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High-dose therapy with stem cell transplantation for mantle cell lymphoma: results and prognostic factors, a single center experience

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Summary:

From 1991 to 1997 18 consecutive patients with well-defined mantle cell lymphoma (MCL) underwent high-dose therapy with unpurged autologous (17 patients) or allogeneic (one patient) stem cell transplantation. Tissue sections were reviewed for morphology, immunophenotype, cyclin D1 and P53 expression as well as proliferation index (PI). Median age of patients was 47 years (range 40–60). Sixteen had stage IV disease with bone marrow involvement in 12 and performance status was $\geqslant$1 in 12 patients. At the time of high-dose therapy 10 patients were in first partial response (PR), one was in second complete remission (CR), four were in second PR and three were refractory to conventional anthracycline-containing chemotherapy. The conditioning regimen consisted of TBI plus chemotherapy in 13 patients and chemotherapy only (BEAM) in five patients. No treatment-related deaths were observed. With a median follow-up of 36 months (range 13–80) after transplant, disease-free survival (DFS) and overall survival (OS) are estimated to be 48 and 80% at 4 years, respectively. Significantly better results are achieved for patients transplanted after a TBI containing regimen with a 4 year OS and DFS estimated at 89 and 71%, respectively compared to 60 and 0% respectively for patients who were conditioned without TBI ($P = 0.07$ for OS and $P < 0.0001$ for DFS). There is a trend towards better DFS when the transplant is performed in PR1 (4 year DFS: 80% with eight patients out of 10 in continuous CR 13 to 80 months, median 36 months after transplant) compared to more advanced stages (4 year DFS: 18% with only three patients out of eight in continuous CR 16, 17 and 58 months after transplant). Blastic histology and P53 overexpression are also associated with a trend towards a worst prognosis.

Keywords: mantle cell lymphoma; high-dose therapy; hematopoietic stem cell transplantation

Mantle cell lymphoma (MCL) is now recognized as a separate entity among non-Hodgkin's lymphomas (NHL) representing 5% of NHL in Europe and North America and 10% of NHL previously classified categories A to E in the working formulation (WF).[1,2] Besides its morphology this entity is better characterized by its specific immunophenotype (sigM$^+$, sigD$^+$, CD5$^+$, CD23$^-$, CD10$^-$) and the presence of a cytogenetic abnormality, t(11;14) resulting in rearrangement of the bcl-1 locus and overexpression of the cyclin D1 (CCND1/PRAD1) gene.[3–5]

The clinical course of patients with well characterized MCL is rather uniform according to several reports. With conventional chemotherapy the median survival is about 40 months and the median progression-free survival for responders is about 20 months.[1,2,6–9] In addition, several factors such as blastic cell morphology[1,2] peripheral blood involvement,[2] increased mitotic activity,[2,7] poor performance status[2,7] and P53 overexpression[10] have been found to correlate with an even worse prognosis. Thus, when any of these characteristics is present, the patients' median survival does not exceed 12–26 months.[2,7,10]

Because of this poor long-term prognosis with conventional chemotherapy, the use of aggressive combination chemotherapy with stem cell transplantation has been suggested for younger patients.[3,11] There are now several reports on high-dose therapy with autologous (or allogeneic) stem cell transplantation in MCL.[11–18] However, the number of patients in most of these studies is too small and the follow-up too short to draw definitive conclusions regarding the value of this type of therapy.

We report the results achieved with high-dose therapy and autologous or allogeneic stem cell support in 18 consecutive patients referred to our unit from July 1991 together with an analysis of the influence of several clinical and biological factors on survival (OS) and disease-free survival (DFS) after a median follow-up of 36 months.

Patients and methods

Patient selection

The diagnostic biopsy material of patients 60 years old or younger referred to our unit with the diagnosis of MCL or NHL classified as working formulation categories A to E, has been reviewed by one of us (FG). Only patients whose biopsy material met the accepted morphological and immunophenotypic criteria for MCL[3] have been included in this study. Twenty patients met those criteria. Two patients did not undergo the planned high-dose therapy with stem cell transplantation. One patient refused the procedure and in

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one patient who was refractory to conventional chemotherapy attempts to harvest a sufficient number of stem cells were unsuccessful. Eighteen patients underwent high-dose therapy with stem cell transplantation and are evaluated.

Morphology

The morphological classification as common or pleomorphic and blastic type followed the recommendations of the European lymphoma task force,[19] further described by Ott *et al*.[20]

Immunohistological studies

Immunophenotyping of lymphoma cells in biopsy specimens was performed on frozen sections when available using a panel of monoclonal antibodies: CD19, CD20, CD21, CD22, CD23, CD35, CD37, CD3, CD4, CD5, CD8, CD10 in addition to the analysis of surface expression of κ λ light chains and IgM and D.

Cyclin D1 and P53 overexpression by abnormal cells were evaluated with 5D4 (Immunotech, Marseille, France) and D07 (Dako, Trappes, France) monoclonal antibodies, respectively.[10,21,22] P53 overexpression was considered as 'positive' if more than 5% of the abnormal cells were strongly positive with the D07 monoclonal antibody.[10]

Proliferation index was evaluated using the MIB1 antibody (Immunotech) detecting the Ki67 antigen on paraffin sections.[20]

Statistical analysis

OS and DFS were calculated using Kaplan and Meier's method.[23] Survival was measured from the time of diagnosis and from the time of stem cell transplantation to death from any cause or to the date of last contact. DFS was calculated from the time of stem cell transplantation to the time of progression or last visit. OS and DFS from the date of stem cell transplantation according to the presence or absence of clinical or biological characteristics were compared univariately by the log-rank-test.[24] Significance of differences between different groups of patients was determined using the χ^2 test.

Results

Patient characteristics (Table 1)

At the time of diagnosis most patients had stage IV disease with bone marrow involvement in 12 and PS $\geqslant$ 1 in 12. The morphology was found to be blastic in three patients. Of the evaluable patients, 43% had 30% or more proliferative abnormal cells according to the Ki67 antigen expression. P53 ($\geqslant$5% of abnormal cell) and cyclin D1 overexpression were present in 36% and 80% of the evaluable patients respectively. The patient classification according to the age adjusted international prognostic index[25] was possible in 12 patients. Eleven patients were in the high–intermediate category and 1 in the high-risk group.

Table 1 Patient characteristics

	No.	*No. evaluated*
No.	18	
Age (year) (median)	40–60 (47)	
Sex		
Male	12	
Female	6	
Stage		
III	2	
IV	16	
Bone marrow involvement	12	
Circulating cells	2	
GI involvement	8	
Bulk	5	
PS $\geqslant$ 1	12	
LDH $>$ N	6	12
Blastic histology	3	18
Proliferating cells $\geqslant$30%	6	14
P53 overexpression $\geqslant$5%	5	14
Cyclin D1 overexpression	9	11

High-dose therapy and stem cell transplantation

Seventeen patients underwent autologous transplantation and one allogeneic transplantation from an HLA-identical sibling. At the time of high-dose therapy (HDT) 10 patients were in first partial response (PR) after first-line therapy consisting of three courses of increased CHOP-like regimen (vindesine 3 mg/m^2 i.v. day 1, cyclophosphamide 1.5 g/m^2 i.v. day 2, doxorubicin 80 mg/m^2 i.v. day 2 and prednisone 80 mg/m^2/day p.o. days 1–5). Four patients were in second response either complete (one patient) or partial (four patients) following second-line therapy with the same anthracycline containing regimen as the first-line patients. Three patients were refractory to two lines of chemotherapy including one with anthracycline. The median time from diagnosis to HDT was 8 months (4–35 months). The source of stem cells for autologous patients was unpurged marrow in four patients and G-CSF-mobilized unpurged peripheral blood stem cells in 13 patients. In seven (50%) out of 14 evaluated patients the bone marrow remained positive at the time of harvest. In no cases were morphologically abnormal cells present in the graft. No immunological or molecular evaluation of graft contamination was performed. Thirteen patients were conditioned with fractionated 12 Gy TBI over 3 days with lung shielding followed by either cytoxan (120 mg/kg over 2 days) in 11 patients or by an association of cytoxan (1800 mg/m^2/day on 4 consecutive days), etoposide (300 mg/m^2/day on 3 consecutive days), BCNU (300 mg/m^2, 1 day) in two patients. The BEAM regimen (BCNU 300 mg/m^2 day 1, etoposide 400 mg/m^2/day days 2–5, cytarabine 400 mg/m^2/day c.i.v.i. days 2–5 and melphalan 140 mg/m^2 day 5) was used in five patients. Patients were housed in laminar airflow rooms and received broad-spectrum empirical i.v. antibiotics in the event of fever greater than 38°5C, and amphotericin B if fever persisted. Irradiated single donor platelets and packed red blood cell transfusions were used to maintain platelet counts above 20×10^9/l and hemoglobin levels above 8 g/dl, respectively. The patients who underwent autologous

transplant received i.v. RhG-CSF at a dose of 5 μg/kg/day from day 7 post transplant until PMN were above 1×10^9/l.

Toxicity

The high-dose therapy (HDT) was well tolerated with no toxic deaths or severe bacterial or fungal infections. The single patient who received an allogeneic transplant had an uneventful post-transplant course with neither acute nor chronic graft-versus-host disease. The median duration of hospitalization was 22 days (19–31 days). The median time to reach 10^9 PMN/l and 50×10^9/l platelets was 13 days (9–17 days) and 15 days (10–119 days), respectively.

Response to high-dose therapy

Within 3 months following stem cell transplantation, patients were restaged for evaluation of response to HDT. The patient in CR2 remained in CR. Of the 17 patients not in CR at the time of transplant, 12 (71%) achieved a CR (eight out of 10 PR1, two out of four PR2 and two out of three refractory to conventional therapy). Three patients remained in PR. Two patients progressed at 2 and 3 months; one was in first PR and one was refractory to standard chemotherapy at the time of high-dose therapy. Comparison of the characteristics listed in Table 2 between responders to stem cell transplantation (ie patients remaining in CR or achieving a CR after high-dose therapy) and non-responders (ie those remaining in PR or progressing early) show no significant differences (data not shown).

Survival – Disease-free survival (Figure 1)

With a median follow-up 36 months (range 13–80 months) post transplant 15 patients are still alive, 11 of whom have no evidence of disease progression. The projected 4 year

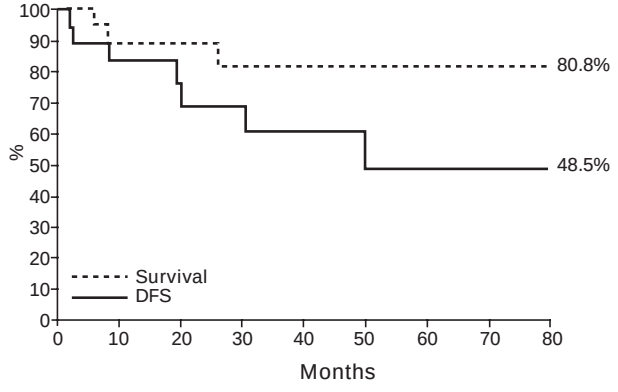

Figure 1 Survival and progression-free survival from BMT.

Table 2 Relationship between clinical, biological or therapeutic characteristics and survival or progression-free survival

	No.	*Survival*			*DFS*		
		Median (m)	*% at 4 years*	*P*	*Median (m)*	*% at 3 years*	*P*
Histology							
blastic	3	NR	67	NS	6	33	0.06
common	15	NR	83		NR	65	
Marrow at diagnosis							
positive	12	NR	83	NS	47	38	NS
negative	6	NR	60		NR	67	
Marrow at harvest							
positive	7	NR	69	NS	25	43	NS
negative	7	NR	86		NR	54	
PS							
$\geqslant$1	12	NR	73	NS	44	40	NS
$<$1	6	NR	100		NR	75	
MI							
$\geqslant$30%	6	25	40	NS	14	28	NS
$<$30%	8	NR	83		47	44	
P53							
$\geqslant$5%	5	25	38	NS	14	27	0.07
$<$5%	9	NR	86		NR	59	
No. pc factors[a]							
0.1	10	NR	89	NS	NR	60	0.06
$\geqslant$2	7	25	40		19	29	
Disease status							
PR1	10	NR	90	NS	NR	80	NS
No PR1	8	NR	66		26	18	
Conditioning							
TBI	13	NR	89	0.07	NR	71	$<$0.0001
No TBI	5	NR	60		6	0	

PS = performance status; MI = mitotic index; NR = not reached.
[a]Number of prognostic factor among: blastic histology, PS $\geqslant$1, MI $\geqslant$30%, P53 $\geqslant$ 5%.

probability of OS and DFS after HDT is 81% (90% confidence interval, 68–94%) and 49% (90% confidence interval, 34–64%), respectively. Despite this therapy, seven patients progressed between 2 months and 51 months (median 20 months). The latest progression presented as an abdominal well-localized tumor in the allotransplant patient who was refractory at the time of BMT. This patient received unmanipulated donor lymphocytes unsuccessfully. A second CR was achieved and maintained after involved field irradiation. Another patient (41 years old) relapsed 11 months after autologous BEAM conditioned bone marrow transplant. After salvage therapy, he achieved a PR2 and an allogeneic BMT from an HLA-identical sibling was performed after a TBI conditioning regimen. This patient is currently alive and well 38 months after allogeneic BMT. Two patients remain alive with disease and three patients died from the disease 6 months, 9 months and 27 months after transplant.

Prognostic factors

The influence of several factors on OS and DFS after BMT was evaluated (Table 2).

Patients who were prepared for transplant with a TBI containing regimen had a significantly better 4 year OS and DFS (89 and 74%, respectively) than those who received chemotherapy only (60 and 0%, respectively) ($P = 0.07$ for difference in survival and $P < 0.001$ for difference in DFS) (Figure 2). The comparison for characteristics such as stage of the disease PS or LDH level at diagnosis, status at the time of BMT, histologic subtype, bcl1 or P53 overexpression and proliferation index showed no significant difference between these two groups of patients. The stage of the disease at time of transplant (PR1 *vs* refractory or PR2 or CR2) did not significantly influence the 4 year OS estimated to be 90% (90% confidence interval, 81–99%) compared to 66% (90% confidence interval, 45–87%) $P = 0.3$. However, although not significant, the 4 year DFS for patients in PR1 is estimated to be 80% (90% confidence interval, 67–93%) with eight out of 10 patients alive in continuous CR a median of 36 months (range 13–80) compared to 18% (90% confidence interval, 2–34% for patients not in PR1 (Figure 3). Of note is the fact that the only

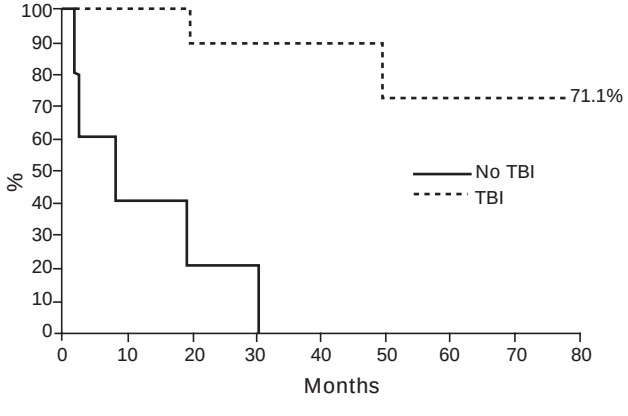

Figure 2 Progression-free survival according to conditioning regimen.

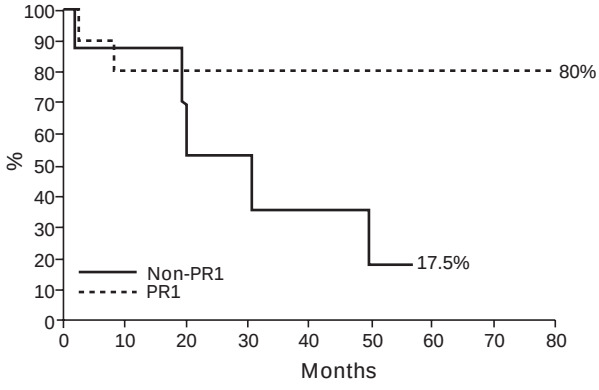

Figure 3 Progression-free survival according to disease status at time of transplantation.

two patiens who relapsed after transplantation in PR1 were conditioned with the BEAM regimen.

As shown in Table 2 there is a trend for a significantly worse DFS when blastic histology is present or when ⩾5% abnormal cells overexpress P53.

The influence of risk category according to the age adjusted international prognostic index could not be evaluated since only 12 patients could be classified, all belonging to the high or high–intermediate risk category.

Influence of the number of adverse prognostic factors among those described with standard chemotherapy (blastic histology, PS ⩾ 1, proliferating cells ⩾ 30%, P53 overexpression) was also evaluated. One patient had none of these factors, nine patients had one (mainly PS ⩾ 1) and seven patients had two or more of these factors. There is a trend for a better DFS in patients with no or one adverse prognostic factor as compared to patients with two or more of these factors (4 year DFS: 60 *vs* 29%, $P = 0.06$). Although not significant, the 3 year probability of OS is 89% in patients with less than two adverse prognostic factors and only 40% when two or more factors are present.

Discussion

In their recent review article Weisenburger and Armitage[3] concluded that 'new and better therapies, rather than conventional chemotherapy were badly needed for this group of lymphomas' (ie mantle cell lymphomas). Indeed, following conventional chemotherapy the median survival is constantly around 40 months in all large cohorts reported with a median PFS around 20 months.[1,2,6–9] Although these results are not modified by any type of conventional chemotherapy[6,7,9] it is clear that this disease is chemosensitive since between 20 and 60% CR rates are regularly reported following conventional chemotherapy (for a review see Ref. 3). Taking advantage of this chemosensitivity, the most readily available 'new therapy' could be high-dose chemo- or chemoradiotherapy followed by autologous or allogeneic stem cell rescue.

Here, we show that high-dose therapy followed by stem cell rescue is effective since, with a median follow-up of 36 months after HDT, 15 patients with well-defined MCL are alive, 11 of them with no evidence of disease pro-

gression. A 4 year probability of OS and of DFS of 81% (90% confidence interval, 68–94%) and 49% (90% confidence interval, 34–64%), respectively, compares favorably with results achieved with conventional chemotherapy. These results were achieved without significant toxicity. One of the issues with high-dose therapy and stem cell rescue is the feasibility of such a treatment. Until now this form of treatment has usually been restricted to younger patients (less than 60–65 years old) while the median age of patients diagnosed with MCL ranges between 55 and 65 years old.[1–3,5,8,9] Furthermore, for various reasons not all younger patients receive this therapy. In our series of 20 consecutive patients younger than 60 with histologically proven MCL only two did not undergo the planned BMT: one because of refusal and one because he was impossible to harvest. The feasibility in our center was good with 18 out 20 patients undergoing HDT (90%). The next question is whether every patient will benefit from HDT with stem cell transplantation. In order to answer that question we evaluated the influence of clinical, biological and therapeutic variables on survival and progression-free survival after BMT. Factors that have been associated with a poor prognosis following conventional therapy are blastic histology, peripheral blood involvement, high proliferation index, P53 overexpression and poor performance status.[1,2,7,10] None of these factors significantly affected our patients' DFS although the median DFS for six patients with high proliferation index and for five patients with P53 overexpression was less than 18 months. When blastic features were present, the median DFS was only 6 months. The presence of two or more of these factors was associated with a median DFS of 19 months only. Thus, it appears that the factors which adversely influence outcome after conventional chemotherapy may also indicate poor prognosis following BMT.

We show that using a conditioning regimen including TBI as well as, although to a lesser extent, performing the transplant while the patients are in PR1, results in a better DFS. Thus, none of the eight patients who were transplanted in PR1 with a TBI containing regimen relapsed or died after a median follow-up of 36 months (range 13–80). These results are comparable to those reported by Kröger *et al*[17] and Haas *et al*.[12] In these two studies of a total of 16 patients in CR1/PR1 who were autotransplanted with a myeloablative conditioning regimen, none have progressed after a follow-up ranging from 9 to 47 months. These results are in sharp contrast with those recently published by Freedman *et al*.[18] In this study, using anti-B cell monoclonal antibody purged autologous bone marrow transplantation after a TBI containing preparative regimen, the results achieved for eight patients in CR1/PR1 are poor. Median duration of DFS is only 49 months and only three patients remain in CR with a median follow-up of 24 months. Such discrepancies are not easily explainable. Selection bias may have occurred. However, a comparison of major characteristics of the patients in our series and in the series published by Freedman *et al* does not show any difference except for the use of a purged graft in the latter. These discrepancies underline the need for prospective randomized trials comparing conventional therapy with high-dose therapy in a well balanced population of patients with MCL.

In conclusion, although retrospective and dealing with a limited number of patients, our study shows that high-dose therapy with stem cell transplantation is effective in younger patients with proven MCL. It seems advisable to recomend both the use of a TBI containing regimen and early transplantation in patients responding to first-line conventional anthracycline-containing regimens. This might improve the 'good-risk' patients since adverse prognostic factors found in conventionally treated patients have also a negative impact when high-dose therapy is performed. For these patients and for the ones with a good prognosis, further studies should aim at evaluating residual disease after transplant and additional therapy such as *in vivo* immunotherapy.

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