First-line treatment with rituximab-hyperCVAD alternating with rituximab-methotrexate-cytarabine and followed by consolidation with ^{90}Y-ibritumomab-tiuxetan in patients with mantle cell lymphoma. Results of a multicenter, phase 2 pilot trial from the GELTAMO group

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ABSTRACT

The prognosis for fit patients with mantle cell lymphoma has improved with intensive strategies. Currently, the role of maintenance/consolidation approaches is being tested as relapses continue to appear. In this trial we evaluated the feasibility, safety and efficacy of rituximab-hyperCVAD alternating with rituximab-methotrexate-cytarabine followed by consolidation with ^{90}Y-ibritumomab tiuxetan. Patients received six cycles followed by a single dose of ^{90}Y-ibritumomab tiuxetan. Thirty patients were enrolled; their median age was 59 years. Twenty-four patients finished the induction treatment, 23 achieved complete remission (77%, 95% confidence interval 60-93) and one patient had progressive disease (3%). Eighteen patients (60%), all in complete remission, received consolidation therapy. In the intent-to-treat population, failure-free, progression-free and overall survival rates at 4 years were 40% (95% confidence interval 20.4-59.6), 52% (95% confidence interval 32.4-71.6) and 81% (95% confidence interval 67.28-94.72), respectively. For patients who received consolidation, failure-free and overall survival rates were 55% (95% confidence interval 31.48-78.52) and 87% (95% confidence interval 70-100), respectively. Hematologic toxicity was significant during induction and responsible for one death (3.3%). After consolidation, grade 3-4 neutropenia and thrombocytopenia were observed in 72% and 83% of patients, with a median duration of 5 and 12 weeks, respectively. Six (20%) patients died, three due to secondary malignancies (myelodysplastic syndrome and bladder and rectum carcinomas). In conclusion, in our experience, rituximab-hyperCVAD alternated with rituximab-methotrexate-cytarabine and followed by consolidation with ^{90}Y-ibritumomab tiuxetan was efficacious although less feasible than expected. The unacceptable toxicity observed, especially secondary malignancies, advise against the use of this strategy. *Trial registration: clinical.gov identifier: NCT2005-004400-37*

Introduction

The treatment of mantle cell lymphoma (MCL) is a clinical challenge. The overall survival of patients has improved over recent years, but the median survival still remains poor, being around 5 years in the majority of patients.[1] With the standard rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) regimen, complete remission rates are lower than 50% and the median failure-free survival is short, ranging from 16 months to 2 years.[2,3]

The outcome has improved most for young, fit patients with the use of intensive first-line strategies, particularly those containing high-dose Ara-C (HDAC) followed or not by autologous stem cell transplantation (ASCT).[4-7] With intensive treatment, complete remission rates rise to 80- 100% and median failure-free survivals of up to 5 years have been reported.[5-10] In spite of this improvement, the updated long-term results obtained with these approaches have shown a continuous pattern of relapse.[11,12] After relapse, the outcome becomes dismal for most patients, who frequently require sequential treatments until death.

Maintenance and consolidation strategies in MCL are a matter of active study in order to achieve longer lasting responses. In fact, the European Mantle Cell Lymphoma Network recently demonstrated a significant improvement in progression-free survival and overall survival when mainte-

 doi:10.3324/haematol.2013.088377
We dedicate this paper to the memory of our dear colleague Javier Pérez-Calvo who passed away last year.
The online version of this article has a Supplementary Appendix.
Manuscript received on March 22, 2013. Manuscript accepted on May 30, 2013.
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nance rituximab therapy is used after R-CHOP although no benefit could be documented for patients treated with rituximab-fludarabine-cyclophosphamide.[13]

Radioimmunotherapy with an anti-CD20 antibody conjugated to a β-emitting radioisotope is a treatment with demonstrated efficacy in follicular lymphoma.[14-17] Efficacy data for radioimmunotherapy in MCL are more limited although it has efficacy as monotherapy in relapsed or refractory disease.[18] In fact, its efficacy appears to be heterogeneous since good results were reported when it was used as consolidation after standard therapy[19,20] whereas the Nordic Group found no benefit from introducing radioimmunotherapy into the conditioning regimen in their MCL3 trial compared to their previous MCL2 trial.[21] To our knowledge, only one other preliminary communication on radioimmunotherapy as consolidation after intensive treatment has been reported so far.[22]

Here we report the results of a prospective, multicenter, pilot phase 2 study, conducted by the *Grupo Español de Linfomas y Transplante Autólogo de Médula Ósea* (GELTAMO) in patients with untreated MCL, who received induction therapy with rituximab (R)-hyperCVAD / R-methotrexate-AraC (R-MA) followed by consolidation with ^{90}Y-ibritumomab tiuxetan.

Methods

The study was performed in 12 Spanish institutions. It was approved by local and central committees and registered at the Clinical Trials Gov web-site (NCT00505232). More detailed information is provided in the *Online Supplementary Material.*

Patients and assessments

Patients between 18 and 70 years old and diagnosed with MCL[23] were eligible. Cyclin D1 or t(11;14))(q13;q32) translocation positivity was required for the diagnosis. Inclusion and exclusion criteria, pre-treatment evaluations and work-up studies are described in detail in the *Online Supplementary Material*.

Complete disease evaluation was carried out before treatment, after the 4th cycle and at the end of the induction treatment. After consolidation, disease was evaluated every 4 months until the 2nd year and every 6 months thereafter.

Treatment

Induction phase

Patients received R-hyperCVAD therapy alternating with R-MA every 21 days.[5] Dose adjustments were considered for patients older than 60 years, those with creatinine values >1.5 mg/dL or after development of febrile neutropenia, hematologic toxicity (platelet count <100x10^9/L or granulocyte count <1x10^9/L on day 21 of each cycle) or non-hematologic grade 3 toxicity at any moment. Treatment was discontinued if patients did not reach hematologic recovery 5 weeks after chemotherapy, had less than a partial response after four cycles or developed grade 4 non-hematologic toxicity. The number of induction cycles was fixed at six.

Support therapy with pegylated-filgastrim and *Pneumocystis jirovecci* prophylaxis were required by protocol. Peripheral blood stem cell collection as back-up was mandatory in the first six patients and recommended for the remaining patients.

Consolidation phase

Consolidation with ^{90}Y-ibritumomab tiuxetan was scheduled 12 weeks after the 6th cycle. The drug was kindly provided by Bayer-Schering and administered following the manufacturer's written instructions. Although a dose escalation to 0.4 mCi/kg was allowed for, the dose for ^{90}Y-ibritumomab tiuxetan was fixed at 0.3 mCi/kg.

Study endpoints and definition of study variables

The main objective was to evaluate the feasibility, safety and efficacy of the whole treatment. Clinical efficacy was evaluated in terms of response and survival. The toxicities were evaluated according to the National Cancer Institute's Common Toxicity Criteria (CTCAE v3.0).

Response criteria were assessed according to The International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma.[24] Patients without response assessment were considered non-responders.

Failure-free survival was defined as the time from the date of study entry until date of recurrence, progression, death from any cause or any toxic event that prohibited treatment. Responding patients who did not complete the whole treatment were censored at the moment this deviation occurred. Progression-free survival was defined as the time from inclusion into the trial until progression, recurrence or death as a result of lymphoma. Overall survival was defined as the interval between the date of study entry until death from any cause.

Variables were calculated in the intent-to-treat population, defined as patients who had received at least one cycle of treatment. For the analysis of survival and serious adverse events, all patients were followed until the closure of the study regardless of treatment discontinuation.

Statistical analysis

The statistical methods are described in the *Online Supplementary Material*.[25,26]

Results

Patients' characteristics

Between February 2006 and July 2008, 38 patients with untreated MCL from 12 institutions were registered for this study. Eight patients were not enrolled in the study because of: positive serology for hepatitis B virus (2 patients), central nervous system involvement (1 patient), old age (1 patient), localized disease (1 patient), patient's refusal (1 patient), protocol deviation (1 patient) and urgency for treatment (1 patient). Therefore, 30 patients were evaluable for results.

The patients' characteristics are described in Table 1. The median age of the group was 59 years (range, 41-70 years). Blastic MCL variant was diagnosed in 21% of the cases. Most patients had advanced disease (97%), with documented bone marrow involvement (93%) and 40% were in the intermediate/high risk group of the Mantle International Prognostic Index (MIPI) classifications.[27] The results of cytogenetic studies on bone marrow/peripheral blood samples to detect t(11;14)(q13;q32) and other cytogenetic abnormalities (del 13q14, +12, del 17p, del 11q22.3) are also shown in Table 1.

Treatment outcome

Response to induction therapy

Twenty-eight (93.3%) out of the 30 patients were evaluable for response after the 4th cycle and 24 (80%) after the 6th. After the 4th cycle, 19 patients achieved complete remission or unconfirmed complete remission (68%, 95% CI: 67%-69%) and nine had partial responses (32%, 95% CI: 31%-33%). Response at the 4th cycle could not be

assessed in two patients because of grade 4 infection in one and an unexpected suicide in another patient without a previously known psychiatric disorder. Four additional patients discontinued treatment between the 4th and 6th cycles due to grade 4 and grade 5 bacterial infections (1 patient each), pulmonary aspergillosis (1 patient) and grade 4 neurological toxicity (1 patient).

At the end of induction treatment 23 patients (77%; 95% CI: 60%-93%) achieved complete remission/unconfirmed complete remission and one patient had progressive disease (3%).

Consolidation therapy

The dose of ^{90}Y-ibritumomab tiuxetan was maintained at 0.3 mCi/kg. Five out of the first six patients treated had lower peripheral blood counts than those required for full dose at 12 weeks after completion of induction therapy.

Eighteen patients (60%), all in complete remission/unconfirmed complete remission, received consolidation treatment. Treatment failed in six patients, because of grade 4 infection (1 patient), patient's decision (1 patient), delayed recovery of peripheral blood counts (2 patients), protocol deviation (1 patient) and progressive disease (1 patient). The study throughput is shown in Figure 1.

Table 1. Characteristics of the patients and cytogenetic findings at diagnosis

Age, years (range)	59 [41-71]
Male gender	23 (77%)
ECOG 0- 1	28 (93%)
Blastic histology	6 (21%)
Ann Arbor IV	29 (97%)
Bone marrow involvement	28 (93%)
Spleen involvement	17 (57%)
Gastrointestinal infiltration	19 (63%)
Lactate dehydrogenase (> upper limit of normal)	9 (30%)
β2 microglobulin (> upper limit of normal)	18 (62%)
MIPI	
Low risk	18 (60%)
Intermediate risk	10 (33%)
High risk	2 (7%)
Cytogenetic findings	22 patients
Bcl 1 alone	68% (15)
Bcl 1 + p53 mutated	9 %(2)
Bcl 1 + p53 mutated + del 13q	4.5 % (1)
Bcl 1 + p53 mutated + del ATM	4.5 % (1)
p53 mutated + del ATM	4.5 % (1)
Negative	9 % (2)

Table 2. Hematologic toxicity during the induction treatment.

Hematological toxicity	All grades		Grades 3-4	
	R- hyperCVAD (88) n (%)	R-MA (82) n (%)	R- hyperCVAD (88) n (%)	R-MA (82) n (%)
Anemia	73 (83%)	81 (99%)	23 (26%)	41 (50%)
Leukopenia	57 (65%)	82 (100%)	43 (49%)	80 (98%)
Neutropenia	54 (61%)	81 (99%)	42 (48%)	74 (90%)
Thrombocytopenia	44 (50%)	81 (99%)	30 (34%)	79 (96%)

Failure-free survival, progression-free survival and overall survival

The median follow-up for survivors was 3.9 years (range, 0.45 – 5.4 years). Two- and 4-year failure-free survival rates were 57% (95% CI: 37.4%-76.6%) and 40% (95% CI: 20.4%-59.6%) respectively. The progression-free survival rates at 2 and at 4 years were 72% (95% CI: 54.36% – 89.64%) and 52% (95% CI: 32.4% – 71.6%), respectively. The median progression-free survival was 4.9 years (range, 2.7 to 7.1 years). The overall survival rates at 2 and 4 years were 89% (95% CI: 79.2% – 98.8%) and 81% (95% CI: 67.28 %– 94.72%) (Figures 2A-2C).

In the group of 18 patients who received the whole treatment, failure-free survival rates at 2 and at 4 years were 78% (95% CI: 58.4% – 97.6%) and 55% (95% CI: 31.48 – 78.52), respectively. Overall survival rates at 2 and at 4 years were 93.8% (95% CI: 82% – 100%) and 87% (95% CI: 70% – 100%), respectively.

High-dose cytarabine (HDAC) has proven to have an outstanding effect on outcome; we, therefore, studied the survival variables according to a cut-off age of 60 years, when significant Ara-C dose adjustments are made. The 4-year failure-free survival rate for older patients was 30% (95% CI: 4.5% – 55.5%) *versus* 50% (95% CI: 22.5% – 77.4%) for the younger ones (P=0.57). The 4-year overall survival rate was not affected by age. In fact, the overall survival rate of older patients was 92% (95% CI: 78% – 100%) *versus* 73% (95% CI: 51.4% – 94.5%) for those younger than 60 years. Other characteristics were similarly distributed between the groups.

The failure-free survival of patients in low or intermediate-high MIPI risk groups was significantly different (P=0.003). The median failure-free survival for low risk patients was 4.8 years (95% CI: 2.7- 6.9) *versus* 1.4 years

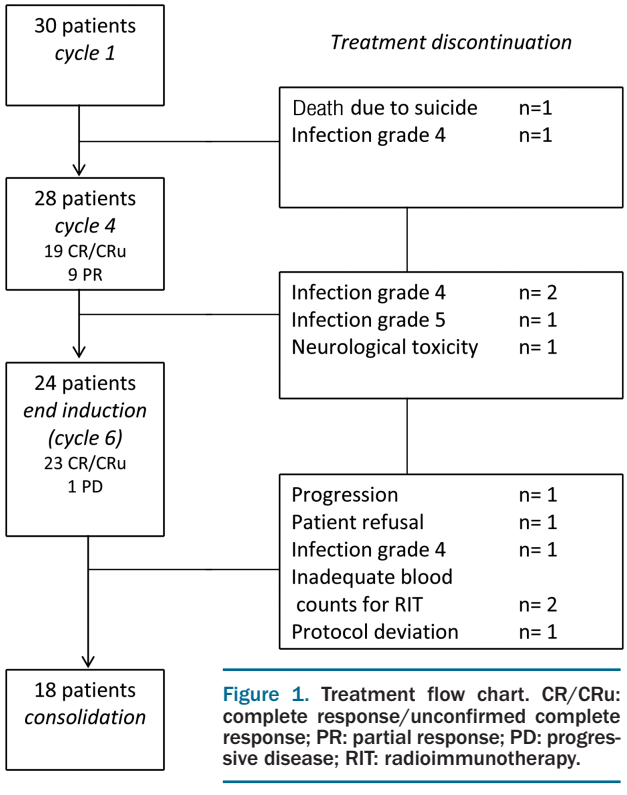

Figure 1. Treatment flow chart. CR/CRu: complete response/unconfirmed complete response; PR: partial response; PD: progressive disease; RIT: radioimmunotherapy.

(95% CI: 0.15- 3.2) for the intermediate-high risk group. Overall survival was also significantly different (P= 0.003), being 93% (95% CI: 81.24% – 100%) for the low-risk group *versus* 31% (95% CI: 0% – 76%) for the intermediate-high risk group (Figures 3A, 3B). No other patients' characteristics had an impact on survival.

Six (20%) out of 30 patients died during the study. Causes of death were unexpected suicide (1 patient), infection (1 patient due to septic shock), relapsed disease (1 patient) and secondary malignancies in three patients (myelodysplastic syndrome, bladder carcinoma and rectal carcinoma). Two of these patients died without evidence of lymphoma.

Toxicity

Six out of 30 patients (20%) did not complete their intended number of cycles during induction treatment because of toxicity (5 patients) and suicide (1 patient).

One hundred and seventy cycles were administered during this phase. Adverse and serious adverse events are reported in Tables 2 and 3. The principal toxicity was hematologic, which was significantly greater during R–MA cycles; indeed, more than 90% of the cycles were associated with grade 3-4 neutropenia and thrombocytopenia, and 50% with grade 3- 4 anemia (P<0.0001). Neutropenic fever and infection accounted for 56 out of 69 serious adverse events (81%) reported during this phase and were again significantly higher in R-MA cycles (49% *versus* 18%; P< 0.05). There was one toxic death due to

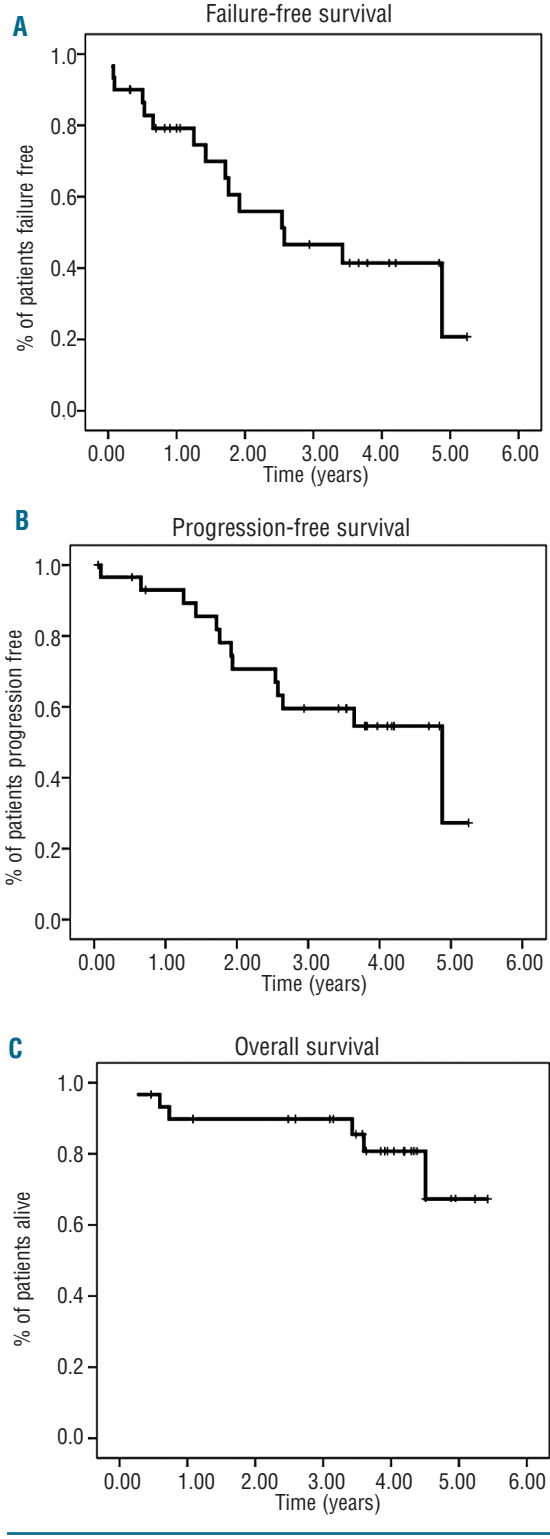

Figure 2. (A) Failure-free survival, (B) progression-free survival and (C) overall survival of the 30 patients by intent-to-treat analysis.

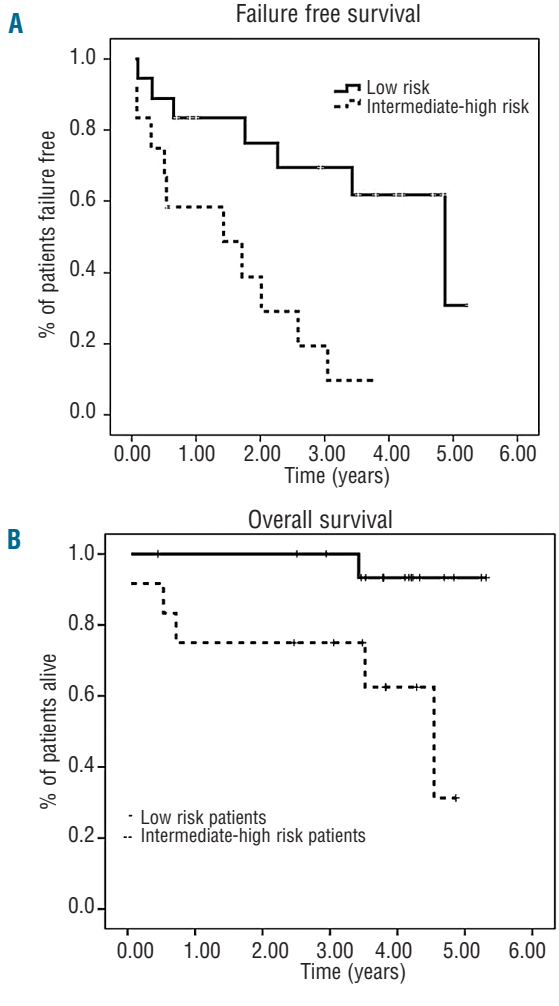

Figure 3. (A) Failure-free survival and (B) overall survival by MIPI: low risk *versus* intermediate-high risks.

septic shock during this period.

Hematologic toxicity was the main adverse event during consolidation. Grade 3-4 neutropenia was seen in 72% of the patients and lasted a median of 5 weeks (range, 2-24 weeks). Grade 3-4 thrombocytopenia was observed in 83% of the patients with a median duration of 12.5 weeks (range, 4-56 weeks). No patient received the back-up peripheral blood stem cells collected.

Secondary malignancies (7 events) and infection with normal neutrophils (5 events) accounted for the total of 16 serious adverse events communicated after consolidation treatment. Six of these neoplasms were reported after the first-line treatment and one occurred after the patient's subsequent exposure to other treatments for relapsed disease. A detailed description of these malignancies is given in Table 4. The crude incidences of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) and solid tumors were 10% each. The 2 and 4- year cumulative incidences were 4% and 17%, respectively. Cytogenetic analysis in two cases with MDS revealed complex karyotypes, with abnormalities of chromosomes 5 and 7. For solid tumors, the 2-year cumulative incidence was 13%. No further solid tumor was diagnosed later on, with a median follow up for the survivors of 3.9 years.

Discussion

The use of intensive treatment approaches in young, fit patients with MCL has significantly improved their outcome. The best strategy remains uncertain so far, although the more extended practice includes performance of ASCT as consolidation of first response. Our trial considered the up-front intensive regimen hyperCVAD alternating with methotrexate-AraC, both in association with rituximab, developed by the MD Anderson Cancer Center (MDACC), given the reported good response rates and their prolonged duration. Of note, updated MDACC

Table 3. Non-hematologic toxicity during the induction treatment.

Non hematologic toxicity	All grades 170 cycles n. (%)	Grades 3-4		Serious adverse events	
		R- hyperCVAD (88) n. (%)	R-MA (82) n. (%)	R- hyperCVAD (88) n. (%)	R-MA (82) n. (%)
Neutropenic fever	77 (45%)	7 (8%)	15 (18%)	6 (7%)	14 (17%)
Infection	78 (46%)	26 (29%)	24 (29%)	10 (11%)	26 (32%)
Bleeding	26 (15%)		2 (2%)		2 (2%)
Nausea/vomiting	32 (19%)	2 (2%)	2 (2%)		
Diarrhea	18 (11%)	1 (1%)	2 (2%)	1 (1%)	
Mucositis	23 (14%)	1 (1%)	1 (1%)	1 (1%)	
Liver (transaminitis)	18 (11%)	1 (1%)			
Renal disorder	11 (6%)				
Cardiac	9 (5%)	1 (1%)	1 (1%)		1 (1%)
Pulmonary/pleural	8 (5%)	1 (1%)	2 (2%)		1 (1%)
Deep vein thrombosis	2 (1%)		2 (2%)		2 (2%)
CNS-cerebellum	1 (0.5%)		1 (1%)		1 (1%)
Stroke	1 (0.5%)	1 (1%)		1 (1%)	
Personality disorder	1 (0.5%)	1 (1%)		1 (1%)	
Allergic reaction	2 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Pain	13 (8%)	3 (3%)	3 (3%)		

Table 4. Description of the second malignancies diagnosed during the study.

UPN	Age	Molecular findings at diagnosis	Years from diagnosis	Years from the end of treatment	Previous lines	Secondary malignancy	Genetics of second malignancy
102	67	BCL1	1.6	0.81	1	Bladder carcinoma	
301	53	BCL1	1.99	1.25	1	Rectal adenocarcinoma	
402	47	BCL1	1.08	0.40	1	MDS/AML-6	t(16;16)
905	65	BCL1	2.06	1.19	1	Endometrial cancer	
1101	63	NA	3.67	3.12	1	MDS	Complex karyotype*
1302	69	IgH	2.97	2.17	1	MDS	Complex karyotype**
1303	59	BCL1	3.56	2.79	3 (including ASCT)	MDS	No metaphases due to marrow fibrosis

UPN: unique patient number; BCL-1= FISH for Bcl-1/IgH *rearrangement; NA: not available; MDS: myelodysplastic syndrome; AML: acute myeloid leukemia; ASCT: autologous stem cell transplantation; (*): G-banding karyotype not available. FISH analysis: 46% del 5q31, 20% trisomy 8, 36% del 20q12, 40% del 5q33-34 CSF1R, 22% del 7 q31 ; (**): G-banding karyotype: 46, XY,r(7) [8]; 47, XY,r(7),+r(7)[8]; 48, XY, r(7),+r(7),+del(7q)[4].*

results showed a progression-free survival of 43% and an overall survival of 56%, quite similar to those reported by the Nordic Group using consolidation with ASCT, with progression-free and overall survival rates of 43% and 58%, respectively.

In this study, treatment with R-hyperCVAD alternating with R-MA (3 cycles of each) followed by consolidation with ^{90}Y-ibritumomab-tiuxetan produced poorer results than expected. Toxicity was unacceptably high and the complete remission rate, median failure-free survival and progression-free survival were 77%, 2.6 years and 4.9 years, respectively, without a plateau.

In our hands, the feasibility of R-hyperCVAD alternating with R-MA was less than previously reported.[5,7] At the MDACC, 70% of the patients received eight cycles. In a multicenter setting, the *Gruppo Italiano Studio Linfomi* administered six cycles to 75% of their patients without mandatory growth factor support. In our study, safety withdrawal events accounted for 83% of the discontinuations throughout the induction phase. Hematologic toxicity was high, particularly in the R-MA cycles, during which grade 3- 4 neutropenia and thrombocytopenia were practically universal. Accordingly, febrile neutropenia and infections were observed in 17% and 32% respectively, which are significantly higher rates than those for the toxic events detected in the R-hyperCVAD cycles (7% and 11%, respectively). The toxicity detected in the R-MA cycles was higher than previously reported for the same schedule of treatment[5,7] and significantly higher than that reported for other intensive strategies.[6,28] Probably, the concomitant administration of methothrexate with HDAC in the R-MA cycles increases hematologic toxicity and impairs renal clearance. In spite of the hematologic toxicity, the mortality rate due to infection was 3.3%, which is similar or even inferior to that reported previously for this treatment.

HDAC seems crucial for improving remission rates and failure-free survival in MCL, as was recently reported by the Mantle Cell Lymphoma Network. In their trial,[28] the introduction of HDAC within the R-CHOP treatment significantly improved patients' outcome compared with that of patients treated only with R-CHOP and followed by consolidation with ASCT. With this information, it would be desirable to clarify the best dose and schedule of this agent. In this study, the total dose of HDAC planned to be administered was 36 g/m^2, similar to that used by the Nordic Group in the MCL^2 trial[6] and higher than the doses of 14 g/m^2 to 16 g/ m^2 used in other treatment regimens[4,8,28] for which compliance rates of up to 89% were reported with a similar median failure-free survival of around 4.5 years.

Even using intensive approaches to treat MCL, a continuous pattern of relapse has been documented.[11,12] Currently, consolidation and/or maintenance approaches are a matter of active clinical research in order to improve the duration of the response achieved. In this study, consolidation with a single dose of ^{90}Y-ibritumomab tiuxetan was planned and administered to 60% of the patients. This finding is concordant with the results recently communicated by Beaven *et al.*, who used consolidation with ^{131}I-tositumomab after an intensive induction regimen[22] in patients with MCL and diffuse large B-cell lymphoma, and significantly lower than that described when radioimmunotherapy was administered after a non-intensive regimen such as R-CHOP.[19] To our knowledge, there are no other published reports on radioimmunotherapy used as consolidation after first-line treatment in patients with MCL.

In this pilot study, consolidation with radioimmunotherapy after intensive treatment did not increase the complete remission rate, failure-free survival or progression-free survival when compared with those in other studies. The 4-year failure-free survival of 55% in our study, which is inferior to that observed by other authors,[4,5,7,8] might have been a consequence of the lesser feasibility of the treatment and the higher related mortality. The high incidence of secondary malignancies observed in patients who received consolidation with radioimmunotherapy is a major concern: in our series three patients (10%) developed MDS/AML and three (10%) developed solid tumors at a median time of 1.22 years (range, 0.4-3.12 years) after radioimmunotherapy.

With regards to the solid tumors, the observed crude and cumulative incidences were 10% and 12.7%, respectively. An unusually increased incidence of second malignancies was suggested for 156 patients with MCL treated with R-hyperCVAD/R-MA, 37% of whom were also transplanted and 32% treated with total body irradiation.[29] With a median follow up of 2 years, the crude incidence of invasive neoplasms was 4.5% soon after the treatment. However, this observation was not confirmed by the same authors in more recent reports, neither has it been mentioned by others using the same induction treatment.[5,7] Geisler *et al.* report a crude incidence of 3% with a median follow up of more than 6 years although they did not consider the malignancies to be treatment-related. With ^{131}I-tositumomab, Bennet *et al.* reported a crude incidence of less than 5% of solid tumors in MCL patients with relapsed and refractory disease previously treated with a median of three chemotherapy lines.

More information about the risk of MDS/AML is available. The incidence in our study was higher than that found by other authors using intensive approaches with or without ASCT but without radioimmunotherapy, ranging from 0% to 5%. Romaguera *et al.* reported a crude incidence of 4% with a median follow-up of 3.3 years,[5] data that remained practically unchanged (5%) in the updated results, with a follow-up of 8 years.[11] The Nordic Group reported an incidence of 0.6% in the updated results of the MCL2 trial, with a median follow up of 6.5 years.[6] Interestingly, the same group in their MCL3 trial, which added ^{90}Y-ibritumomab tiuxetan to the BEAM (BCNU, etoposide, Ara-C, melphalan) conditioning regimen, did not report an increased incidence of MDS/AML with a median of follow-up of 3.2 years.[21] Other authors, using intensive regimens and including ASCT as consolidation, did not mention any secondary malignancies in patients followed for a similar period of time.[4,8]

The reported crude incidence of MDS/AML in patients treated with radioimmunotherapy after R-CHOP or fludarabine-mitoxantrone-rituximab in first-line treatment for MCL and follicular lymphoma was 0%-0.5%.[19,30,31] More accurate data on this complication come from compassionate-use studies in patients exposed to a median of two to three lines of treatment.[32,33] The 2- and 5-year cumulative incidences ranged from 1.7% to 6.3%, respectively. Our figures were 4% and 15%, higher than those reported by Guidetti *et al.* in previously treated patients who were autografted after conditioning with myeloablative doses of radioimmunotherapy.[34]

The cytogenetic findings in the cases of MDS diag-

nosed were those commonly associated with prior exposure to cytotoxic drugs and radiation therapy. Complex karyotypes involving chromosomes 5 and 7 are genetic events associated with these therapies.[35-37] None of the patients with MDS/AML had additional genetic abnormalities besides the Bcl-1 translocation, such as p53, ATM or 13q deletions, detected in 23% of our patients at diagnosis.

To our knowledge, an unacceptable increase in the incidence of either secondary MDS/AML or solid tumors has not been described despite the widespread use of hyperCVAD/MA, which requires the use of stem cell factors in order to decrease toxicity and maintain an adequate dose intensity. The toxicity found in our study could be due to the high cumulative dose of cyclophosphamide followed by systemic radiation, as is radioimmunotherapy, which may entail a second oncogenic event on previously sensitized cells.

In summary, R-hyperCVAD/R-MA followed by consolidation with ^{90}Y-ibritumomab tiuxetan is effective although less feasible than expected. The substantial toxicity observed advises against the use of this strategy. The number of new drugs available for MCL is increasing and it is, therefore, crucial to focus on minimizing adverse events.

Acknowledgments

The authors would like to thank Dr Victor Abraira for his statistical advice.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Swerdlow SH, Campo E, Harris N, Jaffe E, Pileri S, Stein H, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Fourth Edition. Lyon, France: IARC Press; 2008.
2. Howard OM, Gribben JG, Neuberg DS, Grossbard M, Poor C, Janicek MJ, et al. Rituximab and CHOP induction therapy for newly diagnosed mantle-cell lymphoma: molecular complete responses are not predictive of progression-free survival. J Clin Oncol. 2002;20(5):1288-94.
3. Lenz G, Dreyling M, Hoster E, Wörmann B, Dührsen U, Metzner B, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol. 2005;23(9):1984-92.
4. Damon LE, Johnson JL, Niedzwiecki D, Cheson BD, Hurd DD, Bartlett NL, et al. Immunochemotherapy and autologous stem-cell transplantation for untreated patients with mantle-cell lymphoma: CALGB 59909. J Clin Oncol. 2009;27(36): 6101-08.
5. Romaguera JE, Fayad L, Rodriguez MA, Broglio KR, Hagemeister FB, Pro B, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol. 2005;23(28):7013-23.
6. Geisler CH, Kolstad A, Laurell A, Andersen NS, Pedersen LB, Jerkeman M, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood. 2008;112(7): 2687-93.
7. Merli F, Luminari S, Ilariucci F, Petrini M, Visco C, Ambrosetti A, et al. Rituximab plus HyperCVAD alternating with high dose cytarabine and methotrexate for the initial treatment of patients with mantle cell lymphoma, a multicentre trial from Gruppo Italiano Studio Linfomi. Br J Haematol. 2012;156(3):346-53.
8. Lefrère F, Delmer A, Suzan F, Levy V, Belanger C, Djabarri M, et al. 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. Leukemia. 2002;16(4): 587-93.
9. Gianni AM, Magni M, Martelli M, Di Nicola M, Carlo-Stella C, Pilotti S, et al. Long-term remission in mantle cell lymphoma following high-dose sequential chemotherapy and in vivo rituximab-purged stem cell autografting (R-HDS regimen). Blood. 2003;102(2):749-55.
10. Dreyling M, Lenz G, Hoster E, Van Hoof A, Gisselbrecht C, Schmits R, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. Blood. 2005;105 (7):2677-84.
11. Romaguera JE, Fayad LE, Feng L, Hartig K, Weaver P, Rodriguez MA, et al. Ten-year follow-up after intense chemoimmunotherapy with rituximab-hyperCVAD alternating with rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. Br J Haematol. 2010;150(2):200-8.
12. Geisler CH, Kolstad A, Laurell A, Jerkeman M, Räty R, Andersen NS, et al. Nordic MCL2 trial update: six-year follow-up after intensive immunochemotherapy for untreated mantle cell lymphoma followed by BEAM or BEAC + autologous stem-cell support: still very long survival but late relapses do occur. Br J Haematol. 2012; 158(3):355-62.
13. Kluin-Nelemans HC, Hoster E, Hermine O, Walewski J, Trneny M, Geisler CH, et al. Treatment of older patients with mantle-cell lymphoma. N Engl J Med. 2012;367 (6):520-31.
14. Leahy MF, Turner JH. Radioimmunotherapy of relapsed indolent non-Hodgkin lymphoma with 131I-rituximab in routine clinical practice: 10-year single-institution experience of 142 consecutive patients. Blood. 2011;117(1):45-52.
15. Kaminski MS, Tuck M, Estes J, Kolstad A, Ross CW, Zasadny K, et al. 131I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med. 2005; 352(5):441-9.
16. Bishton MJ, Leahy MF, Hicks RJ, Turner JH, McQuillan AD, Seymour JF. Repeat treatment with iodine-131-rituximab is safe and effective in patients with relapsed indolent B-cell non-Hodgkin´s lymphoma who had previously responded to iodine-131-rituximab. Ann Oncol. 2008;19(9): 1629-33.
17. Morschhauser F, Radford J, Van Hoof A, Vitolo U, Soubeyran P, Tilly H, et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. J Clin Oncol. 2008;26(32):5156-64.
18. Wang M, Oki Y, Pro B, Romaguera JE, Rodriguez MA, Samaniego F, et al. Phase II study of yttrium-90-ibritumomab tiuxetan in patients with relapsed or refractory mantle cell lymphoma. J Clin Oncol. 2009;27(31):5213-8.
19. Smith MR, Li H, Gordon L, Gascoyne RD, Paietta E, Forero-Torres A, Kahl BS, et al. Phase II study of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone immunochemotherapy followed by yttrium-90-ibritumomab tiuxetan in untreated mantle-cell lymphoma: Eastern Cooperative Oncology Group Study E1499. J Clin Oncol. 2012;30(25): 3119-26.
20. Jurczak W, Giza A, Zimowska-Curylo D, Zimowska-Curylo D, Sobocinski M, Stella-Holowiecka B, et al. 90Y-Zevalin® (90Y-ibritumomab tiuxetan) radioimmunotherapy (RIT) consolidation in mantle cell lymphoma (MCL) patients, not ilegible for intensive therapy protocols. American Society of Hematology Annual Meeting. 2007. [Abstract 110] Dec; Atlanta: 4497.
21. Kolstad A, Laurell A, Jerkeman M, Gronbaek K, Elonen E, Räty R, et al. Nordic MCL3 study: zevalin combined with high-dose chemotherapy followed by autologous stem cell support as late intensification for mantle cell lymphoma (MCL) patients < 66 years not in CR after induction chemoimmunotherapy: no benefit of zevalin. 2012. [Abstract 747] Dec; Atlanta: 747.
22. Beaven A, Rizzieri D, Zachary Powell ZL,

Li Z, Alton P, Warzecho J, et al. High complete response rates with dose dense/dose intense chemotherapy plus radioimmunotherapy in high risk diffuse large B cell and mantle cell lymphoma. American Society of Hematology Annual Meeting. 2011. [Abstract] Dec 118; San Diego: 2681a
23. Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, et al. The World Health Organization classification of neoplastic diseases of the haematopoietic and lymphoid tissues: Report of the Clinical Advisory Committee Meeting, Arlie House, Virginia, November 1997. Histopathology. 2000;36(1):69-86.
24. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report on an international workshop to standardize response criteria for non-Hodgkin's lymphomas: NCI Sponsored International Working Group. J Clin Oncol. 1999;17(4): 1244.
25. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Statist Assoc. 1958;53:457-81.
26. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing rosks: new representation of old estimatiors. Stat Med. 1999;18(6):695-706.
27. Hoster E, Dreyling M, Klapper W, Gisselbrecht C, van Hoof A, Kluin-Nelemans HC, et al. A new prognostic index (MIPI) for patients with advanced mantle cell lymphoma. Blood. 2008; 111(2):558-65.
28. Hermine O, Hoster E, Walewski J, Ribrag V, Brousse N, Thieblemont C, et al. Alternating courses of 3x CHOP and 3x DHAP plus rituximab followed by a high dose ARA-C containing myeloablative regimen and autologous stem cell transplantation (ASCT) Increases overall survival when compared to 6 courses of CHOP plus rituximab followed by myeloablative radiochemotherapy and ASCT in mantle cell lymphoma: final analysis of the MCL Younger Trial of the European Mantle Cell Lymphoma Network (MCL net). American Society of Hematology Annual Meeting. 2012. [Abstract] Dec 120; Atlanta: 151.
29. Barista I, Cabanillas F, Romaguera JE, Khouri IF, Yang Y, Smith TL, et al. Is there an increased rate of additional malignancies in patients with mantle cell lymphoma?. Ann Oncol. 2002;13(2):318-22.
30. Morschhauser F, Radford J, Van Hoof A, Vitolo U, Soubeyran P, Tilly H, et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. J Clin Oncol. 2008; 26(32):5156-64.
31. Zinzani PL, Derenzini E, Pellegrini C, Rigacci L, Fabbri A, Gandolfi L, et al. Long-term efficacy and toxicity results of the FLUMIZ trial (fludarabine and mitoxantrone followed by yttrium-90 ibritumomab tiuxetan in untreated follicular lymphoma). Ann Oncol. 2012;23(3):805-7.
32. Czuczman MS, Emmanouilides C, Darif, Witzig TE, Gordon LI, Revell S M, et al. Treatment-related myelodysplastic syndrome and acute myelogenous leukemia in patients treated with ibritumomab tiuxetan radioimmunotherapy. J Clin Oncol. 2007; 25(27):4285-92.
33. Bennett JM, Kaminski MS, Leonard JP, Vose JM, Zelenetz AD, Knox SJ, et al. Assessment of treatment-related myelodysplastic syndromes and acute myeloid leukemia in patients with non-Hodgkin lymphoma treated with tositumomab and iodine I131 tositumomab. Blood. 2005;105(12):4576-82.
34. Guidetti A, Carlo-Stella C, Ruella M, Miceli R, Devizzi L, Locatelli SL, et al. Myeloablative doses of yttrium-90-ibritumomab tiuxetan and the risk of secondary myelodysplasia/acute myelogenous leukemia. Cancer. 2011;117(22):5074-84.
35. Armitage JO, Carbone PP, Connors JM, Levine A, Bennett JM, Kroll S. Treatment-related myelodysplasia and acute leukemia in non-Hodgkin's lymphoma patients. J Clin Oncol. 2003;21(5):897-906.
36. Pedersen-Bjergaard J, Specht L, Larsen SO, Ersbøll J, Struck J, Hansen MM, et al. Risk of therapy related leukaemia and preleukaemia after Hodgkin's disease: Relation to age, cumulative dose of alkylating agents, and time from chemotherapy. Lancet. 1987; 2(8550):83-8.
37. Pedersen-Bjergaard J, Andersen MK, Andersen MT, Christiansen DH. Genetics of therapy-related myelodysplasia and acute myeloid leukemia. Leukemia. 2008; 22(2):240-8.