

Familial Disease Predisposition Impacts Treatment Outcome in Patients With Waldenström Macroglobulinemia

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Abstract

Familial disease is common in Waldenström macroglobulinemia (WM). We examined the impact of familial disease status on treatment outcome in WM and observed that familial disease was associated with inferior outcomes. However patients with familial WM receiving a bortezomib-containing regimen showed improved treatment outcomes vs. those receiving non-bortezomib-containing regimens. Bortezomib-containing regimens may therefore represent a more optimal treatment approach for patients with familial WM.

Background: We examined the impact of familial predisposition on treatment outcome in 135 patients with Waldenström macroglobulinemia (WM), 26.7% of whom had first- or second-degree relatives with a B-cell lymphoproliferative disorder. **Patients and Methods:** All patients were rituximab naive and received a rituximab-containing regimen. There were no significant differences in baseline characteristics between cohorts. **Results:** Overall response (93.9% vs. 75.0%; $P = .029$) and complete response/very good partial response (CR/VGPR) (23.2% vs. 16.7%; $P < .0001$), time to progression (TTP) (45.5 vs. 21 months; $P = .015$) and time to next therapy (TTNT) (50.0 vs. 33.0 months; $P = .024$) favored patients with sporadic WM. By multivariate analysis, familial predisposition was an independent marker for disease progression (hazard ratio, 0.554). Patients with familial but not sporadic disease exhibited better responses, including CR/VGPR attainment ($P = .0006$) and a trend for longer progression-free survival (> 33 vs. 20.6 months; $P = .08$), with bortezomib-containing therapy. **Conclusion:** The findings convey that familial predisposition is an important determinant of treatment outcome in WM. Prospective studies to confirm these observations are needed.

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Introduction

Familial predisposition is commonly observed in many B-cell malignancies, including Waldenström macroglobulinemia (WM).¹⁻⁶ In a series of 1948 patients who were prospectively evaluated, Brown et al reported that 12.6% of probands with non-Hodgkin lymphoma, 17.5% of probands with chronic lymphocytic leukemia, and 11.9%

of probands with Hodgkin lymphoma had first- or second-degree relatives with a B-cell lymphoproliferative disorder.⁵ By comparison, in a series of 924 consecutive patients seen at the same institution, Hanzis et al observed that 27.5% of probands with WM had first- or second-degree relatives with a B-cell lymphoproliferative disorder.⁷ The influence of familial disease predisposition on therapeutic outcome remains to be delineated in WM. As such, we investigated the impact of familial disease status on treatment outcome in a cohort of 135 rituximab-naive patients with WM who received a rituximab-containing regimen. Their outcomes relative to those patients with sporadic WM disease are reported in this study.

Patients and Methods

Patients with a consensus diagnosis of WM who were rituximab naive, whose familial disease status was known, and who received a

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rituximab-containing regimen as part of a clinical study whose outcome was known were included in this analysis.⁸⁻¹² The study was approved by the Dana Farber Cancer Institute/Harvard Cancer Center Institutional Review Board. Response determinations were made using modified response criteria that included very good partial responses (VGPRs).^{13,14} A complete response (CR) was defined as resolution of all symptoms, normalization of serum IgM levels with complete disappearance of IgM paraprotein by immunofixation, a bone marrow biopsy demonstrating no evidence of disease, and resolution of any adenopathy or splenomegaly. VGPR, partial response (PR), and minor response were defined as achieving a $\geq 90\%$, 50% to 89%, and 25% to 49% reduction in serum IgM levels, respectively. Major response was defined as PR or better. Progressive disease occurred with $\geq 25\%$ increase in the serum IgM level from the lowest attained response value or progression of clinically significant disease-related symptoms. Time to progression (TTP) and time to next therapy (TTNT) were calculated from the start of therapy using the Kaplan-Meier method. The primary objective of this study was to assess the impact of familial disease status on attainment of best overall response and categorical response, as well as progression-free survival (PFS) and TTNT. Familial disease status was also assessed by multivariate analysis using known covariates for disease progression, ie, advanced age (≥ 65 years), serum β_2 -microglobulin level, serum IgM level, hemoglobin value, and International Prognostic System Score for WM (IPSSWM).

Statistical Analysis

Comparison of treatment outcomes was performed using a 2-tailed Student *t* test on Microsoft Excel software (Microsoft Corp, Redmond, WA). Nonparametric testing was performed by Fisher exact *t* tests (Vassar Stats, <http://www.vassarstats.net/>). Kaplan-Meier curves for PFS and TTNT were plotted and compared with the use of the log-rank test. Factors predictive for disease progression were compared by means of the Cox proportional hazards model using multivariate analysis. A *P* value $\leq .05$ was deemed to be significant for all comparisons. Either *P* value or indication of nonsignificance is denoted in text and figures.

Results

Baseline Patient Characteristics

Baseline patient characteristics by familial disease status are depicted in Table 1; they showed no significant differences in median age, serum IgM levels, hemoglobin value, platelet count, serum β_2 -microglobulin levels, IPSSWM, and treatment type. All patients were rituximab naive and received combination therapy including rituximab with either cyclophosphamide (*n* = 58 [3.0%]), fludarabine (*n* = 21 [15.6%]), an immunomodulatory agent (*n* = 35 [25.9%]), or bortezomib (*n* = 21 [15.6%]) as previously reported.⁸⁻¹²

Impact of Familial Disease Status on Treatment Response

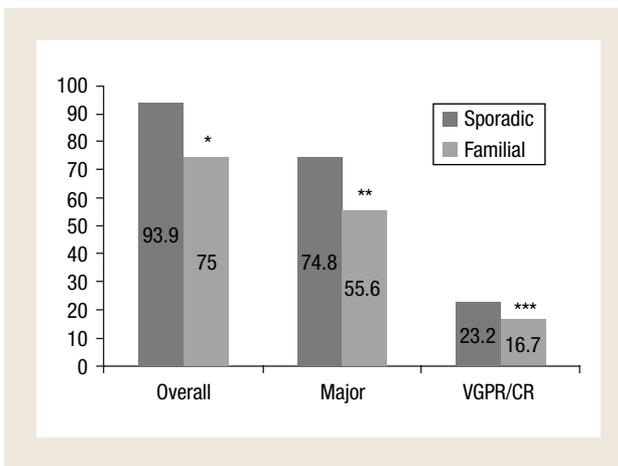
Overall, major and VGPR/CR categorical responses were significantly better among patients with sporadic vs. familial disease (Figure 1). Patients with sporadic WM also exhibited better TTP and TTNT (Figure 2). Median TTP was 45.5 and 21.0 months (*P* = .01) and TTNT was 50.0 and 33.0 months (*P* = .02) for patients with spo-

Table 1 Baseline Patient Characteristics by Familial Disease Status^a

Variable	Familial WM	Sporadic WM
(N)	36	99
Age (y)	63 (47-83)	62 (32-86)
Serum IgM (mg/dL)	3230 (458-10,500)	3690 (551-12,400)
Hemoglobin (g/dL)	10.1 (8-15.1)	10.7 (7.1-17.1)
Platelet Count ($\times 10^9/L$)	233 (65-568)	239 (42-597)
Serum β_2M (mg/L)	3.0 (1.0-13.7)	3.2 (1.2-8.8)
WM IPSS	2 (1-3)	2 (1-3)

Abbreviations: β_2M = β_2 -microglobulin; IPSSWM = International Prognostic System Score for Waldenström Macroglobulinemia; WM = Waldenström macroglobulinemia.
^a *P* = not significant for all comparisons.

Figure 1 Overall Response, Major Response, and Very Good Partial Response/Complete Response (VGPR/CR) for 135 Rituximab-Naive Patients with WM and Sporadic or Familial Disease Who Received a Rituximab-Containing Regimen (**P* = .03; ***P* = .03; ****P* < .001 for differences in categorical responses between patients with familial and sporadic WM)



radic and familial disease, respectively. There were insufficient events to permit for an informative overall survival analysis. Eight and 4 deaths were recorded among sporadic and familial patients, respectively, during the follow-up period of this study (*P* = .89).

Predictive Markers for Disease Progression

We next examined previously established predictive markers along with familial disease status for impact on disease progression by multivariate analysis. Advanced age, serum IgM levels, hemoglobin value, platelet count, serum β_2 -microglobulin levels, and IPSSWM score did not predict for disease progression. In contrast, familial disease status served as an independent marker for disease progression (Table 2).

Impact of Treatment Type on Clinical Outcome in Patients With Familial WM

We next assessed whether the type of treatment used impacted therapeutic outcome in patients with familial WM. Overall re-

Figure 2 Time to Progression (TTP) and Time to Next Therapy (TTNT) for 135 Rituximab-Naive Patients With WM and Sporadic or Familial Disease Who Received a Rituximab-Containing Regimen ($P = .02$ and $P = .01$ for differences between patients with familial and sporadic WM for TTP and TTNT, respectively)

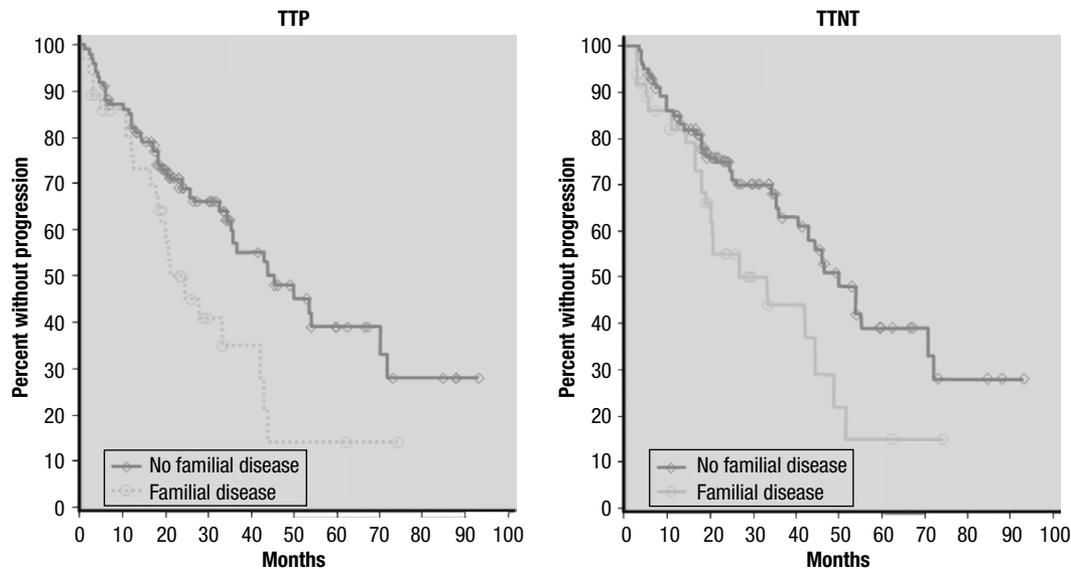


Table 2 Impact of Familial Disease Status on Risk of Disease Progression by Univariate and Multivariate Analyses^a

Parameter	DF	Parameter Estimate	Standard Error	χ^2 Test	Pr > χ^2	Hazard Ratio
Univariate Analysis						
Familial disease	1	-0.66490	0.26764	6.1717	0.0130	0.514
IPSSWM	1	0.20736	0.15232	1.8531	0.1734	1.230
Multivariate Analysis						
Familial disease	1	-0.59016	0.27386	4.6438	0.0312	0.554
Age	1	-0.02276	0.01320	2.9712	0.0848	0.977
Serum IgM	1	0.0000498	0.0000573	0.7538	0.3853	1.000
Serum B ₂ M	1	0.13171	0.05077	6.7293	0.0095	1.141
Hemoglobin	1	0.08309	0.07579	1.2018	0.2730	1.087

Abbreviations: B2M = β_2 -microglobulin; DF = Degrees of Freedom; IPSSWM = International Prognostic Scoring System for Waldenström Macroglobulinemia; PRsquared = partial correlation coefficient squared.

^aTo control for collinearity, IPSSWM was not included in multivariate analysis because covariates for IPSSWM consist of age, serum IGM, serum B2M, and hemoglobin.¹⁶

sponse, major response, and CR/VGPR were better among patients with familial but not sporadic WM who received a bortezomib-containing vs. a non-bortezomib-containing regimen (Figure 3). A longer TTP was also observed for patients with familial but not sporadic WM who received a bortezomib-containing vs. a non-bortezomib-containing regimen (Figure 4). For patients with familial disease, the median TTP was estimated at > 33 vs. 20.6 months for bortezomib-containing and non-bortezomib-containing therapy, respectively ($P = .08$). For patients with sporadic WM, the median TTP was estimated at > 35 vs. 45.5 months for bortezomib-containing and non-bortezomib-containing therapy, respectively ($P = .68$).

Discussion

Although familial predisposition is commonly encountered among patients with WM, its impact on treatment outcome has not been addressed. We therefore undertook this study to clarify the impact of familial disease predisposition on treatment outcome in WM. The strengths of the study are a relatively large population of patients with WM whose proportion of familial to sporadic patients is similar to that reported in a previous large series of patients with WM,⁷ similar baseline characteristics and treatments between cohorts, inclusion of patients with well-documented treatment outcomes and long-term follow-up, and exposure to standard therapeu-

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Figure 3 Overall Response Rate (ORR), Major Response, and Very Good Partial Response/Complete Response (VGPR/CR) for 135 Patients With WM With Sporadic (A) or Familial (B) Disease Who Received Either a Bortezomib-Containing or a Non-Bortezomib-Containing Regimen (* $P = .05$ and ** $P = .0006$ among patients with familial WM who received bortezomib-containing vs. non-bortezomib-containing therapy)

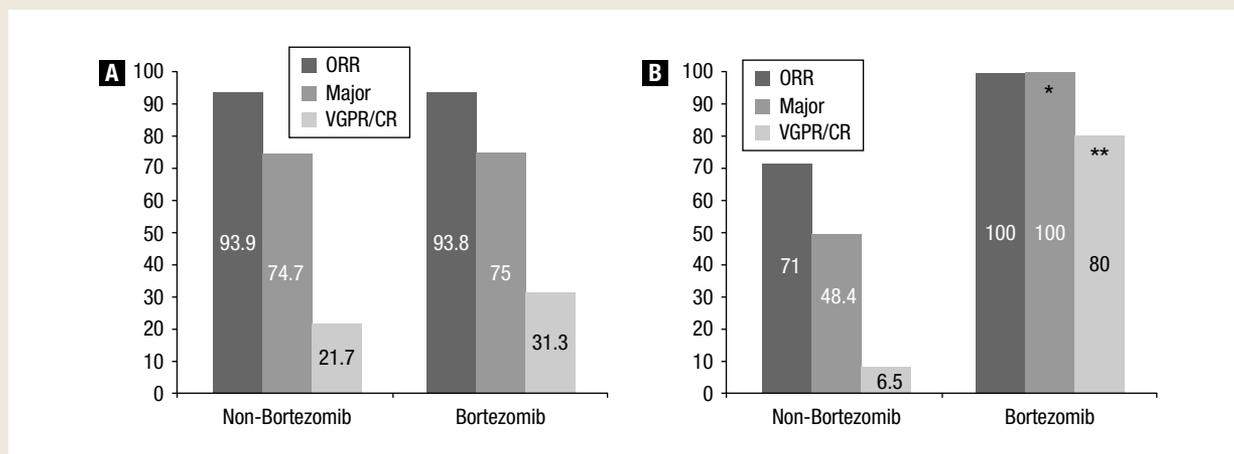
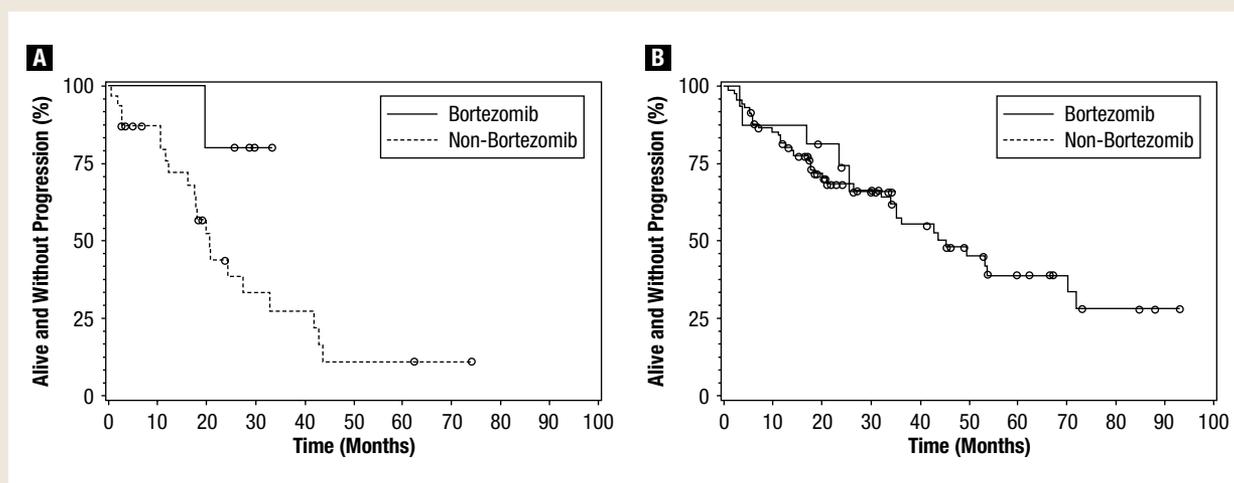


Figure 4 Time to Progression (TTP) for Patients With Familial (A) and Sporadic (B) WM Who Received Bortezomib-Containing (straight line) or Non-Bortezomib-Containing (dotted line) Combination Therapy ($P = .08$ and $P = .68$ for differences between patients with familial and those with sporadic WM for TTP, respectively)



tic regimens typically used in WM therapy. Nonetheless, the retrospective nature of this study may not account for all biases, and therefore the interpretation of these study results should be taken in this context.

Important to the findings of this study are the inferior treatment outcomes observed in patients with familial disease predisposition. These findings included inferior attainment of overall response, major response, and VGPR/CR and shorter TTP and TTNT for patients with familial WM in comparison with patients with sporadic WM. An insufficient number of events occurred during the follow-up period for a meaningful overall survival analysis. The impact of familial disease on overall survival has been examined by others in

patients with other B-cell malignancies and did not show any survival differences.^{3,6} Those studies, however, examined overall survival in patients who largely received treatment before the availability of monoclonal antibody therapy; the population of patients in this study all received rituximab-based therapy. As such, the outcome of those studies may not reflect current survival trends. Invariably, longer term follow-up will be required to clarify the impact of familial predisposition on overall survival in patients with WM.

An unexpected finding in this study was the impact of treatment type on outcome in patients with familial WM. Patients with familial WM who received bortezomib-containing therapy had better responses, as well as a trend for longer TTP than did those patients who

received non-bortezomib-containing therapy, a finding not observed among patients with sporadic WM. Although the sample size for this analysis was moderate, the findings are provocative and warrant further examination in prospective clinical trials. A positive outcome of such studies could signal the use of familial predisposition as a predictive marker and the use of proteasome-based therapy for this patient population. These findings may also be revealing of signaling pathways that are present in patients with familial WM and amenable to select targeting by proteasome inhibition. Differences in tumor transcriptional regulatory factors between patients with familial WM and those with sporadic WM have been described,¹⁵ although their relative impact on disease biological characteristics and treatment outcome still remain to be clarified.

In summary, the findings of this study convey that familial disease predisposition is an important determinant of response, TTP, and TTNT in patients with WM. Treatment with bortezomib-containing rituximab therapy is also associated with better therapeutic outcomes in patients with WM with familial disease predisposition. Prospective studies to confirm these observations are needed.

Clinical Practice Points

- Numerous reports have confirmed the existence of familial disease predisposition in WM.
- Up to 26% of patients with WM have a first- or second-degree relative with either WM or a closely related B-cell disorder.
- The clinical significance for the presence of familial disease predisposition has not been previously addressed.
- In this study, we examined the outcome of patients with WM who received a rituximab-containing regimen in a previously reported clinical study.
- Response rates, PFS, and TTNT were inferior for those patients with familial disease predisposition.
- Subset analysis showed that those individuals with familial disease predisposition who received a bortezomib-containing regimen showed treatment outcomes that were better than those of patients who received non-bortezomib-containing regimens.
- The results of this study strengthen the need for clinicians to extract a good family history in patients with WM and to consider the impact of familial disease predisposition in treatment outcome, including choice of treatment.
- Patients with familial WM may experience better treatment outcomes with a bortezomib-containing regimen, and prospective clinical studies should consider including familial disease predisposition as a determinant for treatment outcome.

Author Contributions

S.P.T. conceived and designed the study and wrote the manuscript. C.H., L.I., C.T., R.J.M., C.J.P., and Z.R.H. performed the

data analysis. S.P.T. and P.S. provided patient care and obtained consent. B.T. performed statistical analysis.

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