Salvage treatment with lenalidomide and dexamethasone in relapsed/refractory mantle cell lymphoma: clinical results and effects on microenvironment and neo-angiogenic biomarkers

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ABSTRACT

Background
Preclinical studies have highlighted the activity of lenalidomide in mantle cell lymphoma and its anti-proliferative synergy with dexamethasone.

Design and Methods
In this prospective, multicenter, phase II study, patients with relapsed/refractory mantle cell lymphoma who were not eligible for, or had relapsed after, intensive treatments received lenalidomide 25 mg/day (days 1-21 of each 28-day cycle) and dexamethasone (40 mg/day on days 1, 8, 15, and 22) for up to 12 months.

Results
The primary end-points, overall and complete response rates, were achieved by 17 of 33 (52%; 95% confidence interval [CI], 35-68%) and 8 of 33 patients (24%; 95% CI, 13-41%), respectively, by the end of treatment. Fifteen patients (45%) discontinued treatment prematurely, 13 due to lack of response. The median progression-free and overall survival were 12 months (95% CI, 5-19 months) and 20 months (95% CI, 12 months to not estimable), respectively. Treatment resulted in a significant increase in microvessel density (P=0.033) and non-significant increases in macrophage and natural killer cell counts, while serum levels of neoangiogenic factors did not change significantly. Grade 3/4 adverse events were neutropenia (53%), leukopenia (25%), thrombocytopenia (22%), infections (12%), and febrile neutropenia (12%).

Conclusions
These results confirm a favorable safety and activity profile of lenalidomide in relapsed/refractory mantle cell lymphoma. The contribution of dexamethasone in achieving these results is unclear because of its possible detrimental effect on the immune activation generated by lenalidomide and a higher risk of developing infectious complications. *(clinicaltrials.gov identifier: NCT00786851).*

Key words: lenalidomide, dexamethasone, mantle cell lymphoma, relapsed/refractory disease, salvage treatment.

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Introduction

Mantle cell lymphoma (MCL) is a relatively rare non-Hodgkin's lymphoma, accounting for approximately 7% of cases.[1] It occurs mostly in middle-aged or older individuals, at a median age of around 60 years and with a male predominance.[2] Although the expected overall survival for patients with MCL has doubled over the past three decades, the prognosis remains poor, with a median overall survival of only 4 to 5 years.[3] Despite the recent introduction of new intensive therapeutic strategies [high-dose sequential chemotherapy with rituximab (HDS-R); cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytosine arabinoside and rituximab (HyperCVAD/MA-R); and autologous or allogeneic stem-cell transplantation], a significant number of patients are not cured. Furthermore, older patients are often not eligible for these intensive treatments.

Lenalidomide is an immunomodulatory agent with anti-tumor activity in several lymphoid neoplasms. This agent has pleiotropic anti-tumoral activity and, in lymphoma, acts principally by decreasing proliferation of tumor cells by means of a direct effect on specific pathways, such as p21 and SPARC.[4,5] Moreover, in recent studies, lenalidomide demonstrated strong immune-modulating activity by enhancing the activity of natural killer (NK) cells and promoting the formation of immune synapses between MCL cells and NK cells.[6]

Previous studies have demonstrated that lenalidomide has clinical activity across a broad range of lymphoma histologies in the relapsed/refractory setting,[7-9] particularly in MCL, in which overall response rates of 42% to 53% and complete response rates of 20% were observed in two small subgroups of patients enrolled in studies investigating aggressive non-Hodgkin's lymphomas.[9,10]

Dexamethasone is also an active agent in non-Hodgkin's lymphoma, and is included in several anti-MCL regimens. *In vitro* studies in MCL cell lines have indicated a potential synergy between lenalidomide and dexamethasone by decreasing tumor proliferation, inducing G0/G1 cell-cycle arrest, and increasing apoptosis.[11] Furthermore, clinical experience in multiple myeloma supports the combination of lenalidomide and dexamethasone.[12,13] However, it remains unclear whether the association of lenalidomide and dexamethasone has a favorable safety and activity profile in patients with refractory/relapsed MCL.

Here we report the results of a phase II clinical trial aimed to evaluate the activity and safety of lenalidomide and dexamethasone as salvage therapy in patients with MCL.

Design and Methods

This prospective, multicenter, phase II trial was designed to evaluate the safety and activity of the combination of lenalidomide and dexamethasone in patients with relapsed/refractory MCL. Accrual started in July 2008 and was concluded in July 2009. Ten Italian centers, which are members of the Italian Lymphoma Foundation, participated in this trial. The study protocol was approved by the local Ethical Committee of Human Experimentation and each patient gave written informed consent.

Patients

We enrolled patients aged over 18 years with a diagnosis of cyclin D1-positive MCL, as confirmed by a central pathology expert, with measurable disease; the patients had relapsed or were refractory to at least one previous line of chemotherapy, and were not eligible for, or had relapsed after, more intensive treatments. Moreover, in order to be included, patients had to: have an Eastern Cooperative Oncology Group performance status of 2 or less, adequate blood counts, hepatic and renal function, absence of any relevant diseases that could interfere with the study treatment, no serological evidence of human immunodeficiency virus or hepatitis C virus infections (patients positive for hepatitis B core or surface antibodies and negative for hepatitis B surface antigen were eligible if treated with lamivudine prophylaxis), absence of peripheral neuropathy or meningeal or brain involvement by the lymphoma, no deep-vein thrombosis in the preceding year; agree to practice adequate birth control (no pregnant or lactating women); and have a life expectancy of more than 6 months.

Treatment

The study was divided into three stages: an induction phase (cycles 1-3), a consolidation phase (cycles 4-12), and a follow-up phase. During each 28-day cycle, lenalidomide was given orally in a single daily administration at a dose of 25 mg on days 1-21, while dexamethasone was administered orally in a single dose of 40 mg on days 1, 8, 15, and 22. Patients who had achieved a partial response or stable disease at the end of the induction phase continued to the consolidation phase, consisting of treatment with lenalidomide and dexamethasone until disease progression, unacceptable toxicity, or complete response, for a maximum of 12 cycles (i.e., a maximum of 48 weeks). Patients with a complete response at the end of the induction phase, and those who had a complete response during the consolidation phase, received three additional cycles of lenalidomide and dexamethasone, with a maximum of 12 cycles in total. The treatment was mainly administered in an outpatient setting.

Lenalidomide dose modification

For patients who experienced grade 3 or higher non-hematologic toxicity, grade 3 or 4 neutropenia with fever (temperature ≥38.5°C), or grade 4 thrombocytopenia, treatment was suspended until the toxicity reduced to grade 2 or lower and any infection resolved. Incremental (5 mg) dose reduction was allowed for grade 3 or higher non-hematologic toxicity to a minimum dose of 5 mg daily.

For patients with bulky disease or a leukocyte count greater than 40×10^9/L, pretreatment with a single administration of vincristine 1 mg and prednisone 1 mg/kg/day for 5 days was permitted; non-responders to pretreatment and patients who did not undergo this treatment because of contraindications started the first cycle of lenalidomide and dexamethasone with a reduced dose of lenalidomide (50%) to prevent the risk of tumor lysis syndrome.

Dexamethasone dose modification

For patients who experienced grade 3 or higher dexamethasone-related toxicity, the dose was reduced to 20 mg on each dose day in subsequent cycles.

Concomitant treatments

Concomitant treatments that were allowed included antibacterial prophylaxis (levofloxacin or ciprofloxacin, if neutrophil count $<1.0\times10^9$/L), anti-pneumocystis prophylaxis (cotrimoxazole or pentamidine, throughout the study period); filgrastim or lenograstim in the case of neutropenia higher than grade 2; erythropoietin (in accordance with the American Society of Hematology/American Society of Clinical Oncology guidelines);

immunoglobulin in case of immunoglobulin G level less than 0.3 to 0.5 g/L and frequent infectious events. Deep-vein thrombosis prophylaxis consisted of subcutaneous enoxaparin 4000 U daily during the first 3 months of therapy for all patients. After the third month, patients continued deep-vein thrombosis prophylaxis with either enoxaparin 4000 U daily, warfarin 1 mg/day, or acetylsalicylic acid 100 mg/day.

Evaluation of patients and response criteria

Overall and complete response rates were the primary end-points, while overall survival, progression-free survival, response duration (the time from response to the first documentation of relapse or progression), and assessment of the safety profile were secondary end-points.

Patients were evaluated at the end of the induction phase, every three cycles during the consolidation phase, and at the end of treatment. Response was assessed according to revised response criteria for malignant lymphoma.[14] Responders were defined as patients reaching a complete or partial response. Patients not assessed for response (for any reason) were considered to have had no response.

Safety was monitored during the study, with follow-up for the incidence of severe life-threatening serious adverse events and common toxicities. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Biological studies

As an exploratory end-point, we evaluated the modifications of some biomarkers related to the microenvironment and neo-angiogenesis, in particular, microvessel density (MVD), and the number of macrophages and NK cells in the bone marrow of patients who had marrow infiltration. For this purpose, bone marrow specimens were analyzed by immunohistochemistry at baseline and at the end of therapy. In order to evaluate the impact of lenalidomide and dexamethasone on the modification of these biomarkers, the same analysis was performed in a control group of ten patients with MCL and bone marrow infiltration who were treated with the HyperCVAD/MA-R regimen. Blood vessels were detected in 6 μm 4% paraformaldehyde-fixed paraffin-embedded bone marrow sections, depleted of their endogenous peroxidase by 7.5% hydrogen peroxide, by staining endothelial cells sequentially with the anti-FVIII-RA mouse monoclonal antibody M616 (IgG1, Dako, Glostrup, Denmark), revealed by a polyclonal goat anti-mouse peroxidase-conjugate (Sigma Chemical Co., St Louis, MO, USA). The developing reaction (red staining) was obtained with 3-amino-9-ethylcarbazole (Sigma Chemical Co.) as the chromogen, counterstaining with hematoxylin and mounting in buffered glycerin. Angiogenesis was measured as FVIII-RA$^+$ microvessel areas on four to six 250× fields (area 12.5×10^{-2} mm^2 per field) covering almost the whole of two sections per antibody by using a square mesh inserted into the eyepiece of an Axioplan 2 photomicroscope (Zeiss). The MVD was estimated by using the direct planimetric method of 'point counting', according to which the microvessel area equaled the sum of points that hit microvessels. In addition, a computed image analysis was performed using dedicated software (KS-300, Zeiss).

Macrophages and NK cells were highlighted in two bone marrow sections adjacent to those stained for MVD. The sections were incubated with anti-CD68 mouse monoclonal antibody (Abcam, Cambridge, UK) or with NKG2A rabbit monoclonal antibody (Abcam) for macrophages and NK, respectively. After incubation with polyclonal goat anti-mouse or anti-rabbit peroxidase-conjugate polyclonal antibodies (Sigma Chemical Co.), the sections were developed and mounted as above. Positive cells were counted in six to eight 250× fields inside the reticulum and the mean ± standard deviation were calculated.

To evaluate the impact of therapy on circulating angiogenic factors, serum samples from peripheral blood were collected to assess vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF or FGF-2), platelet-derived growth factor (PDGF), and hepatocyte growth factor (HGF) levels using enzyme-linked immunosorbent assays (ELISA), before and after treatment with lenalidomide and dexamethasone. Aliquots of sample proteins (pg/mL) were measured using the Bradford method and tested in triplicate by applying a sandwich ELISA (ELISA-SearchLight® Human Angiogenesis Array 2 Kit, TEMA Ricerca S.r.l., Bologna, Italy), according to the manufacturer's instructions. The colorimetric reaction was blocked and sent for reading to the TEMA Ricerca laboratories, where plates were read with a Search Light CCD Image and Analysis System.

Statistical analysis

The sample size was determined according to a Simon's two-stage Minimax Design, using an alpha error of 0.05 and a beta error of 0.20. An early stopping rule was established to interrupt the study in case of futility (corresponding to a level of clinical activity <20% or <5 responders out of 18 patients enrolled in the first stage). At the end of treatment, the desirable level of activity for the lenalidomide and dexamethasone combination was defined as an overall response rate of 40% or more (corresponding to at least 11 responders out of 33 patients). All enrolled patients were analyzed for both treatment activity and safety. Results are presented as descriptive statistics, and corresponding 95% confidence intervals (CI) were estimated for the major end-points. Survival measures were assessed according to the Kaplan-Meier estimation method. The exploratory analyses of the modification of biomarkers were performed using paired-samples t-test or Wilcoxon's test for paired samples, as appropriate.

Results

Patients' characteristics

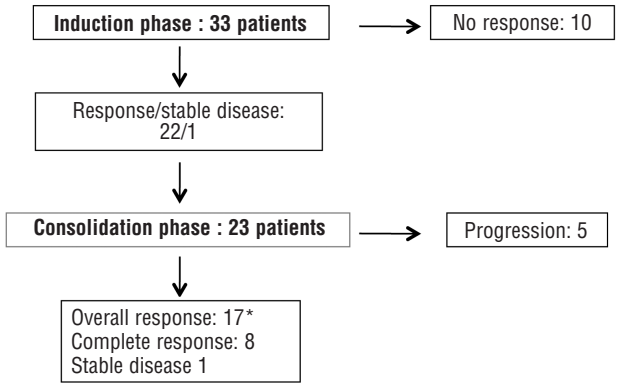
Between July 2008 and July 2009, 33 patients were enrolled in this study. Their baseline clinical and laboratory characteristics are summarized in Table 1. The median

Table 1. Baseline characteristics of the patients.

Characteristic	All patients (n=33)
Males, n (%)	21 (64)
Median age, years (range)	68 (51-80)
Histology, n (%)	
Classic	30 (91)
Blastoid	3 (9)
Median number of prior therapies, n (range)	3 (2-7)
Lines of prior therapy, n (%)	
2	10 (30)
3	10 (30)
> 3	13 (39)
Prior autologous stem cell transplant, n. (%)	12 (36)
Prior bortezomib, n (%)	8 (24)
Response to last therapy, n (%)	
Complete response	12 (36)
Partial response	9 (27)
Stable disease	2 (6)
No response/progressive disease	10 (30)

Table 2. Response to lenalidomide plus dexamethasone after the initial induction phase (months 1-3) and at the end of study treatment in 33 patients.

N. (%)	Overall response	Complete response	Partial response	Stable disease	No response/ progressive disease
Induction phase	22 (67)	5 (15)	17 (52)	1 (3)	10 (30)
At the end of study treatment	17 (52)	8 (24)	9 (27)	1 (3)	15 (45)



*1 patient in partial response discountinued therapy after 6 months due to poor compliance

Figure 1. Consolidated Standards of Reporting Trials flow diagram of progress through the study phases.

age of the patients was 68 years (range, 51-80 years), the median number of previous treatments was three (range, 2-7) and 11 patients had received more than four lines of therapy. All patients had previously received a rituximab-containing regimen and, in 21, rituximab was included in the last therapy before lenalidomide and dexamethasone. Thirty patients (91%) had a diagnosis of classical MCL, while three (9%) had the blastoid variant; two patients had a mild leukemic phase (lymphocytic count 10×10^9/L and 7.2×10^9/L, respectively). Notably, 12 patients (36%) had undergone an autologous stem-cell transplantation (ASCT), and eight (24%) had previously been treated with bortezomib.

Treatment activity

Overall, 230 cycles of therapy were administered. Fifteen patients (45%) discontinued therapy prematurely and so did not receive the full 12 cycles because of: no response or progressive disease (13 patients); poor compliance (1 patient with partial response after 6 months of therapy); and toxicity (1 patient with no response after the first month of therapy).

Response at the end of the induction phase

Overall and complete response rates were 67% (95% CI, 50-80%; 22 patients) and 15% (95% CI, 7-31%; 5 patients), respectively; 3% had stable disease (1 patient) and 30% had no response or progressive disease (10 patients) (Table 2). The overall response rate was 50% among patients previously treated with bortezomib (4/8 patients; all partial responses) and among those who had undergone prior ASCT (6/12 patients; two complete responses and four partial responses). None of the three patients with blastoid variant or the two patients with leukemic phase disease responded to therapy.

Response at the end of study treatment

At the final assessment of response upon therapy completion, the overall response rate was 52% (95% CI, 35-68%; 17 patients), with a complete response rate of 24% (95% CI, 13-41%; 8 patients); 3% (1 patient) had stable disease, while 45% (15 patients) had no response or progressive disease (Table 2). A complete or partial response was achieved in 11 out of 19 patients (58%) who had received three or fewer previous lines of therapy and in six out of 14 patients (43%) who received more than three previous lines of therapy. Among the 17 responders, five had received two previous lines of therapy, seven had received three lines, three had received four lines, one had received five lines and one had received six lines.

Response according to response to last therapy

Of the ten patients who did not respond to their last anti-MCL therapy prior to study treatment, four (40%) achieved a response to lenalidomide and dexamethasone, including one patient who had a complete response (10%). As expected, the overall response rate was higher (8/12 patients; 67%) among those who achieved a complete response after their last prior treatment.

Progression-free survival, overall survival and response duration

After a median follow-up of 16 months, the median progression-free and overall survival times were 12 months (95% CI, 5-19 months) and 20 months (95% CI, 12 months to not estimable), respectively (Figure 2A,B). The median response duration was 18 months (95% CI, 12 months to not estimable), but this estimate is highly unstable since the one patient at risk progressed at 18 months, representing both the median and the maximum response duration (Figure 2C).

Modification of microenvironment and neo-angiogenic factors

Microenvironment

Six patients with bone marrow infiltration were evaluable for the assessment of treatment effects on MVD, macrophage and NK cell counts. In this small cohort of patients, the comparison before and after therapy showed a significant increase in MVD (P=0.033) and a trend toward an increase in macrophage and NK cell counts in patients treated with lenalidomide and dexamethasone, while these parameters remained unchanged in the control group who received the HyperCVAD regimen (Table 3).

Neo-angiogenic factors

Levels of neo-angiogenic factors could be evaluated in 19 patients: the comparison before and after therapy did not show significant modifications in the levels of FGF-2, VEGF, HGF, or PDGF (Table 3).

Safety

Two patients, one with no response and one with a partial response, interrupted therapy at months 1 and 6, respectively, because of toxicity (grade 3 cutaneous rash) and poor compliance to lenalidomide and dexamethasone.

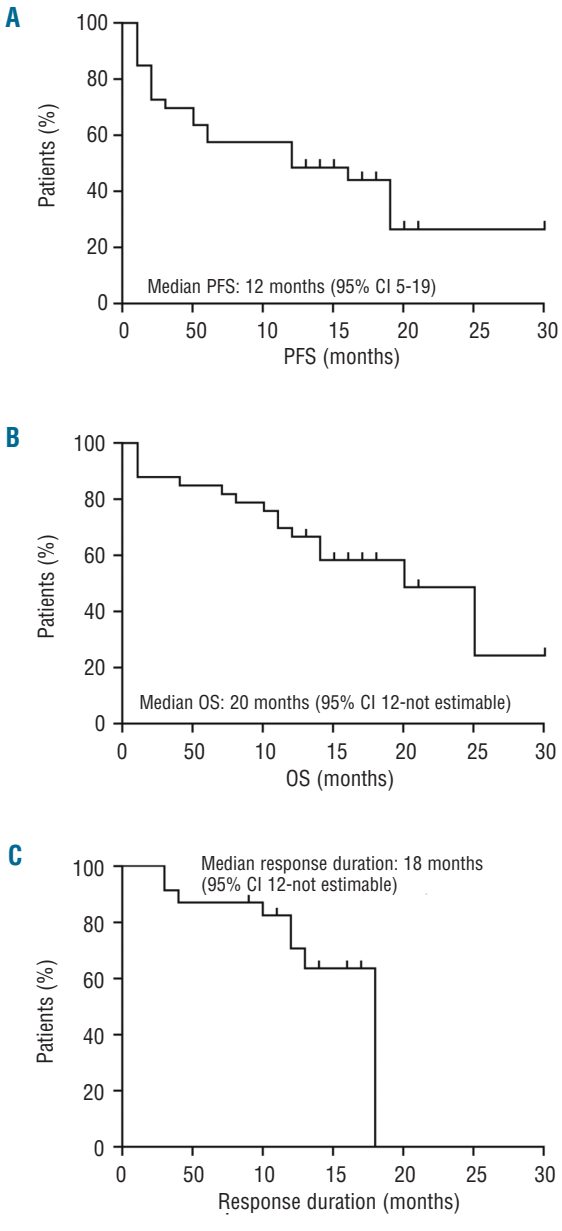


Figure 2. Kaplan-Meier survival graphs following treatment with lenalidomide and dexamethasone. (A) Progression-free survival (PFS). (B) Overall survival (OS). (C) Response duration. CI: confidence interval.

Table 4 summarizes the grade 3 to 5 toxicity observed with the study treatment. Neutropenia was the most frequent event, being recorded in 53% of patients (eight patients grade 3, nine patients grade 4). Filgrastim or lenograstim supplementation was necessary in 15 patients during 54 of the 230 cycles of therapy. Four patients (12%) developed grade 3/4 infectious complications, all during the first cycle of therapy. There were three cases of bacterial pneumonia and one of lung aspergillosis; this last infection developed during the first course of therapy in a patient previously treated with six cycles of R-CHOP who had a very aggressive relapse and died early from lymphoma progression. Another patient who had previously received five lines of therapy (HyperCVAD/MA-R, R-ICE, autologous stem cell transplant, R-GEMOX, R-bendamustine) had radiological evidence of grade 2 pulmonary aspergillosis that improved with oral antimycotic therapy. Neither of these two patients had received prophylactic antifungal therapy. Grade 3/4 febrile neutropenia was reported in 12% of patients. Grade 3/4 thrombocytopenia and anemia were reported in 22% and 6% of patients, respectively, with five patients requiring erythropoietin (during 13 of 230 cycles) and three patients requiring platelet transfusions (also during 13 of 230 cycles). During the first cycle of therapy, one patient had a very rapid onset of acute respiratory insufficiency with severe hypotension and fever; he was admitted to the emergency room where he received antibiotics and supportive therapy but died a few hours later. Another patient experienced grade 3 dyspnea that subsequently improved with salvage chemotherapy.

Table 5 summarizes the occurrence of expected and unexpected serious adverse events. Overall, nine serious adverse events were observed, two of which were fatal. One serious adverse event was related to treatment, three were possibly related, two were unlikely to have been related, and three were unrelated to lenalidomide and dexamethasone.

Discussion

In this study, lenalidomide at a dose of 25 mg was administered along with four weekly doses of dexamethasone 40 mg as salvage treatment for patients with MCL. Our data show a good safety profile and high therapeutic activity, with an overall response rate of 52% at the end of the study treatment, similar to that reported in two earlier studies in small subgroups of patients who received lenalidomide monotherapy, in which overall response rates of 42% to 53%, and complete response rates of 20% were achieved.[9,10]

Dexamethasone was included in the study in an attempt to achieve synergistic clinical effects based on *in vitro* observations[11] as well as positive clinical results observed in combination with lenalidomide in multiple myeloma.[12,13] However, *in vitro* studies in lymphoma cells have recently demonstrated that lenalidomide alone may improve immune function and tumor killing in MCL. In particular, lenalidomide has been shown to activate T, NK, and NKT cells,[15-17] and enhance direct immune synapse formation between MCL and NK cells.[6] Additionally, in patients with MCL, dexamethasone might not be the optimal agent for combination therapy with lenalidomide because of its possible detrimental effect on immune activation resulting from suppression of cell-mediated immunity, which might explain why, in our study, we did not achieve better results than those reported with lenalidomide monotherapy in similar groups of patients.[9,10] The kinetics of response were quite fast, and at the time of the first response assessment, after the end of cycle 3 (induction phase), the overall and complete response rates were 67% and 15%, respectively. Notably, 50% of patients previously treated with bortezomib or ASCT responded to treatment. As expected, the response rate was lower in patients who were refractory to their last therapeutic regimen, with the overall and complete response rates in these patients being 40% and 10%, respectively; however, the response seen was still significant. These data indicate

Table 3. Effect of therapy with lenalidomide and dexamethasone on biomarkers.

	Lenalidomide plus dexamethasone			HyperCVAD/MA		
	Before therapy	After therapy	*P*	Before therapy	After therapy	*P*
Bone marrow evaluation, number of cells*						
Microvessel density	3.8±2.32	7.2±2.85	0.033	2.6±1.43	3.5±2.27	0.159
Macrophages	4.3±1.21	6.5±2.43	0.093	7.4±2.50	7.9±2.60	0.692
Natural killer cells	2.2±1.17	4.0±2.19	0.150	2.8±0.92	2.8±1.23	1
Serum evaluation, pg/mL†						
Fibroblast growth factor	23±17	19±20	0.219	NA	NA	NA
Vascular endothelial growth factor	171±128	175±207	0.470	NA	NA	NA
Hepatocyte growth factor	325±156	286±165	0.349	NA	NA	NA
Platelet-derived growth factor	434±389	308±358	0.286	NA	NA	NA

*Data are mean±standard deviation. *Microvessel density, macrophages, and natural killer cell expression in the bone marrow of six patients with marrow infiltration were evaluated by means of immunohistochemistry to assess the mean number of cells expressing factor VIII, CD69, or CD94. Results were compared with those observed in a control group of 10 patients with mantle cell lymphoma with marrow infiltration treated with the HyperCVAD/MA regimen. †Serum levels of the various angiogenic factors were analyzed in 19 patients. HyperCVAD/MA: cyclophosphamide, vincristine, doxorubicin, and dexamethasone, with methotrexate and cytarabine; NA: not available.*

Table 4. Grade 3 to 5 adverse events in 32 patients.*

N. (%)	Grade 3	Grade 4	Grade 5
Neutropenia	8 (25)	9 (28)	0
Leukopenia	4 (13)	4 (13)	0
Thrombocytopenia	4 (13)	3 (9)	0
Infections	3 (9)	1 (3)	0
Bacterial	3 (9)	0	0
Fungal	0	1 (3)	0
Febrile neutropenia	3 (9)	1 (3)	0
Pulmonary	1 (3)	0	1 (3)
Anemia	1 (3)	1 (3)	0
Cardiotoxicity	0	1 (3)	0
Cutaneous rash	1 (3)	0	0

Data not evaluable for one patient due to early drop-out.

Table 5. Expected and unexpected serious adverse events.

	Relationship	Severity	Action taken	Outcome
Pneumonitis	Possible	Severe	Withdrawn	Unchanged
Cholecystitis	Unlikely	Severe	Treatment delayed	Resolved
Intestinal perforation after biopsy	Unrelated	Moderate	Treatment delayed	Resolved
Multi-organ failure, disease progression	Unrelated	Fatal	-	Fatal
Femur fracture	Unrelated	Life threatening	Treatment delayed	Resolved
Anemia (progression)	Possible	Life threatening	Therapy stopped	Resolved
Pneumonitis	Unlikely	Severe	Withdrawn	Resolved with sequelae
Diffuse cutaneous rash	Definitely	Moderate	Therapy stopped	Resolved
Dyspnea/ hypotension	Possible	Fatal	-	Fatal

that lenalidomide may be an active salvage therapy for patients with MCL, including those with refractory disease.

Among the 22 initial responders, nine relapsed or progressed either during treatment (four cases) or in the subsequent phase of follow-up (five cases); this group of patients consisted of two who had achieved a complete response, six who had achieved a partial response and one who had stable disease. Two patients (one with a partial response and one with no response) interrupted therapy because of poor compliance or toxicity, while 13 (39%) and 15 (45%) patients required dose reduction of lenalidomide or dexamethasone, respectively, because of toxic events. We, therefore, suggest that in every-day clinical practice, patients start on a lower dose of lenalidomide (10 or 15 mg/day on days 1-21), with subsequent dose escalation, particularly in elderly patients or in those with limited marrow reserve. As in previous studies, there were no thromboembolic events, suggesting that, in contrast to the setting of multiple myeloma, in patients with lymphoma the prothrombotic effect of lenalidomide is less important and thromboembolic prophylaxis may be reserved for patients who are at high risk of developing venous thromboembolism.

Hematologic toxicities, particularly neutropenia, were the most frequent adverse events, and the principal cause of lenalidomide dose reduction. Four patients (12%) experienced grade 3/4 febrile neutropenia and four (12%) had infectious complications; there were radiological or microbiological findings consistent with pulmonary aspergillosis in two patients (one grade 2 and one grade 3). Notably, the rate of infections observed in the present study was higher than rates observed in studies with lenalidomide monotherapy in similar groups of patients, indicating a possible relationship with the use of dexamethasone.

Additional correlative analysis was conducted to explore the biological effect of lenalidomide and dexamethasone on tumor microenvironment and neovascularization. This analysis had major limitations due to the small number of patients evaluable; however, when compared with control patients treated with the HyperCVAD/MA-R regimen, we found a trend toward an increase in MVD, macrophage and NK cell counts in the bone marrow of patients who received lenalidomide and

dexamethasone, which supports the potential immunomodulatory effect of lenalidomide. The increase in bone marrow MVD could be the expression of indirect angiogenesis from macrophage activation. However, the absence of modification of serum angiogenic markers confirms the limited direct effect of lenalidomide on neovascularization. These biological data are in line with recent findings supporting the primary immune-stimulatory effect of lenalidomide in patients with lymphoma.[6]

In conclusion, the combination of lenalidomide and dexamethasone demonstrated encouraging clinical activity in patients with relapsed/refractory MCL, with a favorable safety profile. Biological data support its positive immunemodulatory effect. However, the contribution of dexamethasone in achieving these results in patients with MCL is unclear, and further studies comparing other combinations, such as lenalidomide with anti-CD20 monoclonal antibodies, are warranted.

Authorship and Disclosures

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