

The Role of Autologous Transplantation in the Management of Mantle Cell Lymphoma: A Study From the EBMT

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ABSTRACT

The curative potential of high-dose chemotherapy (HDC) in mantle cell lymphoma (MCL) is unknown: the European Group for Blood and Marrow Transplantation (EBMT) carried out a retrospective analysis of MCL cases autografted between 1983 and 1998. The cases were reviewed by a national lymphoma panel or specialist hematopathologist. One hundred ninety-three patients from 98 centers were identified; 43 cases were excluded after pathology review ($n = 14$), because slides were unavailable for central review ($n = 32$), or because no details were available from first transplant.

The outcome of 150 patients (112 male and 38 female; mean age at diagnosis, 47 years) was analyzed. Median time to transplant was 416 days (range, 48–2689 days). One hundred sixteen patients (92%) had stage III/IV disease at diagnosis, and 66 (52%) received >1 chemotherapy regimen pre-HDC. Status at transplant was complete remission (CR), 64; partial remission (PR)/chemosensitive disease, 71; and refractory/progressive disease, 15. Total body irradiation (TBI) conditioning was used in 61 patients. Status at 100 days was CR, 96; PR, 23; refractory/progressive disease, 6; death from disease, 2; and toxic death, 6.

The overall and progression-free survival (OS and PFS) rates at 5 years were 48% and 30%, respectively, with no plateau in the curve and a median follow-up of 25 months. OS from diagnosis at 5 years was 61%. Status at transplant was significant for survival ($P=.0029$) by univariate analysis and multivariate analysis ($P=.001$), and 70% of patients transplanted in first CR were alive at 5 years. HDC prolongs survival, but for most patients cure remains elusive in MCL.

INTRODUCTION

Mantle cell lymphoma was included as a distinct clinicopathological entity in the Revised European American Lymphoma (REAL) classification system described in 1993.¹ Subsequent clinicopathological studies have confirmed the poor prognosis that these predominantly middle-aged to elderly men with stage III/IV disease have, with a median survival of 34–40 months.^{2–6} Because of this dismal prognosis, many centers offer high-dose chemotherapy with peripheral stem cell rescue to patients <65 years of age with MCL, despite the lack of randomized trial data showing the efficacy of this approach. Numerous unrandomized small series have been published with conflicting conclusions, possibly because of small numbers or inadequate follow-up.^{7–10}

We undertook a retrospective study of all patients who were autografted for MCL between 1988 and 1998 and who were registered with the EBMT, in an attempt to clarify (1) whether HDC conferred a survival advantage to patients with MCL, (2) whether HDC cured patients with MCL, and (3) whether it was possible to identify different prognostic subgroups.

MATERIALS AND METHODS

A study protocol defining study objectives and a minimum data set was agreed on by a working group from the EBMT.

All patients who were registered with the EBMT and allografted or autografted for MCL between 1988 and 1998 were initially included. Each center with eligible patients was approached for information about diagnostic methodology. Patient material that had been reviewed by a national lymphoma pathology group was included without further review. Centers that did not participate in this form of review and whose center pathologist was not part of a lymphoma review panel were asked to send material for review by an expert hematopathologist (P.I.). If the material was not made available for review, the case was excluded from further study. The patients who were allografted were excluded from this study but will be analyzed later.

The basic data set deemed necessary for inclusion in the study included age at diagnosis and transplant, sex, and updated outcome data. Disease status was defined as CR, no evidence of disease; PR, >50% response to therapy; refractory disease, <50% response to therapy; and progressive disease, disease progression after therapy. If patients had been transplanted more than once, outcome was analyzed from first transplant; however, data were collected on all patients.

Other parameters analyzed included disease stage at diagnosis, nodal disease, measurable disease, bone marrow involvement at transplantation, number of regimens used prechemotherapy, interval from diagnosis to transplantation, disease

status at transplant and 100 days posttransplant, type of conditioning used, use of in vitro purged stem cell/marrow rescue, and cytokines administered posttransplant.

The Kaplan-Meier method was used to calculate OS, PFS, and disease-free survival (DFS). Univariate analysis was done using the log-rank method. Multivariate analysis to study the relevance of individual prognostic factors on OS and PFS used the proportional hazard (Cox regression). Proportionality assumptions were tested using standard methods.

RESULTS

Two hundred fifteen patients from 98 centers were initially identified, of whom 22 were allografted and were therefore excluded from the current study. A further 45 cases were excluded following pathology review (14 cases), because diagnostic material was not made available for central review (28 cases), or because of inadequate data (3 cases).

The final cohort of 150 patients included 112 male and 38 female patients with a mean age at diagnosis of 47 years. Disease stage at diagnosis was stage I/II ($n = 10$), stage III/IV ($n = 116$), and stage unknown ($n = 34$). Numbers of regimens used before transplantation were 1 ($n = 50$), 2 ($n = 51$), >2 ($n = 15$), and unknown ($n = 34$). The interval from diagnosis to transplantation was 416 days (range, 48–2689 days). Eleven patients had 2 transplants, of which 2 had allografts for the second procedure.

Status at transplant was CR ($n = 64$), PR or sensitive relapse ($n = 71$), and refractory/progressive disease ($n = 15$). Seventy-four patients were conditioned with chemotherapy and 61 with radiotherapy and chemotherapy; in the remaining cases, the conditioning data were unavailable. Mean time to engraftment was 12 days (range, 8–33 days), with 4 engraftment failures. Fifteen patients received in vitro purged marrow/stem cells, and no purging information was available on 27 patients. The outcome at 100 days was CR ($n = 96$), PR ($n = 23$), no change or progressive disease ($n = 6$), death from progressive disease ($n = 2$), toxic death ($n = 6$), and unknown ($n = 17$). The 5-year OS and DFS rates from transplantation were 48% and 30%, respectively (Tables 1 and 2), with no plateau in the curves. The 5-year OS from diagnosis was 61%.

Disease status at transplant was the only significant prognostic factor for OS ($P = .0029$). Disease status and age at transplant (<50 years) were significant by multivariate analysis.

DISCUSSION

The OS from diagnosis of this group of patients is 61%, with a median follow-up of 25 months, which compares favorably with conventionally treated historical

Table 1. Demographic and Clinical Details*

	<i>n</i>	<i>Unknown</i>
Sex, M/F	112/38	
Median age at diagnosis, y (range)	47 (18–66)	
Stage III/IV at diagnosis	116	34
Number of regimens before HDC		34
1	50	
>1	66	
Median time to HDC, d (range)	416 (48–2689)	
Lymph nodes involved at HDC	23	43
Bone marrow involved at HDC	25	40
Measurable disease at HDC	37	46
TBI conditioning	61	14
In vitro purging	15	27
Cytokines after HDC	47	79
Median time to engraftment, d (range)	12 (4–33)	

*HDC, high-dose chemotherapy; TBI, total body irradiation.

series. Transplanted patients are highly selected by being young and fit enough to undergo the procedure. Outcome in the EBMT patients is not as good as in the other 2 reported series with follow-up—these have OS and PFS rates of 80% and 58% at 4 and 9 years, respectively.^{6,7} Unfortunately, there appears to be no plateau in the survival curve, indicating that the number of patients with MCL cured by high-dose chemotherapy may be small.

The success of HCVAD (cyclophosphamide, vincristine, dexamethasone, adriamycin, high-dose methotrexate, and high-dose Ara-C)—with projected 4-year OS and EFS rates of 90% and 79%, respectively, at a median follow-up of 34 months—suggests that intensifying initial treatment and transplanting in first CR or PR may improve outcome.¹¹ Data from a recently published article¹² showed

Table 2. Disease Status

	<i>Pretransplant</i>	<i>At 100 days</i>
Clinical remission	64	96
Chemosensitive disease	18	NA
Partial remission	53	23
Refractory/progressive disease	15	6
Death from mantle cell lymphoma	NA	2
Toxic death	NA	6
Unknown	NA	17

improved outcome for patients treated with transplant in first CR/PR, compared with later transplantation: OS of 93% vs. 63% at a median of 4 years from diagnosis. The current study confirms that patients transplanted in first remission have a significantly better outcome, with OS of 70% at 5 years. In contrast to the EBMT data, TBI-containing conditioning regimens were associated with improved OS and PFS at 4 years: 89% vs. 60% and 71% vs. 0%, respectively, in 1 study.⁷

Novel strategies such as conventional chemotherapy to maximal response followed by allogeneic transplantation or the use of in vivo purging agents such as the anti-CD20 antibody with autologous transplantation are currently being assessed and may improve outcome.

The logistical difficulties of carrying out this sort of retrospective analysis were compounded by our requirement for stringent pathological assessment before inclusion in the study. It is interesting that only 14 cases were excluded on review because of an incorrect diagnosis and that analysis of OS and PFS was not significantly altered by including these cases. It is encouraging that most centers have effective pathology review for patients before proceeding to high-dose chemotherapy. This may allow future retrospective studies to proceed with more confidence without central review. An alternative explanation could be that only centers with specific hematopathology expertise and interest reclassified cases in accordance with REAL criteria, and many transplants for MCL in the registry have therefore not been identified for this study.

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