collected using cytokine mobilization with granulocyte-macrophage colony-stimulating factor (GM-CSF), G-CSF, erythropoietin, or PIXY-321, depending on the mobilization trial in effect at the time. No chemotherapy mobilization was used. Peripheral blood progenitor cells were preserved in 10% DMSO and frozen at a controlled rate or, more recently, preserved in 5% DMSO and 6% hydroxyethyl starch, frozen at –130°C, and stored in liquid nitrogen.

At the time of their enrollment, patients were treated with IRB-approved regimens based on histology and chemotherapy sensitivity; these regimens were either total body irradiation (TBI)-based (n = 6, 15%) or chemotherapy only (n = 34, 85%). Patients in the TBI-based group received cyclophosphamide, 60 mg/kg × 2 days, and 200 cGy TBI BID × 3 days (Cy/TBI) (n = 6). The patients in the chemotherapy-only groups received ifosfamide, 3 g/m^2 per day × 4, carboplatin, 1.2 g/m^2 over 96 hours by continuous infusion, and etoposide, 400 mg/m^2 per day × 3 (ICE) (n = 1); carmustine, 300 mg/m^2, etoposide, 100 mg/m^2 bid × 4, cytarabine, 100 mg/m^2 bid × 4, and cyclophosphamide, 35 mg/kg × 4 (BEAC) (n = 25); BEAC with ^{131}I anti-CD20 (n = 3); 300 mg/m^2 carmustine, 100 mg/m^2 etoposide, 100 mg/m^2 cytarabine, and 140 mg/m^2 melphalan (BEAM) (n = 2); and BEAM with rituximab (n = 2). Because no outcome differences were noted with the different protocols, the TBI-based and the chemotherapy-only regimens were grouped together for the purposes of this study.

Patients were treated in private rooms with high-efficiency particulate air filtration. During the study, GM-CSF, G-CSF, or PIXY-321 was administered posttransplantation depending on the protocol in effect at the time. Irradiated platelet transfusions were given to keep the platelet count ≥20,000/μL, and irradiated packed red blood cell transfusions were given to maintain hemoglobin levels >8 g/dL.

Response Evaluation

Staging evaluations were performed before transplantation, approximately 100 days after transplantation, and then at yearly intervals. A complete response (CR) was defined as disappearance of all clinical and radiographic evidence of disease (lymph nodes <1.5 cm) at the day-100 evaluation. Patients with small residual radiographic abnormalities who did not progress between the day-100 evaluation and at a subsequent evaluation at least 3 months after the day-100 evaluation were considered to have a CR-unconfirmed (CR-u). A partial response (PR) was defined as a ≥50% reduction in the surface area of measurable disease at the day-100 evaluation. All other patients were classified as having had no response to transplantation. Bone marrow was evaluated with histologic methods, and molecular methodology was not used in the determination of response.

Statistical Methods

The association between patient and transplant characteristics and histology was examined using the chi-square test for association. Transplantation outcome was analyzed with respect to overall survival and event-free survival. Overall survival time was defined as the time from transplantation until death from any cause or until last follow-up, for surviving patients. EFS was defined as the time from transplantation until relapse from CR, disease progression, death from any cause, or last follow-up if none of those events had occurred. Survival times and EFS distributions were calculated using the product-limit Kaplan-Meier method [15]. Comparisons of these time-to-event distributions were made using the log-rank test [16]. Multivariate analysis was performed using the Cox proportional hazards regression model [17].

RESULTS

The 40 patients ranged in age from 34 to 67 years (median, 56 years), and 78% of the patients were men. Other characteristics of patient are noted in Table 1. Of the patients, 26 (65%) had diffuse mantle cell lymphoma, 5 (13%) had nodular or mantle zone lymphoma, and 9 (23%) had blastic mantle cell lymphoma. Bone marrow involvement was present at the time of transplantation in 26 (67%) of the patients. An elevated serum lactate dehydrogenase (LDH) level was present at the time of transplantation in 14 (35%) of the patients. A total of 70% of patients had never been in a complete remission before transplantation (primary

Table 1. *Characteristics of Patients at Transplantation**

n	40
Age, y	56 (34-66)
Male	31 (78)
Lactate dehydrogenase above normal	14 (35)
≥3 Prior therapies	5 (13)
Lymphoma mass ≥10 cm	1 (3)
Bone marrow positive	26 (67)
Disease status	
Primary induction failure	28 (70)
Relapse sensitive	7 (18)
First complete response	5 (13)

*Data are n, median (range), or n (%).

induction failure). However, 93% of the patients remained chemotherapy sensitive at the time of transplantation. The median time from diagnosis to transplantation was 11 months (range, 3-40 months).

None of the 40 patients died early during the transplantation. The median time to reach an absolute neutrophil count of >500/μL was 12 days (range, 8-38 days). The median time to platelet transfusion independence was also 12 days (range, 7-154 days). Red blood cell transfusion independence was attained at a median of 10 days (range, 4-98 days). The response to transplantation was a CR in 14 patients (35%), CR-u in 9 (23%), and PR in 11 (28%). The overall response rate was 86%.

With a median follow-up of 24 months (range, 4-68 months) for the surviving patients, the 2-year EFS for all patients was 35% (Figure 1) and the 2-year overall survival was 65% (Figure 2) with no obvious plateau on the curves. The majority of deaths (11 of 13) were due to lymphoma progression or recurrence; however, 1 patient died of acute graft-versus-host disease after a second allogeneic transplantation and another patient died of renal failure. One patient also developed a glioblastoma multiforme at 18 months after the transplantation for mantle cell lymphoma but remains alive with no recurrent lymphoma at 32 months after transplantation.

A univariate analysis of prognostic factors identified histologic diagnosis of blastic mantle cell lymphoma (P = .019) (Figure 3) and receiving ≥3 prior chemotherapy regimens (P = .004) (Figure 4) as significant predictors of a worse EFS. A factor of borderline significance was bone marrow involvement at any time before transplantation (P = .075). Age (P = .50), sex (P = .41), disease status at transplantation (P = .33), elevated LDH (P = .57), prior radiotherapy (P = .19), chemosensitivity (P = .49), TBI regimen (P = .36), and time from diagnosis to transplantation >1 year (P = .49) did not have statistically significant effects on EFS.

Multivariate analysis identified ≥3 prior chemotherapies received as the only characteristic maintaining independent predictive significance. Of those patients who had received 3 or more prior therapies, the 2-year EFS was zero compared with a 45% 2-year EFS for those patients who had received 2 or fewer therapies (P = .004) (relative risk 5.1, 95% CI 1.6-15.8). No cases of secondary myelodysplasia or acute myelogenous leukemia have been reported in these patients to date.

DISCUSSION

Mantle cell lymphoma is now recognized as a distinctive disease entity characterized by generalized lymphadenopathy and frequent bone marrow, blood, and splenic involvement [8]. Typical immunohistologic features of mantle cell lymphoma are positivity for pan-B-cell antigens such as CD19 and CD20, and HLA-DR antigen. Cells usually have the pan-T-cell antigen CD5 on the surface and are negative for CD10. Cells are also usually positive for the CD43 antigen and negative for the CD23 antigen [5,6]. The characteristic cytogenetic abnormality is t(11;14)(q13;q32). The molecular counterpart of the t(11;14) abnormality involves an error in V-D-J joining during immunoglobulin (Ig) heavy-chain gene rearrangement, resulting in the movement of a putative cellular oncogene adjacent to the bcl-1 (11q13) breakpoint into proximity of the enhancer region of the Ig heavy-chain gene (14q32) [7,8]. The putative oncogene deregulated by the t(11;14) abnormality has been named PRAD1 or CCND1 and encodes for cyclin D1, which is overexpressed in nearly all cases of mantle cell lymphoma [7,8].

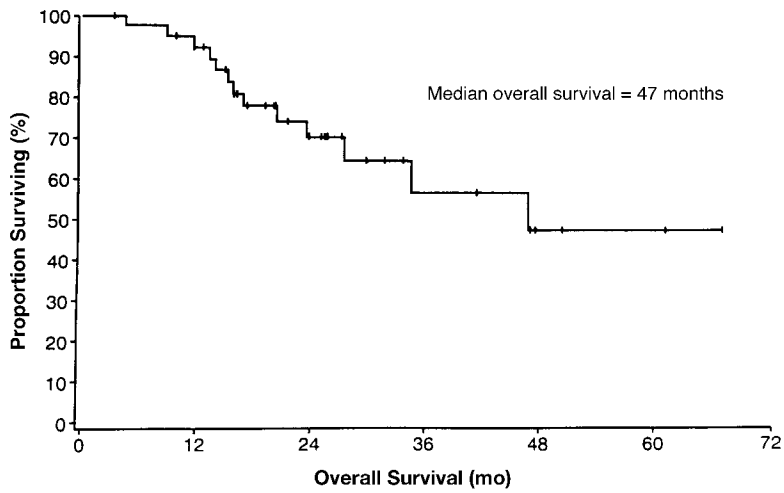

Figure 1. Overall survival for mantle cell lymphoma patients after autologous transplantation (n = 40).

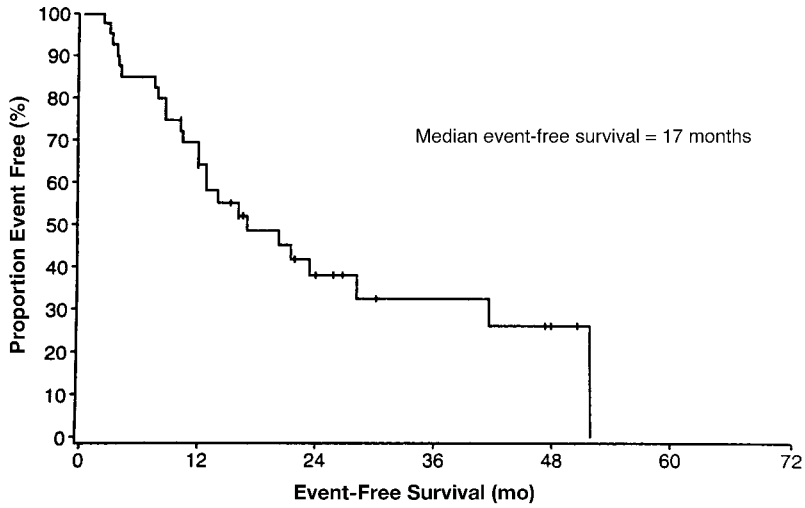

Figure 2. Event-free survival for mantle cell lymphoma patients after autologous transplantation (n = 40).

Now that this specific clinicopathologic entity has been recognized, retrospective reclassification of prior clinical trials and prospective studies of conventional chemotherapy have been performed. The majority of the trials evaluating anthracycline-based and non–anthracycline-based regimens have failed to demonstrate prolonged disease-free survival in the majority of patients, with the median time to treatment failure being 12 to 18 months and a median survival of only 3 to 4 years in most series [12]. The International Prognostic Index, which was originally designed for other types of aggressive lymphomas, does segregate patients with an improved prognosis over others; however, none of the subgroups appear to have a prolonged disease-free survival [18]. Other studies have demonstrated alternative poor-prognosis characteristics such as blastic histology and *p53* mutations [19,20].

Because of the poor outcome of mantle cell–lymphoma patients treated with standard induction and salvage chemotherapy, the use of HDC and autoHSCT has become an option for some patients. Initially, this therapy was used for patients with relapsed or refractory disease and, more recently, for patients in first complete remission. Several studies with a small number of patients receiving transplants after relapse have documented some patients with a sustained disease-free survival, ranging from 24% to 75% with varying follow-up [21,22]. Factors that appear to be predictive of a worse outcome are *p53* mutations, blastic histology, and extensive pretreatment of patients [21,22]. One study by Milpied et al. [23] also demonstrated an improved outcome in patients who received a TBI-based regimen over a non–TBI-based regimen.

More recently, because of concern over the results of transplantation in relapsed patients, patients have been offered transplantation in first complete remission. The results of transplantation in this patient population are somewhat controversial. Several small studies done in Europe have demonstrated a 50% to 80% disease-free survival with 1 to 3 years of follow-up [24,25]. However, a study done at the Dana Farber Cancer Center (Boston, MA) demonstrated that 5 of 8 patients with mantle cell lymphoma

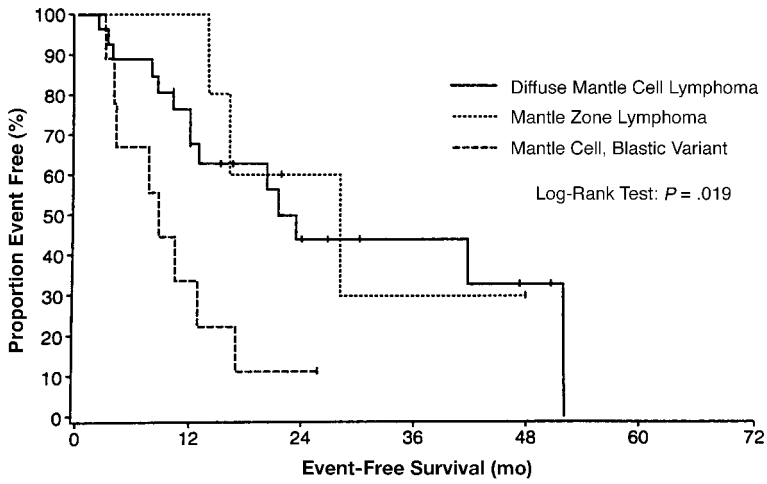

Figure 3. Event-free survival by histologic subtype.

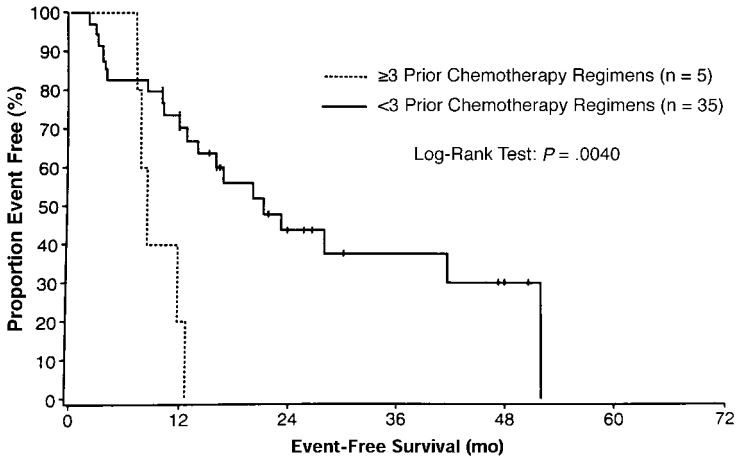

Figure 4. Event-free survival by number of prior chemotherapies received.

who underwent transplantation in first CR/PR relapsed with a median of 2 years of follow-up [26]. It has also been documented that bone marrow involvement with mantle cell lymphoma is less amenable to antibody purging [27].

In a recent study from the M.D. Anderson Cancer Center (Houston, TX), 25 previously untreated patients with mantle cell lymphoma received an intensive induction regimen with hyper-CVAD (cyclophosphamide, vincristine, adriamycin, and dexamethasone) and high-dose methotrexate/cytarabine followed by high-dose chemotherapy/radiotherapy and autoHSCT. For these previously untreated patients, the overall survival and EFS were reported as 92% and 72%, respectively, at 3 years of follow-up [28]. These results were compared with an historical control group of similar mantle cell lymphoma patients treated with CHOP-like regimens (CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone). However, the historical control group had a median 3-year EFS of 28% with conventional therapy.

This article evaluates a large number of patients with mantle cell lymphoma who received HDC and autoHSCT at various points during their disease course. Our results are similar to other reports of transplantation in this disease demonstrating that patients who have relapsed multiple times and have received many prior therapies do not benefit from this therapy. In fact, our study found that no patients were disease free at 2 years after transplantation if they had received 3 or more prior therapies before undergoing transplantation. At the present time, the best results appear to be attained when transplantation is used in less heavily treated patients, preferably in first complete remission. Our study did not find any difference in the outcome by transplantation regimen. However, the numbers of patients treated with different regimens were small in this study, and further evaluation of enhanced transplantation regimens, such as the incorporation of monoclonal antibodies, should be evaluated further. Because our center is a referral center, certain selection bias is present in the patients enrolled in this study. This approach may not be able to be generalized to a large percentage of patients because many patients with mantle cell lymphoma are older.

Another alternative in selected young patients may be the use of a related allogeneic donor. In the small number of cases reported using an HLA-identical related donor, the relapse rate is much smaller [29]. However, because of the other toxicities associated with allogeneic transplantation, the long-term overall EFS may not be significantly different than that for autologous transplantation. Hopefully, with future developments in modulating graft-versus-host disease and the antitumor effect of allogeneic or nonmyeloablative transplantation, results may improve. However, because none of the current approaches appear to be satisfactory in patients with mantle cell lymphoma, enrollment of patients in clinical trials should be encouraged.

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