

Lenalidomide and Rituximab in Waldenstrom's Macroglobulinemia

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Abstract Purpose: Thalidomide and its more potent immunomodulatory derivative lenalidomide enhance rituximab-mediated antibody-dependent cell-mediated cytotoxicity. We therefore evaluated lenalidomide and rituximab in symptomatic Waldenstrom's macroglobulinemia (WM) patients naive to either agent.

Experimental Design: Intended therapy consisted of 48 weeks of lenalidomide (25 mg/d for 3 weeks and then 1 week off) along with rituximab (375 mg/m²/wk) dosed on weeks 2 to 5 and 13 to 16. Sixteen patients were enrolled, 12 of whom were previously untreated.

Results: Unexpectedly, we observed an acute decrease in hematocrit in 13 of 16 patients (median hematocrit decrease, 4.8%), which was attributable to lenalidomide patients and which led to cessation of further enrollment on this study. Lenalidomide-related anemia was observed even at doses as low as 5 mg/d and occurred in the absence of hemolysis or other cytopenias. The overall response and major response (<50% decrease in serum IgM) rates were 50% and 25%, respectively, on an intent-to-treat basis. With a median follow-up of 31.3 months, 4 of 8 responding patients have progressed with a median time to progression of 18.9 months.

Conclusion: Lenalidomide produces unexpected but clinically significant acute anemia in patients with WM. In comparison with our previous study with thalidomide and rituximab in an analogous patient population, the responses achieved in WM patients with lenalidomide and rituximab appear less favorable.

Waldenstrom's macroglobulinemia (WM) is a B-cell disorder characterized primarily by bone marrow infiltration with lymphoplasmacytic cells along with demonstration of an IgM monoclonal gammopathy (1). This condition is considered to

be lymphoplasmacytic lymphoma as defined by the REAL and WHO classification systems (2, 3). Despite advances in therapy, WM remains incurable. As such, novel therapeutic agents are needed for the treatment of WM.

One class of therapeutics that has been successfully used in patients with WM are monoclonal antibodies. Both rituximab and alemtuzumab have been evaluated in WM as single agents with major response rates of 30% to 40%, whereas the combination of rituximab with chemotherapy has resulted in response rates of 70% to 90% (4). With the attainment of higher response rates with chemo-antibody therapy, considerably more short-term and long-term toxicities have been reported (4, 5). In an effort to augment monoclonal antibody responses in WM patients while averting short-term and long-term chemotherapy-induced toxicities, we have sought the development of immunomodulatory agents for combination with rituximab. Thalidomide and its more potent immunomodulatory derivative lenalidomide augment antibody-dependent cell-mediated cytotoxicity (5). Moreover, these agents also lead to expansion of natural killer cells, which serve as important effector cells for rituximab activity in patients with indolent non-Hodgkin's lymphoma (6–9). As a follow-up to these findings, we recently performed a clinical trial exploring the combined use of thalidomide and rituximab in patients with WM who were naive to either agent (10). The results of this study demonstrated a higher (70%) major (≥50% decrease in IgM) response rate than observed previously with either thalidomide (20–25%) or rituximab (30–40%) alone as upfront therapy in WM patients. Responses in this

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Note: S.P. Treon, A.R. Branagan, Z.R. Hunter, N.C. Munshi, and K.C. Anderson designed and wrote the study. J.D. Soumerai, C.J. Patterson, and L. Ioakimidis oversaw the data collection. S.P. Treon, L. Chu, P. Musto, A.D. Baron, J.C. Nunnink, J.J. Kash, T.O. Terjanian, P.M. Hyman, E.L. Nawfel, and D.J. Sharon treated the study patients and provided study data.

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Translational Relevance

The intent of this study was to examine the potential for the immunomodulator lenalidomide to augment rituximab activity in patients with WM. The study showed a unique idiosyncrasy for this drug in this patient population, which consisted of acute anemia and which persisted despite dose reduction and resulted in numerous hospitalizations for patients due to anemia complications. This aggravated anemia was seen even with dose reduction. We believe that this study is very important to alerting clinicians to this novel and unexpected toxicity, which appears idiopathic to WM patients. The mechanism for this finding remains to be delineated. The findings of this study are particularly important given the relatedness of WM to multiple myeloma and the interchange of therapeutics among these disease entities by clinicians. Moreover, in comparison with our previous study with thalidomide and rituximab in an analogous patient population, the responses achieved in WM patients with lenalidomide and rituximab appear less favorable. We believe that the results of this study will be important not only to clinicians caring for patients with WM but also to investigators examining the role of lenalidomide in related low-grade B-cell malignancies.

study were durable, with time to progression (TTP) of ≥ 38 months observed among responders. The response rate and TTP for combined thalidomide and rituximab therapy was comparable with that reported with combinations of cytotoxic agents or nucleoside analogues and rituximab (4). However, we observed a high incidence (44%) of reversible grade ≥ 2 peripheral neuropathy. A higher incidence of peripheral neuropathies has also been observed by us in WM patients treated with bortezomib in comparison with patients with other B-cell malignancies, suggesting a constitutive predisposition to neuropathy (11). As such, given the greater immunomodulatory activity as well as diminished neuropathic potential for lenalidomide relative to thalidomide, we performed this phase II study of lenalidomide and rituximab in WM patients naive to either agent and reported herein the toxicities and activity of this novel combination.

Patients and Methods

Patients with a clinicopathologic diagnosis of WM requiring therapy based on the consensus recommendations of the Second International Workshop on Waldenstrom's Macroglobulinemia (12), and who were naive to rituximab and lenalidomide, and with CD20⁺ tumor cells as determined by previous bone marrow immunohistochemistry or flow cytometry were eligible for this study. To meet eligibility, patients had to show a monoclonal IgM protein, minimum IgM level ≥ 2 times the upper limit of normal, baseline platelet count $\geq 25,000/\mu\text{L}$, absolute neutrophil count $\geq 500/\mu\text{L}$, serum creatinine < 2.5 mg/dL (unless nephropathy was attributable to their WM), serum total bilirubin and SGOT < 2.5 times the upper limit of normal, and Eastern Cooperative Oncology Group performance status 0 to 2. No chemotherapy, steroid therapy, or radiation therapy within 30 days of study entry was permitted. Patients who were pregnant or lactating, had serious comorbid disease, had any uncontrolled bacterial, fungal, or viral infection, or an active second malignancy were not eligible. All men and

women of reproductive potential were required to agree to use an acceptable method of birth control before, during treatment, and for 6 months after completion of study treatment.

All patients provided informed written consent and the institutional review board approved the protocol. Intended therapy consisted of lenalidomide administered at a starting dose of 25 mg/d by mouth for 3 weeks and then 1 week off on a syncopated schedule as part of a 4-week cycle. Patients could receive up to 48 weeks of therapy with lenalidomide. Dose de-escalation was permitted to 15 mg/d on days of treatment. Following enrollment of the first 11 patients, the protocol was amended to initiate patients on a start dose of 20 mg/d on the same syncopated schedule as before, with dose de-escalation permitted to 10 mg/d on days of treatment. Following the enrollment of one patient at the start dose of 20 mg/d, the protocol was again amended to initiate patients at a start dose of 15 mg/d, on the same syncopated schedule as before, with dose de-escalation permitted to 5 mg/d on days of treatment.

Rituximab was administered at 375 mg/m²/wk during weeks 2 to 5 and 13 to 16 for a total of 8 infusions. Patients who did not tolerate the first cycle (4 infusions) of rituximab therapy were removed from the study and not replaced. Sixteen patients were enrolled in this study, which used a Simon two-stage design. Sample size was based on the assumption that the expected response rate would be at least 50%. Therefore, to have a 95% confidence interval of $\sim 20\%$, a sample size of 25 was required.

Response determination. A baseline evaluation was obtained for enrollment within 30 days before initiation of therapy. Patients underwent re-staging studies every 3 months while on therapy and thereafter every 3 months until progression of disease. As part of their response evaluation, all patients underwent history and physical exam, laboratory studies consisting of a complete blood count and differential, serum IgM levels, β_2 -microglobulin levels, and bone marrow biopsy and aspiration. Response determinations were made using modified consensus panel criteria from the Third International Workshop on Waldenstrom's Macroglobulinemia, and response rates determined on an evaluable basis (13). A complete response was defined as having resolution of all symptoms, normalization of serum IgM levels with complete disappearance of IgM paraprotein by immunofixation, and resolution of any adenopathy or splenomegaly. Patients achieving a major response and a minor response were defined as achieving $\geq 50\%$ and $\geq 25\%$ reduction in serum IgM levels, respectively. Patients with stable disease were defined as having $< 25\%$ change in serum IgM levels in the absence of new or increasing adenopathy or splenomegaly and/or other progressive signs or symptoms of WM. Progressive disease was defined as occurring when a $> 25\%$ increase in serum IgM level occurred from the lowest attained response value or progression of clinically significant disease-related symptom(s). For patients undergoing plasmapheresis, serum IgM levels were used for purposes of assessing response only after steady-state attainment (≥ 5 weeks from last plasmapheresis). TTP was calculated from the start of therapy using the Kaplan-Meier method.

Analysis of peripheral blood effector cells. Serial changes in the absolute levels of peripheral blood effector cells following lenalidomide monotherapy during the first week (and before introduction of rituximab to prevent effector cell alterations) were done as described previously (10).

Statistical analysis. Comparison of pretreatment and post-treatment variables was done using a two-tailed Student's *t* test on Microsoft Excel software. $P \leq 0.05$ was deemed to be significant for the above studies.

Results

Patient and disease characteristics. The clinical features of the 16 patients enrolled in this study are summarized in Table 1. Of the 16 patients enrolled on study, 12 were previously untreated. Of the 4 previously treated patients, all

Table 1. Baseline characteristics for all 16 patients enrolled on study

	Median (range)
Gender	12 male/4 female
Untreated	12/16 (75%)
Age (y)	65 (49-85)
Prior therapies	0 (0-2)
Bone marrow involvement (%)	37.5 (5-90)
Serum IgM (mg/dL)	4,000 (1,180-7,130)
β_2 -Microglobulin (mg/L)	3.3 (1.8-6)
Hematocrit (%)	32.1 (24-36.6)
Platelets (k/ μ L)	282.5 (78-568)
Leukocytes (k/ μ L)	6.05 (3-22)

had relapsed to their prior therapy. The median cumulative dose of lenalidomide administered for the intended 48-week treatment period among all enrolled patients was 455 mg (range, 140-5,670), and the median number of weeks on lenalidomide therapy was 15.8 (range, 1.1-48). The median number of cycles of rituximab among all enrolled patients was 8 (range, 3-8). Twelve patients were evaluable for response. Four patients were unevaluable for response due to their premature withdrawal resulting from adverse events associated with lenalidomide ($n = 3$) and rituximab ($n = 1$).

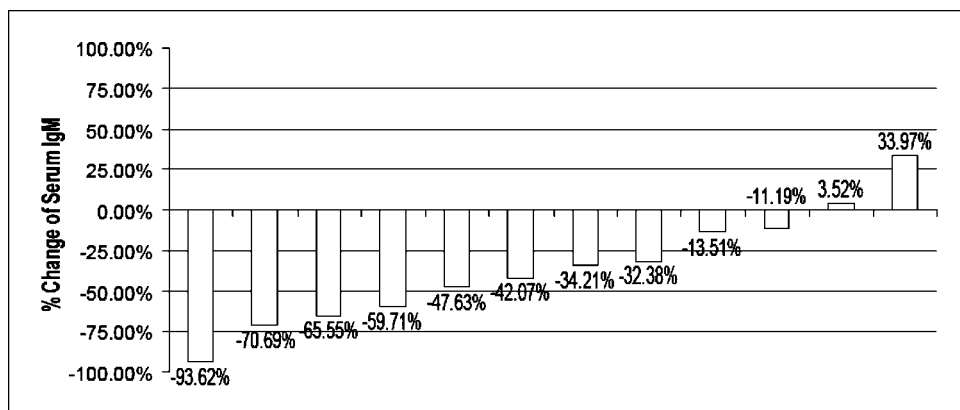
Clinical response to therapy. The individual changes in serum IgM levels at best response for all evaluable patients are shown in Fig. 1. Median serum IgM levels for all evaluable patients declined from 2,980 mg/dL (range, 1,180-7,130) to 1,775 mg/dL (range, 83-4,220) at best response ($P = 0.015$). Pre-therapy, 6 of 12 (50%) showed a serum IgM level $\geq 3,000$ mg/dL; at best response, only 3 of 12 (25%) had an IgM level $\geq 3,000$ mg/dL. Overall, 8 of 16 patients enrolled in this study showed at least a minor response as their best response. Of these patients, 4 of 16 (25%) achieved a major response and 4 of 12 (25%) achieved a minor response. There were no complete responders. Among responding patients, the median time to best response was 11.8 months (range, 6-26.4), and the median time for a 25% reduction in serum IgM among responders was 3.6 months (range, 1.1-7.3). Among major responders, the median time to achieving a 50% reduction in serum IgM was 4.6 months (range, 2-13). Two patients displaying bulky adenopathy ($n = 2$) and/or splenomegaly ($n = 1$) had complete resolution of their extramedullary disease

after experiencing pain at these disease sites following administration of lenalidomide and rituximab.

Time to progression. The median TTP for all evaluable patients was 17.1 months (range, 2-34.3) (Fig. 2). With a median follow-up of 31.3 months, 4 of the 8 responding patients have progressed. The median TTP for all responding patients was 18.9 months (range, 11.4-34.3; Fig. 2).

Changes in hematologic variables. Pre-therapy, 2 (16.6%) and 1 (8.3%) of the 12 evaluable patients showed hematocrit $\leq 30\%$ and platelet count $\leq 100,000/\mu\text{L}$, respectively. Following therapy, at best response, 1 (8.3%) and none of the 12 evaluable patients showed hematocrit $\leq 30\%$ and platelet count $\leq 100,000/\mu\text{L}$, respectively. A significant increase in the median hematocrit at best response was noted for the 12 evaluable patients from 32.1% (range, 24-36.6%) to 36% (range, 29-40.8%) following therapy ($P = 0.037$). The observed increase in median hematocrit with therapy followed cessation and/or dose modification of lenalidomide. Pre- and post-therapy, median platelet counts remained unaffected by therapy ($P = 0.22$).

Toxicities. Premature discontinuation of lenalidomide therapy occurred in 14 of 16 (88%) patients despite dose reduction in 13 of these patients and led to cessation of further enrollment on this study. Discontinuation of lenalidomide was based on aggravated anemia or anemia-related complications for 13 patients, and/or concurrent myelosuppression (neutropenia, $n = 1$; thrombocytopenia, $n = 1$), as well as development of lenalidomide-related palpitations in 1 patient. Acute decreases in hematocrit were observed during first 2 weeks of lenalidomide therapy in 13 of 16 (81%) patients (Fig. 3). Within the first 2 weeks of therapy, the median hematocrit declined from 32.3% (range, 26.4-36.6%) to 27.1% (range, 24-32.4%). This decline was observed for most patients even after 1 week of being on lenalidomide alone and before receiving the first rituximab infusion. The median decrease in absolute hematocrit values at lowest point in the 2 weeks following start of lenalidomide was similar for all three start doses examined: -3.15% (25 mg; $n = 11$), -5.4% (20 mg; $n = 1$), and -3.75% (15 mg; $n = 4$). The decrease in hematocrit observed following initiation of lenalidomide therapy was deemed to be a factor, at least in part, for the hospitalization of 4 patients due to congestive heart failure ($n = 2$), arrhythmia ($n = 1$), and syncope ($n = 1$). Examination of lactic dehydrogenase and reticulocyte counts post-lenalidomide in 4 patients who became anemic were unrevealing for hemolysis, and a bone marrow biopsy and aspiration done in 2 patients

Fig. 1. Individual changes (%) in serum IgM levels at best response following treatment with lenalidomide and rituximab.

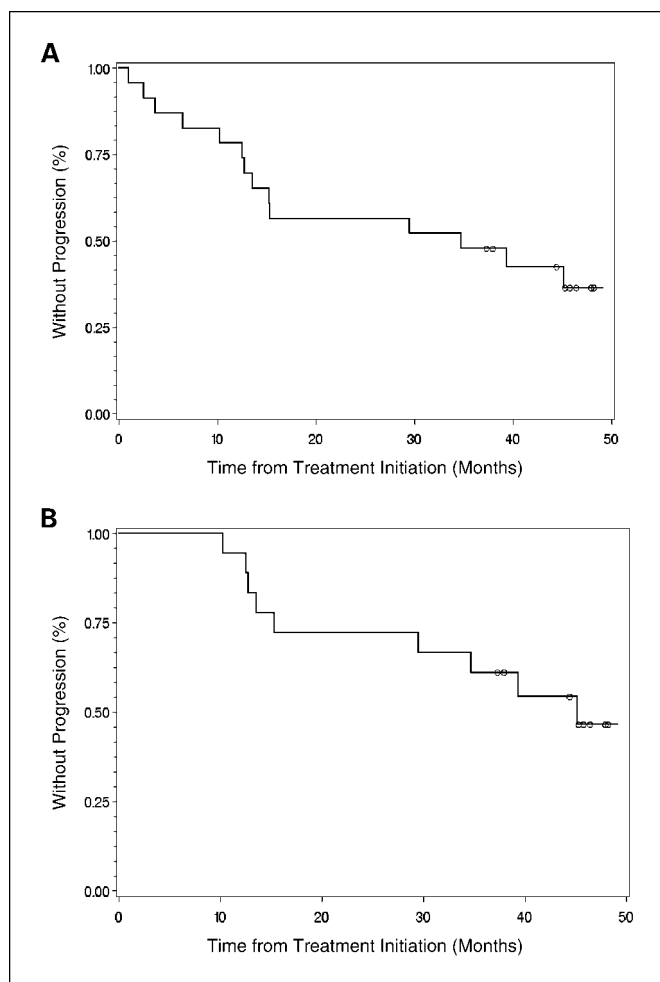


Fig. 2. TTP for (A) all evaluable patients and (B) those who responded to lenalidomide and rituximab. Open circles, patients who had not progressed at last follow-up.

showed normal or mildly decreased erythroid elements. No overt blood loss was seen. Erythropoietin administration was required for 10 patients along with transfusional support consisting of packed RBC and platelets for 7 and 1 patients, respectively, as a consequence of lenalidomide. Although no dose reduction in rituximab was permitted on this study, premature discontinuation for this treatment occurred in 3 patients for rituximab-induced symptomatic hyperviscosity ($n = 2$) or anaphylaxis ($n = 1$). A complete list of all grade ≥ 2 toxicities and the treatment (lenalidomide, rituximab, or both) to which they are possibly, probably, or definitely attributed to appears in Table 2.

Paradoxical increases in serum IgM levels. Abrupt and paradoxical increases in serum IgM levels have been reported with the use of rituximab in patients with WM and can aggravate hyperviscosity and contribute to hyperviscosity-related symptoms (14, 15). For this reason, plasmapheresis was strongly encouraged for patients who had a pre-therapy serum viscosity of ≥ 3.5 CP. Six patients underwent pre-therapy plasmapheresis. During the first four infusions of rituximab, an increase in serum IgM above baseline of $\geq 25\%$ was observed in 12 of 16 (75%) patients and prompted the use of plasmapheresis in 7 of 16 (44%) patients. This paradoxical spike in serum IgM levels was not observed for the 10 patients who received the second 4-week course of rituximab, and none required plasmapheresis just before or during the second course of rituximab treatment. No spike in IgM levels was observed during the period patients were on lenalidomide monotherapy (during the first week) and only occurred following initiation of rituximab therapy.

Effect of lenalidomide on immune effector cell levels. As part of this study, we assessed the effect of lenalidomide as an immunomodulating agent by determining changes in absolute median levels of total T cells ($CD3^+$), natural killer cells ($CD16^+CD56^+$), helper T cells ($CD4^+$), cytotoxic T cells ($CD8^+$), as well as monocytes following 7 days of lenalidomide monotherapy and before the first rituximab infusion. The baseline and day 7 levels for these effector cells are provided in Table 3. No significant change in the level of total, CD4 and CD8 lymphocyte, natural killer cell, and monocyte peripheral blood levels was observed. In addition, no association with changes in any effector cell population and response was observed.

Discussion

Despite robust expression of CD20 in WM, responses to rituximab monotherapy are seen in less than half of treated patients, paralleling the experiences reported in other indolent non-Hodgkin's lymphoma (4). Tumor-related variables including CD20 antigen loss, complement resistance antigen expression, and tumor burden have been addressed previously by us and others and do not account for the heterogeneous response observed in WM patients treated with rituximab (16–18). The possibility that patient-related differences might account for the heterogeneity in rituximab response in WM patients was suggested by our previous studies, showing a high degree of dependence for its activity on polymorphisms present within the rituximab binding domain of Fc γ RIIIA (CD16; ref. 19). These studies also implicated antibody-dependent

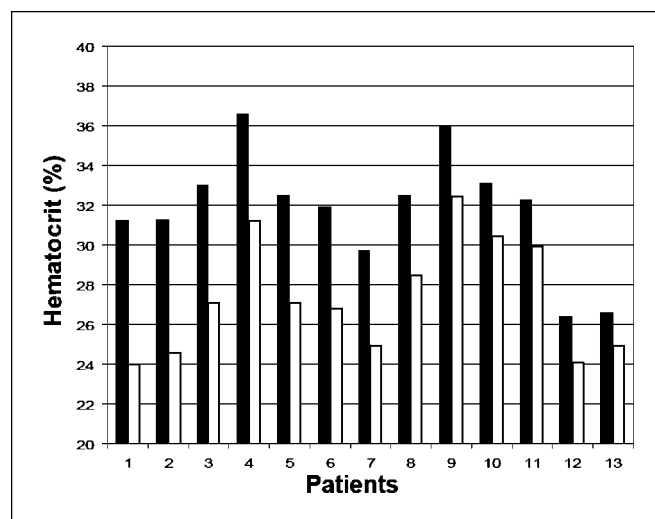


Fig. 3. Pre-therapy and lowest post-therapy hematocrit for 13 WM patients who showed aggravated anemia within a 2-week period of initiation of lenalidomide therapy.

Table 2. Toxicities experienced by the 16 patients on study deemed to be possibly, probably, or definitely related to either lenalidomide, rituximab, or both

Toxicity	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Attribution
Allergic reaction	1 (6.2)	NA	NA	Rituximab
Anemia	8 (50.0)	1 (6.2)	NA	Lenalidomide
Arrhythmia	2 (12.5)	1 (6.2)	NA	Lenalidomide
Back pain	1 (6.2)	NA	NA	Both
Chest pain	NA	1 (6.2)	NA	Rituximab
Diaphoresis	1 (6.2)	NA	NA	Lenalidomide
Fatigue	4 (25.0)	NA	NA	Lenalidomide
Headache	2 (12.5)	NA	NA	Rituximab
Infection	2 (12.5)	NA	NA	Both
Leukopenia	6 (37.5)	NA	NA	Both
Liver function abnormalities	2 (12.5)	NA	NA	Both
Nausea	1 (6.2)	NA	NA	Lenalidomide
Neutropenia	3 (18.7)	5 (31.2)	NA	Lenalidomide
Peripheral neuropathy	1 (6.2)	NA	NA	Lenalidomide
Pleural effusion	NA	1 (6.2)	NA	Rituximab
Pruritus	1 (6.2)	NA	NA	Lenalidomide
Pulmonitis	NA	1 (6.2)	NA	Rituximab
Thrombocytopenia	1 (6.2)	1 (6.2)	NA	Lenalidomide
Tinnitus	2 (12.5)	NA	NA	Lenalidomide
Urinary urgency	1 (6.2)	NA	NA	Lenalidomide
Visual impairment	1 (6.2)	NA	NA	Rituximab

Abbreviation: NA, not applicable.

cell-mediated cytotoxicity function, particularly mediated by Fc γ R1IIIA-expressing natural killer cells, as being essential to rituximab response in WM patients. We therefore focused our efforts on enhancing rituximab efficacy by use of agents, which could augment natural killer cell levels as well as antibody-dependent cell-mediated cytotoxicity activity. Our previous findings showed that thalidomide could enhance circulating natural killer cells in MM patients, whereas thalidomide and more so its analogue lenalidomide enhanced rituximab-mediated antibody-dependent cell-mediated cytotoxicity activity (6, 20). As such, we initiated clinical trials first examining the activity of thalidomide and thereafter lenalidomide in combination with rituximab.

The results of the present study examining lenalidomide in combination with rituximab showed overall and major response rates of 50% and 25%, respectively, on an intent-to-treat basis. No complete responses were observed. The median TTP for responding patients was 18.9 months. Disappointingly,

however, the overall and major response rates as well as the TTP observed with lenalidomide and rituximab appeared inferior to the results attained in our recent study with thalidomide and rituximab in a highly comparable patient population, wherein the overall and major response rates were 72% and 64%, respectively, and TTP for responding patients was 38.7 months. This finding is unexpected, particularly in context of previous findings by us and others showing greater immunostimulatory properties including enhanced antibody-dependent cell-mediated cytotoxicity activity for lenalidomide versus thalidomide (6, 20). Potential reasons for this discrepancy in activity for lenalidomide versus thalidomide could include higher rate of premature discontinuation of therapy due to intolerance (88% versus 44%) as well as greater nonimmunomodulatory mechanisms of action for thalidomide such as phosphodiesterase-4 inhibition. Impressive, however, was the observation of complete nodal responses in 2 patients with bulky adenopathy, which included 1 patient with marked (22 cm) splenomegaly.

Table 3. Changes in peripheral blood effector cell levels following 7 days of lenalidomide therapy in 16 patients with WM

Peripheral blood effector cells	Baseline level	Post-7 days lenalidomide	P
Lymphocytes	1,185 (740-7,260)	770 (400-12,560)	0.87
Monocytes	630 (110-1,320)	520 (10-1,900)	0.62
CD3 ⁺	827 (310-2,066)	436 (284-6,028)	0.89
CD4 ⁺	536 (140-1603)	273 (55-7,132)	0.76
CD8 ⁺	273 (131-856)	180 (64-1,632)	0.80
CD4/CD8 ratio	1.68 (0.46-6.55)	1.87 (0.39-9.71)	0.94
CD16 ⁺ /CD56 ⁺	208 (37-392)	259 (4-1,005)	0.51

NOTE: Levels were determined before administration of first rituximab infusion. Median (range) for absolute circulating levels of total lymphocytes, monocytes, CD3⁺, CD4⁺, CD8⁺, and CD16⁺/56⁺ cells.

This finding may hold particular relevance for the investigation of lenalidomide and rituximab in patients with other types of lymphomas.

An important recognition in this study was the unexpected anemia produced by lenalidomide in patients with WM, particularly the acuity in which such decreases in hematocrit occurred. The mechanism for this finding remains to be clarified but suggests that lenalidomide may aggravate an underlying constitutional genetic defect perhaps central to the pathogenesis of WM itself given the uniqueness of this toxicity in WM patients. The immunomodulatory derivatives of thalidomide including lenalidomide and pomalidomide are known to dampen both erythroid maturation and/or erythroid colony formation in part through down-regulation of GATA-1, GATA-2, EKLF, and Gfi-1b (21, 22). Studies delineating the relative expression levels of these and other red cell transcription factors in stem cells of WM patients may help elucidate this idiopathic finding of lenalidomide-related anemia in this patient population. Unfortunately, despite aggressive dose reduction in lenalidomide, many patients did not tolerate lenalidomide because of faltering hematocrits at the doses and schedule examined in this study. Future trials using lower start doses of lenalidomide or alternative schedules could be considered in WM patients, although in view of the inferior outcomes observed in this trial with lenalidomide versus thalidomide with rituximab, other combinations should be considered, such as with bortezomib.

Lastly, this study underscores the importance of conducting clinical trials in patients with various malignancies, because unexpected toxicities can often occur even among patients considered to have similar diseases. Although lenalidomide is known to produce late neutropenia and thrombocytopenia in patients with multiple myeloma at the same dose levels and schedule used in this study, WM patients experienced unexpected aggravation of anemia as their drug-limiting toxicity. Similarly, we and others have reported unexpected or exaggerated toxicities in WM patients with agents commonly employed in other related B-cell disorders such as the paradoxical IgM spike seen with rituximab or the higher incidence of peripheral neuropathy with bortezomib.

In summary, the results of this study show that lenalidomide at conventional dosing and schedule can produce unexpected and acute declines in hematocrit in patients with WM, which are clinically significant and can result in hospitalizations. Moreover, in comparison with thalidomide and rituximab, the combination of lenalidomide and rituximab produced inferior outcomes in terms of both response rates and TTP in an analogous patient population.

Disclosure of Potential Conflicts of Interest

S.P. Treon, N.C. Munshi, and K.C. Anderson are members of the speakers' bureau of and have received research support from Celgene, Inc. S.P. Treon is also a member of the speakers' bureau of and has received research support from Genentech, Inc.

References

- Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenström's macroglobulinemia: Consensus Panel Recommendations from the Second International Workshop on Waldenström's Macroglobulinemia. *Semin Oncol* 2003;30:110–5.
- Harris NL, Jaffe ES, Stein H. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994;84:1361–92.
- Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: Report of the Clinical Advisory Committee Meeting, Airlie House, Virginia, November 1997. *J Clin Oncol* 1999;17:3835–49.
- Treon SP, Gertz MA, Dimopoulos M, et al. Update on treatment recommendations from the Third International Workshop on Waldenström's Macroglobulinemia. *Blood* 2006;107:3442–6.
- Leleu X, Soumerai JD, Hunter ZR, et al. Increased incidence of transformation and myelodysplasia/acute leukemia in patients with Waldenström's macroglobulinemia treated with nucleoside analogues. *J Clin Oncol* 2008. In press.
- Davies FE, Raju N, Hideshima T, et al. Lenalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. *Blood* 2001;98:210–6.
- Janakiraman N, McLaughlin P, White CA, et al. Rituximab: correlation between effector cells and clinical activity in NHL. *Blood* 1998;92:337a.
- Gluck WL, Hurst D, Yuen A, et al. Phase I studies of interleukin (IL)-2 and rituximab in B-cell non-Hodgkin's lymphoma: IL-2 mediated natural killer cell expansion: correlations with clinical response. *Clin Cancer Res* 2004;10:2253–64.
- Khan KD, Emmanouilides C, Benson DM, et al. A phase 2 study of rituximab in combination interleukin-2 for rituximab-refractory indolent non-Hodgkin's lymphoma. *Clin Cancer Res* 2006;12:7046–53.
- Treon SP, Soumerai JD, Branagan AR, et al. Thalidomide and rituximab in Waldenström's macroglobulinemia. *Blood* 2008. In press.
- Treon SP, Hatjiharissi E, Leleu X, et al. Novel agents in the treatment of Waldenström's macroglobulinemia. *Clin Lymph Myeloma* 2007;7:199–206.
- Kyle RA, Treon SP, Alexanian R, et al. Prognostic markers and criteria to initiate therapy in Waldenström's macroglobulinemia: Consensus Panel Recommendations from the Second International Workshop on Waldenström's Macroglobulinemia. *Semin Oncol* 2003;30:116–20.
- Kimby E, Treon S, Anagnostopoulos A, et al. Update on recommendations for assessing response from the Third International Workshop on Waldenström's Macroglobulinemia. *Clin Lymph Myeloma* 2006;6:380–3.
- Treon SP, Branagan AR, Hunter Z, et al. Paradoxical increases in serum IgM and viscosity levels following rituximab in Waldenström's macroglobulinemia. *Ann Oncol* 2004;15:1481–3.
- Ghobrial IM, Fonseca R, Greipp PR, et al. Initial immunoglobulin M "flare" after rituximab therapy in patients with Waldenström macroglobulinemia: an Eastern Cooperative Oncology Group study. *Cancer* 2004;101:2593–8.
- Treon SP, Mitsiades C, Mitsiades N, et al. Tumor cell expression of CD59 is associated with resistance to CD20 serotherapy in B-cell malignancies. *J Immunother* 2001;24:263–71.
- Dimopoulos MA, Zervas C, Zomas A, et al. Treatment of Waldenström's macroglobulinemia with rituximab. *J Clin Oncol* 2002;20:2327–33.
- Treon SP, Emmanouilides C, Kimby E, et al. Extended rituximab therapy in Waldenström's macroglobulinemia. *Ann Oncol* 2005;16:132–8.
- Treon SP, Hansen M, Branagan AR, et al. Polymorphisms in FcγRIIIA (CD16) receptor expression are associated with clinical responses to rituximab in Waldenström's macroglobulinemia. *J Clin Oncol* 2005;23:474–81.
- Hayashi T, Hideshima T, Akiyama M, et al. Molecular mechanisms whereby immunomodulatory drugs activate natural killer cells: clinical application. *Br J Haematol* 2005;128:192–203.
- Koh KR, Janz M, Mapara MY, et al. Immunomodulatory derivative of thalidomide (IMiD CC-4047) induces a shift in lineage commitment by suppressing erythropoiesis and promoting myelopoiesis. *Blood* 2005;105:3833–40.
- Pomalidomide and lenalidomide regulate erythropoiesis and fetal hemoglobin production in human CD34⁺ cells. *Clin Invest* 2008;118:248–58.

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