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Anti-tumor activity of rituximab plus thalidomide in patients with relapsed/refractory mantle cell lymphoma

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ABSTRACT

We evaluated a treatment strategy targeting both lymphoma cells (by rituximab) and the microenvironment (by thalidomide) in 16 patients with relapsed/refractory mantle cell lymphoma (MCL). Rituximab was administered at 375 mg/m² for four weekly doses concomitantly with thalidomide (200 mg daily, with a dose increment to 400 mg on day 15), which was continued as maintenance therapy until progression/relapse. Thirteen patients (81%) experienced an objective response, with 5 complete responders (31%). Median progression-free survival (PFS) was 20.4 months (95% CI, 17.3 to 23.6), and estimated 3-year survival was 75%. In patients achieving a complete response, PFS after rituximab plus thalidomide was longer than PFS after the preceding chemotherapy. Severe adverse events included two thromboembolic events and one grade IV neutropenia associated with thalidomide. Our results suggest that rituximab plus thalidomide has marked anti-tumor activity in relapsed/refractory MCL and a low toxicity profile, which warrants further evaluation in MCL.

Key words: relapsed mantle cell lymphoma, rituximab, thalidomide

INTRODUCTION

Mantle cell lymphoma (MCL), which represents a distinct clinicopathologic entity among the non-Hodgkin's lymphomas, is characterized by a low response rate to and short progression-free survival (PFS) after conventional chemotherapy.^{1,2} Administration of high-dose therapy with autologous stem cell rescue has also not resulted in long-term disease-free survival of patients with MCL,^{1,3,4} emphasizing the need for novel treatment strategies for this lymphoma entity. It has been recognized that stromal cells deliver important stimuli for growth and survival of normal and malignant B cells.^{5,6} Interactions between tumor and stromal cells can be modulated by agents like thalidomide and proteasome inhibitors. Activity of thalidomide has already been demonstrated in B cell malignancies, in particular multiple myeloma^{7,8} and Waldenstroem's macroglobulinemia.⁹ In a patient with heavily pretreated and rapidly progressive MCL, we have observed stabilization of the disease for a period of 6 months following administration of thalidomide (J.D., unpublished observation, 2000). We therefore hypothesized that a treatment strategy targeting both lymphoma cells and the microenvironment could be active in MCL. We evaluated this treatment approach in chemotherapy pretreated patients with MCL and combined thalidomide with rituximab, an antibody with documented efficacy in MCL.¹⁰

STUDY DESIGN

Patient characteristics

All 16 patients (compare Table 1) enrolled into this phase II protocol had already been treated by CHOP (n = 14) or a CHOP-like regimen (n = 2). Fifteen patients were at relapse (7 patients after ≥ 2 prior regimens), one patient was primary refractory to CHOP. Two patients

had prior high-dose chemotherapy with autologous transplantation, and one patient had an allogeneic stem cell transplantation after reduced intensity conditioning. Three patients had prior rituximab (single-agent rituximab at relapse in two patients, and R-CHOP as induction treatment in one patient). Median time between initial diagnosis of MCL and initiation of study treatment was 21 months (range, 4 to 52 months).

Treatment regimen

Treatment with rituximab consisted of four weekly doses at 375 mg/m², with standard premedication (diphenhydramine and paracetamol). Thalidomide was started on the evening of day 1 (scheduled daily dose: 200 mg during the first two weeks, then 400 mg) and continued as maintenance treatment after completion of rituximab until progression or relapse. The study protocol was approved by the institutional ethics committee.

Toxicity was assessed weekly during the first month of treatment and thereafter once a month during thalidomide-maintenance using standard National Cancer Institute common toxicity criteria. Response to treatment was assessed according to the International Workshop Response Criteria Guidelines,¹¹ with restaging every three months. PFS and overall survival (OS) was estimated by the method of Kaplan and Meier.

RESULTS AND DISCUSSION

Response

Objective responses to rituximab plus thalidomide (R+T) were achieved in 13 of the 16 patients (overall response rate 81%; 95% CI, 59.8 – 102.7), one patient experienced stable disease. Five patients (31%; 95% CI, 5.7 – 56.8) achieved a CR (4 CR, 1 CRu) including the patient with primary CHOP-resistance and one patient at relapse after autologous

transplantation. Eight patients (50%; 95% CI, 22.5 – 77.5) had a PR; among them was the patient after allogeneic transplantation with reduced intensity conditioning. Responses were observed both at nodal and extranodal manifestations of MCL (remission of gastrointestinal manifestations in 5 patients, disappearance of a lymphoma in the breast in one patient). In responding patients, shrinkage of peripheral lymph nodes and/or significant improvements of laboratory parameters (clearance of lymphoma cells in the peripheral blood in 3 patients, hematological improvement, reduction of elevated serum levels of LDH) were noted during the first month of treatment.

Among the 13 responders, 8 patients experienced a relapse or progressive disease. In three of them, one course of rituximab (4 weekly infusions at 375 mg/m²) was again added to thalidomide as re-induction treatment. Second remissions were induced in two of them, and PFS was 18+ months (versus 20 months after the first administration of R+T) and 13 months (versus 30 months), respectively.

Progression-free and overall survival

Median PFS of the 16 patients was 20.4 months (95% CI, 17.6 to 23.6; Figure 1), as opposed to 12.7 months after the line of chemotherapy preceding R+T. Improvement of PFS after R+T was particularly evident among the 5 patients achieving a CR (see Figure 1C). Median OS has not yet been reached, with 13 patients alive at the time of analysis (February 22, 2004) and an estimated 3-year survival of 75%.

Toxicity

It was assumed that combination of R+T should not lead to added toxicity, which was confirmed during the course of this trial. All patients completed the scheduled four infusions of rituximab. Infusional reactions to rituximab consisting of fever, rigors, and chills (grade I

to II) developed in 7 patients (44%), mainly during the first application, but no other adverse events (grade II or greater) were encountered.

Fatigue, somnolence, and constipation were common, dose-dependent side effects of thalidomide; therefore, the planned dose of 400 mg daily could only be achieved in 6 patients, and it was necessary to adapt the maintenance dose of thalidomide on an individual basis (compare Table 1). A daily dose of 50 to 200 mg could be maintained with only limited toxicity, which was also reported by Damaj et al.¹² Peripheral neuropathy (grade I – II) occurred in 7 patients (44%). Due to neuropathy, one patient discontinued thalidomide after 30 months. Grade IV neutropenia associated with thalidomide was observed in one patient, and his neutrophil counts recovered after discontinuation of thalidomide. As previously reported, there were two events of venous thromboembolism¹³ (one deep-vein thrombosis 5 weeks after initiation of therapy, and one asymptomatic pulmonary embolism at routine CT scanning during follow-up).

The efficacy of R+T is clearly beyond that of rituximab alone (35% remission rate of single-agent rituximab in MCL patients, with virtually no CR and a median PFS of 12 months),^{10,14,15} and its activity compares favorably with results of other salvage strategies in MCL. For example, among 21 evaluable patients with relapsed MCL, the recently reported R-FCM (rituximab, fludarabine, cyclophosphamide, mitoxantrone) regimen induced remissions in 13 patients (62%), with a CR in 7 patients (33%).¹⁶ As recently published in two case reports,^{12,17} thalidomide has single-agent activity in relapsed MCL, and we can now assume that it may be additive to or synergistic with rituximab. Thalidomide is known to have pleiotropic effects,¹⁸ which mainly exert an indirect effect on tumor cells by modulating cytokine secretion¹⁹ and expression of adhesion molecules,²⁰ and by enhancing the activity of NK cells and cytotoxic T lymphocytes.^{21,22} It is worth noting that rituximab can induce cytotoxic T cell responses against lymphoma-associated antigens in vitro,²³ an effect that

could be further enhanced by the immunomodulatory activity of thalidomide. Finally, effects of thalidomide on the microenvironment also include inhibition of angiogenesis.²⁴ Further studies are required to delineate the precise mechanism of action of thalidomide in MCL.

Despite the limited number of patients, our study provides evidence for promising anti-tumor activity and a low toxicity profile of R+T in patients with relapsed/chemotherapy refractory MCL. The observation of durable remissions warrants further evaluation in an attempt to improve the overall grim prognosis in MCL. We are therefore studying rituximab plus CHOP plus thalidomide as induction treatment, followed by thalidomide maintenance, in patients with previously untreated MCL.

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Table 1. Dose of thalidomide actually administered in patients with MCL

Patient	Age ^a	IPI ^b	Response	Thalidomide dose	
				Maximum	During maintenance
1	56	intermediate-low	PR	400 mg	200 mg (12 weeks) ↯ 100 mg (26 weeks) ↯ 50 mg (88 weeks, continued during retreatment)
2	68	intermediate-high	PR	400 mg	400 mg (8 weeks) ↯ 300 mg (4 weeks) ↯ 200 mg (47 weeks) ↯ 100 mg (19 weeks, continued during retreatment)
3	50	low	CR	400 mg	400 mg (70 weeks) ↯ 200 mg (8 weeks, continued during retreatment)
4	70	intermediate-high	PR	400 mg	400 mg (8 weeks) ↯ 300 mg (8 weeks; discontinued due to neutropenia)
5	74	intermediate-high	CR	400 mg	400 mg (8 weeks) ↯ 300 mg (15 weeks) ↯ 200 mg (32 weeks) ↯ 100 mg (36 weeks)
6	65	intermediate-high	CRu	200 mg	200 mg (36 weeks) ↯ 100 mg (42 weeks) ↯ 50 mg (22 weeks; discontinued due to neuropathy)
7	64	intermediate-high	PR	200 mg	200 mg (3 weeks) ↯ 100 mg (83 weeks)
8	70	intermediate-low	SD	400 mg	400 mg (8 weeks) ↯ 200 mg (15 weeks)
9	74	intermediate-low	CR	200 mg	200 mg (20 weeks) ↯ 100 mg (60 weeks) ↯ 50 mg (55+ weeks)
10	71	high	PR	200 mg	200 mg (36 weeks) ↯ 100 mg (20 weeks)
11	62	intermediate-high	PR	200 mg	200 mg (32 weeks) ↯ 100 mg (44+ weeks)
12	45	low	CR	200 mg	100 mg (8 weeks) ↯ 50 mg (44+ weeks)
13	76	high	NR	200 mg	100 mg (8 weeks)
14	64	intermediate-low	PR	200 mg	200 mg (20 weeks)
15	72	intermediate-low	NR	200 mg	200 mg (8 weeks)
16	61	high	PR	200 mg	200 mg (12+ weeks)

^a Age (years) at the time of initiation of study treatment

^b International Prognostic Index

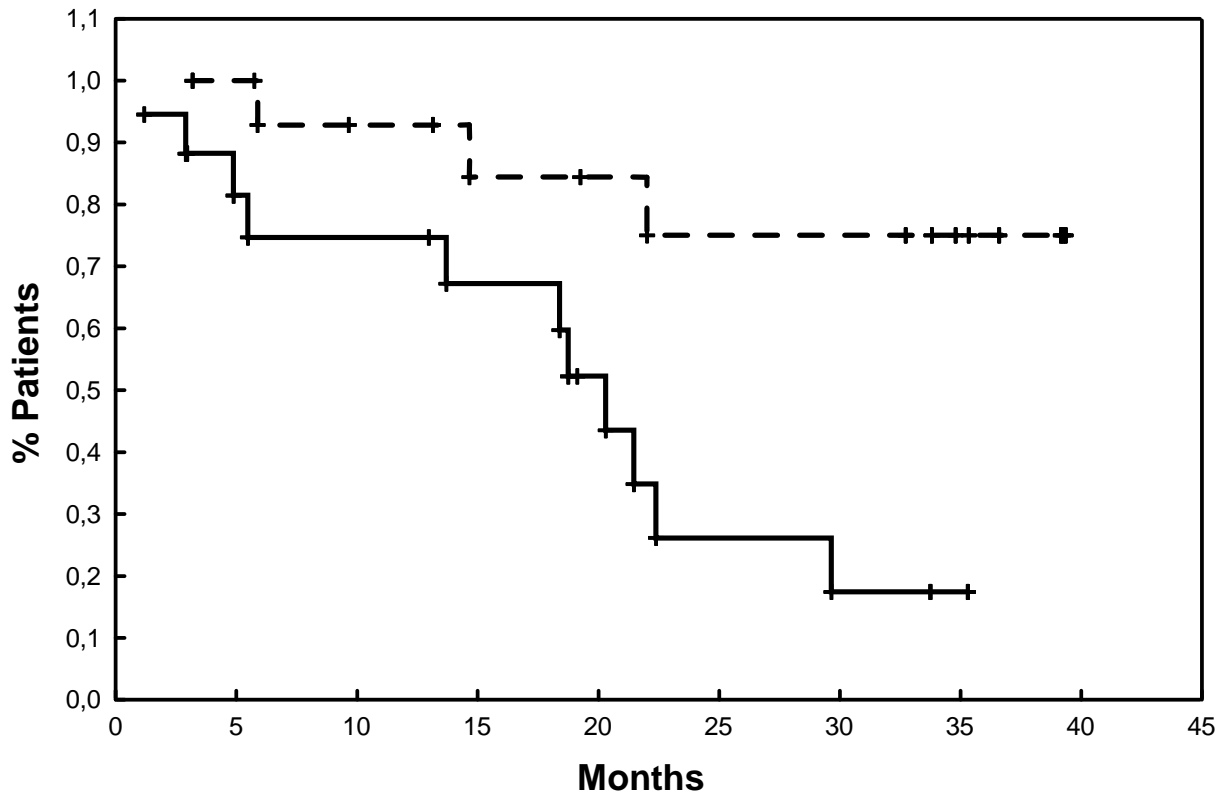
LEGEND TO THE FIGURE 1:

(A) Progression-free (median, 20.4 months; solid line) and overall survival (dotted line) of relapsed/refractory MCL patients from the time of initiation of rituximab plus thalidomide.

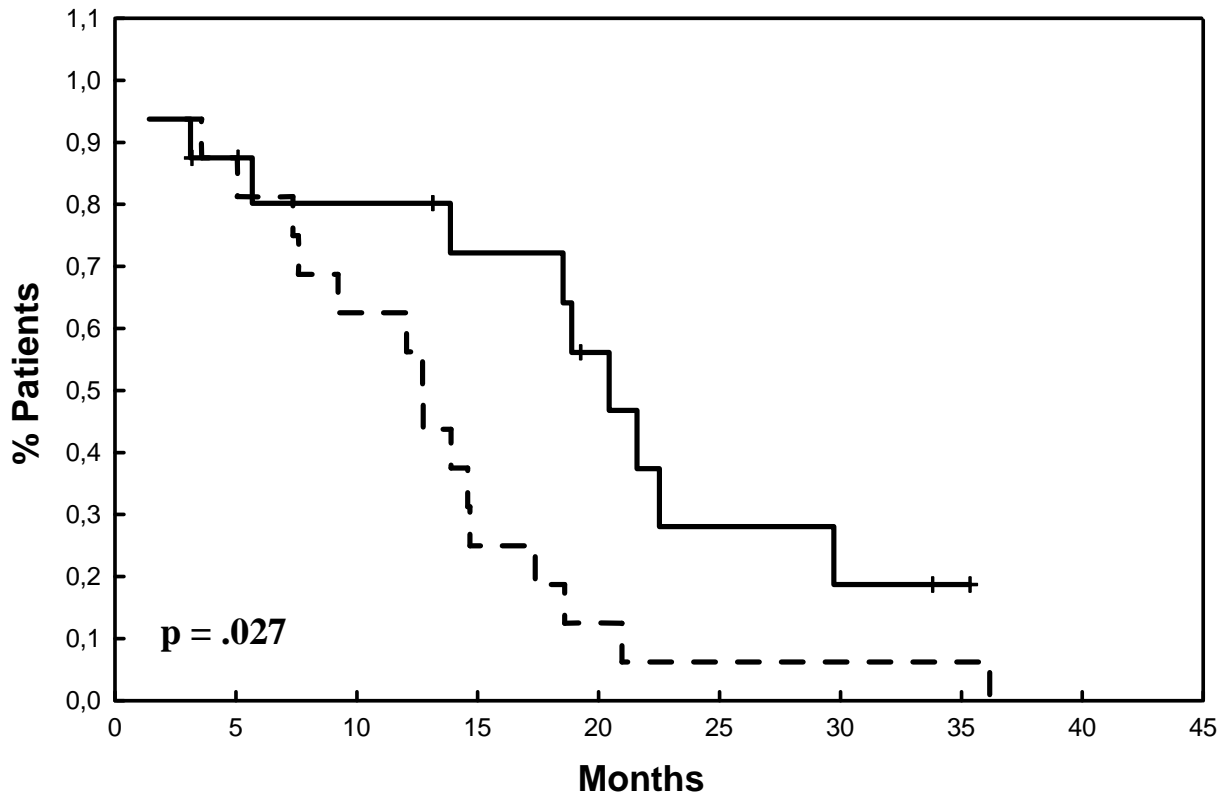
(B) Progression-free survival after rituximab plus thalidomide (median, 20.4 months; solid line) was significantly longer compared to progression-free survival after the previous line of chemotherapy (median, 12.7 months; dotted line) ($P = .027$).

(C) Progression-free survival (PFS) of MCL patients achieving a CR after rituximab plus thalidomide (black bars) compared to PFS after the previous line of chemotherapy (grey bars).

A



B



C

