Sequential chemotherapy by CHOP and DHAP regimens followed by high-dose therapy with stem cell transplantation induces a high rate of complete response and improves event-free survival in mantle cell lymphoma: a prospective study

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Mantle cell lymphoma (MCL) is a distinct clinico-pathological entity with a poor prognosis. We have conducted a prospective study in patients with MCL to evaluate a therapeutic strategy in which CHOP polychemotherapy was followed by DHAP if CHOP failed to induce complete remission. Responding patients then proceeded to an intensification therapy with autologous peripheral blood stem cell transplantation (APBSCT). Twenty-eight consecutive patients with newly diagnosed aggressive MCL were included. After four cycles of CHOP regimen, two complete responses (CR) were obtained (7%) and 14 (50%), five (18%) and seven (25%) patients achieved partial (PR), minor (MR) and no response, respectively (one patient died from septic complications during CHOP induction). The two patients in CR after CHOP underwent intensification with TBI, high-dose cyclophosphamide-etoposide and APBSCT. The other twenty-five patients received DHAP and in this group a response rate of 92% (21 CR (84%), two PR (8%)) was observed. Two patients had progressive disease. The twenty-three responding patients received high-dose therapy (TAM8 regimen: TBI–cytarabine–melfalan) followed by APBSCT. One of the two partial responding patients achieved CR after TAM8. After a median follow-up of 47.6 months (range, 14–70), seven patients have relapsed. Our data confirm that: (1) CHOP regimen induces a low CR rate in MCL; (2) CHOP plus DHAP appears to be much more efficient and allows a large proportion of patients to proceed to high-dose therapy in CR; (3) consolidation therapy including TBI and high-dose Ara-C followed by APBSCT may improve event-free survival.

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Introduction

Mantle cell lymphoma (MCL) has been recently described as a distinct clinico-pathological entity characterized by a predominantly diffuse or nodular proliferation of atypical small B lymphoid cells effacing the nodal architecture.^{1,2} These cells are characterized by their immunophenotype (CD5⁺, CD23[−], CD10[−], SIgM⁺, SIgD⁺). MCL is frequently associated with the t(11;14) translocation, which results in the overexpression of cyclin D1 gene within the bcl-1 locus.^{3,4–7} Despite an initial relatively indolent clinical presentation, the prognosis of MCL remains poor with a median survival time of less than 3 years.^{3,8–11} Adverse prognostic factors such as poor performance status (PS), B symptoms, high LDH and β 2-microglobulin

levels are observed in more than 50% of patients during the progression of the disease. However, although the international prognostic factor index may be applied to MCL patients, it does not allow clear discrimination of good and poor risk patients since both groups have a nearly comparable poor outcome.^{12,20}

MCL is characterized by its refractoriness to most usual therapeutic strategies for lymphomas. Although CHOP or CHOP-like regimens are considered as a reference therapy for non-Hodgkin's lymphoma (NHL), in MCL they have been reported to induce a low rate of complete response with a range between 10% and 50%.^{10,13} When we began our study (May 1995) no other regimen had demonstrated a better value in order to increase response rate, event-free survival and overall survival. As observed in other NHL, a complete clinical response after initial therapy seems to be associated with a longer disease-free survival (DFS), but in MCL the impact of CR on overall survival remains to be determined. Preliminary reports have suggested that high-dose therapy (HDT) especially with total body irradiation (TBI) and autologous peripheral blood stem cell transplantation (APBSCT) for patients with MCL increases response rates and seems to produce better DFS than conventional therapy.¹⁴ This treatment, however, has not been proved to cure any patients. Furthermore, APBSCT does not seem to increase response rate and median DFS in patients who are not in the first phase of their disease.¹⁴

Therefore, due to the poor prognosis of MCL treated with conventional chemotherapy and taking into account results of earlier studies, we initiated a prospective study based on the response to initial CHOP therapy with the aims of increasing response rates before APBSCT and increasing event-free and overall survival. Patients who achieved CR after four cycles of CHOP underwent TBI plus high-dose cyclophosphamide and etoposide (Cy-Eto) myeloablative regimen and APBSCT. Patients who did not enter CR after CHOP were treated by a salvage therapy with high-dose cytarabine regimen (DHAP) followed by TBI plus high-dose Ara-c plus melfalan (TAM8)¹⁵ and APBSCT.

Patients and methods

Patients eligibility

After giving their informed consent, adult patients younger than 65 years with previously untreated aggressive MCL⁸ were enrolled in this prospective study. In accordance with Ann

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Arbor criteria, only patients with stages III and IV were included in the study.¹⁶ Patients with CNS involvement, leukemic phase were also eligible. After nodal biopsy, which was performed in all patients, aggressive MCL histological subtypes were included (nodular, diffuse or blastic). The diagnosis was based on a combination of morphologic, immunologic, cytogenetic and molecular criteria as previously described.^{2,7,8,14,17} Patients with mantle zone pattern, which is associated with a favorable course, were excluded from the study.¹⁸ All cases were reviewed by expert hematopathologists for confirmation of diagnosis.

Immunophenotypic studies were performed by flow cytometry or by *in situ* immunohistochemistry using antibodies, to the following cluster antigens, as previously described: CD3, CD5, CD19, CD10, CD20, CD23, CD43, FMC-7, immunoglobulin M (IgM) and IgD.^{7,17}

Cytogenetic analysis, cyclin D1 mRNA expression and IgH/Bc11 translocation were performed when fresh or cryopreserved material was available as described earlier.^{6,7} Patients with any of the following were ineligible: cardiac ejection fraction less than 50%, insufficient pulmonary function, severe renal or hepatic function impairment.

Clinical evaluation

Disease stage was evaluated in accordance with Ann Arbor criteria.¹⁶ The staging work-up included physical examination, blood cell count, liver function test, serum lactate dehydrogenase (LDH) and β 2-microglobulin level determination, chest X-ray, computed tomography scans of the thorax, abdomen and pelvis, bone marrow aspirate and biopsy, gastrointestinal endoscopies and lumbar puncture for lymphomatous involvement.

Protocol design

The protocol design is shown in Figure 1. The initial chemotherapy consisted of four courses of CHOP regimen (cyclophosphamide 750 mg/m² day 1, adriamycin 50 mg/m² day 1, vincristine 1.4 mg/m² day 1 prednisone 40 mg/m²/day days 1–5) with meningeal prophylaxis (methotrexate 10 mg, prednisone 40 mg) every 21 days. After the four CHOP courses, a complete evaluation, without bone marrow biopsy, was performed.

Patients in complete clinical response (clinCR) or in partial response (PR) were planned to have peripheral blood stem cell (PBSC) mobilization after cyclophosphamide (4.5 g/m²) and etoposide (450 mg/m²) plus G-CSF (5 μ g/kg/day) administration (Cy-Eto). After PBSC collection, a new complete evaluation including bone marrow biopsy was performed. Patients in complete response (CR), including bone marrow biopsy, received two more courses of CHOP regimen followed by an intensive conditioning regimen with TBI, cyclophosphamide (Cy, 60 mg/kg/day, days 1 and 2), etoposide (VP16, 300 mg/m²/day, days 1–3) plus APBSCT.

Patients in failure, in minor response or in progression after or during the CHOP regimen respectively and patients who did not reach CR after Cy-VP16 mobilization regimen were planned for a second line chemotherapy with 4 or 3 monthly courses of DHAP, respectively (cisplatin 100 mg/m² day 1, cytarabine 4 (2 g/12 h) g/m² day 2, dexamethasone 40 mg/day days 1–4). Patients who responded to DHAP were planned for PBSC harvested under G-CSF after the second course of

Figure 1 Protocol design and response rate after treatment. clinCR, clinical complete response; CR, complete response (clinCR and negative bone marrow result); PR, partial response; MR, minor response; TBI, total body irradiation; APBSCT, autologous peripheral blood stem cell transplantation; Cy + Eto, cyclophosphamide + etoposide; CHOP, cyclophosphamide 750 mg/m² day 1, adriamycin 50 mg/m² day 1, vincristine 1.4 mg/m² day 1, prednisone 40 mg/m²/day days 1–5; DHAP, cisplatin 100 mg/m² day 1, cytarabine 4 g/m² day 2, dexamethasone 40 mg/day days 1–4; TAM8, TBI 12 Gy days 1–3, cytarabine 4 g/m²/day days 5–6, melphalan 140 mg/m² at day 8; Pt, patient.

DHAP. Autologous unpurged PBSC transplantation was scheduled within 6 weeks after the last DHAP using the TAM8 regimen (TBI 12 Gy days 1–3, cytarabine 4 g/m²/day days 5–6, melphalan 140 mg/m² day 8). TBI was performed over 3 days as twice daily fractions at a dose of 200 cGy treatment for a total dose of 1200 cGy (800 cGy on the lungs). Patients who did not exhibit PR or CR after DHAP were not eligible for intensification by TAM8.

A novel complete clinical evaluation was planned for each patient just before and 3 months after intensification regimen and then every 4 months.

Response and toxicity

Complete clinical response (clinCR) was defined as the disappearance of all clinical and morphological evidence of lymphoma. Complete response (CR) was defined as clinCR plus normal bone marrow biopsy. PR was defined as a reduction of more than 50% of the initial tumor mass, MR as a reduction of less than 50% of the initial tumor mass and/or of the lymphocytosis. Failure or progressive disease was defined as stability or as any increase greater than 25% of the tumor mass, respectively. Toxicity was evaluated according to World Health Organization (WHO) criteria.

Statistical method

The Stuart–Maxwell test was used to evaluate the response after CHOP and after CHOP followed by the DHAP regimen

(χ^2 test). Event-free survival (EFS) was calculated from entry into the protocol until death, progressive disease or last contact. Survival was calculated from the date of study entry to the date of death whatever the cause. Overall survival curves were plotted using the Kaplan–Meier method.¹⁹ Statistical analysis was performed on the S. Plus 4.5 software.

Results

Patients

Between March 1995 and June 1999, 17 consecutive patients from Necker Hospital and 11 patients from other French centers were registered. Patients' characteristics are listed in Table 1. All patients had stage III/IV disease. Twenty-five patients had bone marrow involvement and malignant lymphoid cells were observed in the blood of 14 patients. Eleven out of 23 patients investigated had a gastrointestinal involvement. LDH value was found above normal count in 12 patients. Elevated β 2-microglobulin level was observed in 14 patients. PS did not exceed 1 for all patients (WHO classification). Diagnosis criteria for mantle cell lymphoma are listed for each patient in Table 2.

Response

In Figure 1 the response rates are summarized after chemotherapy and high-dose therapy. Twenty-five patients received the four planned cycles of CHOP regimen. Three patients did not complete this regimen. One patient died of septic complication after the third course (patient 2), one patient presented recurrent cyclophosphamide severe allergic pneumopathy (patient 4) and one was in clinical progression after one course (patient 16). Two clinCR (7%) were obtained, 14 patients (50%) and five patients (18%) achieved PR and MR, respectively (Table 3). Failure or progression was noted for six (21%). One patient who died from septic complication could not be evaluated (4%). The 14 partial responding patients

were treated by one course of Cy-Eto for PBSC collection and did not exhibit further significant improvement as assessed by a new evaluation including bone marrow biopsy. Thus, only two patients reached CR after CHOP plus Cy-Eto (patients 20 and 21). The other twenty-five surviving patients received the DHAP regimen.

After DHAP, CR and PR (the two PR being >75%) were observed for 21 (84%) and two (8%) patients, respectively (Table 3). Two progressions occurred (patients 10 and 22).

The two patients in CR after CHOP and Cy-Eto received the intensification therapy with high-dose Cy-Eto and APBSCT. The twenty-three patients who responded and survived after DHAP underwent therapeutic intensification by TAM8 regimen. Among the two partial responders after DHAP, one patient in PR achieved CR following TAM8 plus APBSCT (patient 8). Our strategy induced a total response rate (CR + PR) of 0.78% (95% confidence interval (CI), 0.59 to 92).

Stem cell mobilization

Autologous PBSC mobilization was attempted after Cy-Eto plus G-CSF for the 16 patients with partial or complete response after the CHOP regimen. Others had stem cell mobilization following DHAP plus G-CSF. All patients achieved an adequate hematopoietic progenitor collection with a median of 6.8×10^6 CD34⁺ cells/kg harvested (range, 2.2–19).

Event-free survival and survival

Median follow-up from diagnosis and initial therapy is 47.6 months (range, 14–70 months). Median survival has still not been reached. One of the two patients treated by TBI plus cyclophosphamide-etoposide relapsed at 12 months (patient 20). Six patients relapsed after CR following the TAM8 regimen (patient 6 (48 months), patient 7 (63 months), patient 13 (40 months), patient 14 (48 months) and patient 16 (54 months), patient 19 (23 months). Median follow-up time from CR is 33 months (range, 9–61 months). The EFS and survival are shown in Figures 2 and 3, respectively. The EFS rate at 3 years is 83.3% (95% CI, 69.2 to 100). The overall survival rate at 3 years is 90.4% (95% CI, 78.2 to 100). Due to the low number of events, no prognostic factors are evaluable.

Toxicity

WHO grades 3 and 4 for granulocytopenia and/or thrombocytopenia were observed in eight (29%) and 25 (100%) patients after CHOP and DHAP regimen, respectively. One patient died from pneumococcus septic complication during CHOP-induced neutropenia but no treatment-related death was observed after DHAP and APBSCT. Severe mucositis (grade >2, WHO) occurred in all patients following the TAM8 regimen. Five patients presented resolutive but severe idiopathic interstitial pulmonary syndrome (grade 3 or 4, WHO) after the TAM8 regimen before white blood cell recovery, and were treated with large spectrum antibiotic and symptomatic treatment. One patient needed transient artificial ventilation. Diffuse pulmonary infiltrates were present on scan and bacteriological results from bronchoalveolar aspiration were negative in all cases. All patients recovered without pulmonary sequelae. Extensive or recurrent VZV infection was observed in seven patients after hematopoietic recovery fol-

Table 1 Initial clinical features of patients

	Number of patients	
	28	%
Age, year: median (range)	56 (33–64)	
Male/Female	23/5	
B symptoms	14	50
Performance status $\leq$ 1	28	100
Generalized lymphadenopathy	25	89
Splenomegaly	10	35
Waldeyer's ring involvement	3	11
Hepatomegaly	3	11
Gastrointestinal involvement	11/23 ^a	48
Mediastinal involvement	7	25
Lung localization	2	8
Bone marrow involvement	25	89
Leukemic phase	14	50
Central nervous system localization	1	4
Ann Arbor stage III–IV	28	100
Elevated LDH	12	41
Elevated β 2-microglobulin	14	50

^aOnly 23 patients underwent gastrointestinal endoscopy. The remaining five had no gastrointestinal signs.

Table 2 Histologic, immunologic, cytogenetic and molecular data

Patient No.	Histologic form	Immunophenotype			Cytogenetic	Overexpression of cyclin D1 (slot blot analysis)	Bcl1-IgH rearrangement (PCR analysis)
		CD5	CD23	FMC7			
1	Nodular	+	NP	NP	NP	+	—
2	Diffuse	+	—	+	NP	—	+
3	Diffuse	+	NP	NP	NP	+	+
4	Diffuse	+	—	+	t(11;14)	+	—
5	Nodular	+	—	—	N	—	—
6	Diffuse	+	—	+	t(11;14)	+	—
7	Diffuse blastic	+	—	+	t(11;14)	+	—
8	Nodular	+	—	+	trisomy 12	—	—
9	Nodular	+	—	+	t(11;14)	+	—
10	Diffuse	+	—	NP	trisomy 3	+	—
11	Diffuse	+	+	+	N	NP	NP
12	Nodular	+	—	+	t(11;14)	NP	NP
13	Diffuse	+	NP	NP	trisomy 3	NP	NP
14	Diffuse	+	—	+	N	+	+
15	Diffuse	+	—	NP	NP	+	+
16	Nodular	+	—	+	t(11;14)	+	+
17	Nodular	+	—	+	t(11;14)	+	+
18	Nodular	+	—	+	del (6q)	+	+
19	Diffuse	+	—	+	t(11;14)	+	+
20	Diffuse	+	—	+	t(11;14)	NP	NP
21	Diffuse	+	—	NP	del 3p21	NP	NP
22	Diffuse	+	—	NP	N	+	—
23	Diffuse	+	—	+	t(11;14)	+	+
24	Diffuse	+	—	+	del (6)	+	+
25	Nodular	+	—	NP	t(11;14)	+	+
26	Nodular	+	—	+	NP	+	+
27	Diffuse	+	—	NP	N	—	+
28	Diffuse	+	—	+	t(11;14)	+	—
					t(11;14)	+	+

NP, not performed; N, normal.

lowing TAM8 and APBSCT. Despite a sufficient CD34⁺ cell count transfused after TAM8 regimen, one patient did not reach a sufficient hematologic recovery following high-dose therapy and APBSCT and required regular red blood cell transfusion for 1 year.

Discussion

MCL is a B cell lymphoproliferation well individualized in the recent lymphoma classifications, characterized by its refractoriness to therapeutic strategies with a very poor prognosis.^{3,8–11} MCL exhibits the shortest median time to progression and the shortest median survival of all small B cell lymphoma subtypes.^{8,10} In most studies, whatever the initial therapy, patients present partial regression of the lymphoma for 6 to 18 months and then progress and die with a median overall survival of 3 to 4 years.^{9,21} We report here, that DHAP regimen is very efficient in inducing CR in patients who did not fully respond to CHOP regimen. Furthermore, although median follow-up is still short, intensification with the TAM8 regimen followed by APBSCT seems to prolong EFS and survival from historical studies^{3,8–11} and may induce molecular remission at the 10^{−4} sensitivity.

All patients fulfilled the histological, immunophenotypic, molecular or cytogenetic criteria of aggressive MCL except

patients 5 and 8 who exhibited negative Bcl1-IgH rearrangement and no detectable overexpression of cyclin D1 from the sample studied. All patients presented severe and advanced disease and our series confirms the classic clinical presentation of aggressive MCL with a median age of 55 years (46–62), male preponderance (90%), and frequent extranodal disease (100%) with bone marrow and/or gastrointestinal involvement. Moreover, half of the patients had an increased β 2-microglobulin level, which has been reported as a poor prognosis factor in MCL.²² Patients with mantle zone pattern, because of their relatively good prognosis (CR rate of 75% and 3-year survival rate of 100%) were not included in this trial.¹⁸ The t(11;14) and overexpression of cyclin D1 were found in 56% and 81% of investigated patients, respectively. Therefore our group of patients was comparable with other previous published studies.^{14,22}

After the first line therapy with the CHOP regimen, two CR were obtained and 50% of our patients reached a PR. This finding is in agreement with some reports²² but much lower than others.^{1,21} Majlis *et al*¹⁸ reported in newly diagnosed patients a CR rate of 20% with a CHOP-like regimen. Furthermore, one previous study which evaluated increased CHOP-like regimen in 18 patients showed only one CR while other patients presented PR or were refractory.¹⁴ In contrast, other retrospective studies using doxorubicin-containing regimens have shown high response rates ranging from 60% to 83%.^{1,21}

Table 3 Clinical response after therapy and follow-up

Patient No.	No. of CHOP	Response after CHOP	Response after DHAP	TAM8	Response after graft	Follow-up from diagnosis and status (months)	Last status
1	4	MR	PR	yes	PR	Evolution on 39th month	Alive CR2 48th month
2	3	NE ^a	—	—	—	—	Dead
3	4	PR	CR	yes	CR	47	CR
4	2 ^b	PR	CR	yes	CR	44	CR
5	4	failure	CR	yes	CR	44	CR
6	4	PR	CR	yes	CR	Relapse 48th month	CR
7	4	PR	CR	yes	CR	Relapse 63rd month	Dead 70th month
8	4	failure	PR	yes	CR	45	CR
9	4	PR	CR	yes	CR	67	CR
10	4	PR	progression	no	—	Progression 13th month	Dead 21st month
11	4	MR	CR	yes	CR	30	CR
12	4	PR	CR	yes	CR	30	CR
13	4	failure	CR	yes	CR	Relapse 40th month	Alive and PR2 42nd month
14	4	MR	CR	yes	CR	Relapse 48th month	Alive and PR2 58th month
15	4	failure	CR	yes	CR	57	CR
16	1	progression	CR	yes	CR	Relapse 54th month	Alive 63rd month
17	4	progression	CR	yes	CR	45	CR
18	4	PR	CR	yes	CR	60	CR
19	4	PR	CR	yes	CR	Relapse 23rd month	Alive and PR2 26th month
20	4	CR	—	—	CR	Relapse 12th month	Alive and PR2 18th month
21	4	CR	—	—	CR	21	CR
22	4	PR	Progression	no	—	Progression 14th month	Alive in MR 18th month
23	4	PR	CR	yes	CR	22	CR
24	4	PR	CR	yes	CR	20	CR
25	4	PR	CR	yes	CR	18	CR
26	4	PR	CR	yes	CR	18	CR
27	4	MR	CR	yes	CR	15	CR
28	4	MR	CR	yes	CR	14	CR

CR, complete response, PR, partial response, MR, minor response, NE, not evaluable.

^aPatient died of septic complications.^bRecurrent cyclophosphamide allergic pneumopathy. **Figure 2** Event-free survival (Kaplan–Meier). **Figure 3** Overall survival (Kaplan–Meier).

Likewise, the continuous infusion of anthracycline using the classical VAD regimen associated or not with chlorambucil showed in MCL patients a 43% rate of CR.²³ However, response criteria in all these studies did not include bone marrow and gastrointestinal examination. Taken together, these studies suggest that for a large proportion of patients with MCL, CHOP or CHOP-like regimens failed to obtain a minimal tumor burden before stem cell collection and intensive therapy plus APBSCT.

In order to increase the response rate before APBSCT, we have tested a second line therapy with high-dose Ara-c regi-

men (DHAP). We have chosen DHAP because high-dose Ara-c is an effective therapy in obtaining complete response in patients in relapse of aggressive NHL.^{23–25} Furthermore, this drug allows intensification with APBSCT and may induce cure of aggressive relapsing NHL. In our series this regimen produced a high rate of CR (84%) and good PR (8%) after failure of CHOP without life-threatening toxicity. However, due to the particular course of MCL and the design of our protocol, the impact of DHAP cannot be dissociated from the previous therapy by CHOP and we could not totally exclude that four more courses of CHOP could have induced CR in a subgroup

of good partial responder patients. Therefore, we cannot conclude that DHAP alone used as first line therapy would induce similar responses as those obtained after the sequence CHOP–DHAP. This question might be solved by setting-up a cross-randomized study comparing CHOP and DHAP followed by DHAP or CHOP, respectively, in case of no response after the first line therapy. Our data are in agreement with the results of a recently published study using the hyper-CVAD/MTX-Ara-c regimen that contains high-dose Ara-c. Indeed, in this study, the authors reported a high response rate of 93.5% (CR 38%, PR 55%) for patients with MCL previously treated (or not).²⁶ However, the response rate for the subgroup of previously untreated patients was not given and some patients (some of whom have been previously treated with chemotherapy) failed to obtain enough PBSC yield for autografting. It is noteworthy that in our study two courses of DHAP after four CHOP cycles did not compromise stem cell harvesting, since no patient failed to have adequate peripheral stem cell collection.

Earlier reports suggested that a TBI conditioning regimen before PBSC transplantation improved the prognosis of MCL¹⁴ compared to other procedures. The high response rate that we observed with DHAP suggests that high-dose Ara-c may be included in the conditioning regimen. Thus, we have chosen the TAM8 regimen, which contains both Ara-c and TBI, and which is a feasible conditioning regimen as previously shown in the treatment of acute lymphoblastic leukemia.¹⁵

All our partial or complete responder patients after DHAP undertook intensification by TAM8 plus APBSCT. One out of two in PR before TAM8 achieved CR, emphasizing the value of the conditioning regimen. No conditioning transplant-related mortality was registered. However, the morbidity was high with occurrence of many recurrent and/or extensive herpes-zoster reactivations. Thus, a prophylactic therapy with acyclovir should be recommended following TAM8 regimen. Moreover, five patients presented severe but resolvable interstitial pulmonary syndrome without identified etiology. Thus, such therapeutic strategy needs accurate pulmonary evaluation before high-dose therapy. One patient exhibited late platelet and hemoglobin recovery and was transfusion dependent for 1 year after autograft despite an adequate number of CD34⁺ cells being transfused.

After a median follow-up of 27 months after CR (and 37 months after diagnosis and initial therapy), 83% of autografted patients remain in CR. These results strongly suggest that our treatment strategy may improve EFS when compared with historical studies.^{8–13} These results are encouraging because long-term disease-free survival is uncommon for patients with MCL, especially for those with advanced disease.²⁷ However, relapses occurred in patients with longer follow-up, which may suggest that the curve is not yet achieved. Recent studies have reported that anti-CD20 monoclonal antibodies may induce significant response rates in MCL relapsing patients.²⁸ In future protocols, our results may be improved by using a combination of CHOP/DHAP and anti-CD20 as suggested by Romaguera *et al*²⁹ with the combination of HyperCVAD and anti-CD20.

In conclusion, stimulating results were obtained after CHOP followed by salvage therapy with DHAP and further APBSCT after TAM8 regimen which argues for the use of a high-dose Ara-c regimen in the induction therapy for patients with MCL. A further step with consolidation therapy by TBI and high-dose Ara-c sustained by APBSCT seems promising to improve the outcome of MCL patients. Longer follow-up is, however, warranted to assess the impact of our strategy on survival.

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