Treatment with a bortezomib-containing regimen is associated with better therapeutic outcomes in patients with Waldenstrom's Macroglobulinemia who have familial disease predisposition.

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BACKGROUND

We examined the impact of familial predisposition on treatment outcome in 135 Waldenstrom's macroglobulinemia (WM) patients, 26.7% of whom had first or second degree relative(s) with a B-cell lymphoproliferative disorder. All patients were rituximab-naïve and received a rituximab-containing regimen. There were no significant differences in baseline characteristics between cohorts. Overall (93.9% vs. 75.0%; p=0.029) and CR/VGPR (23.2% vs. 16.7%; p<0.0001) responses, time to progression (45.5 vs. 21 months; p=0.015), and to next therapy (50.0 vs. 33.0 months; p=0.024) favored sporadic patients. 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=0.0006), and a trend for longer progression free survival (>33 versus 20.6 months, p=0.08) with bortezomib containing therapy. The findings convey that familial predisposition is an important determinant of treatment outcome in WM. Prospective studies to confirm these observations are needed.

PATIENTS AND METHODS

Patients with the consensus diagnosis of WM, who were rituximab-naïve, whose familial disease status was known, and who received a rituximab containing regimen as part of a clinical study whose outcomes were known were included in this analysis. One hundred fifty nine patients were included in these 5 clinical studies, with familial cancer history available for 135 (85%) of these patients. 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 best overall (ORR) and categorical response attainment, as well as PFS and TTNT. Familial disease status was also assessed by multivariate analysis utilizing known covariates for disease progression, i.e. advanced age (>65), serum B2M level, serum IgM level, hemoglobin, and WM International Prognostic System Score (WM IPSS).

Impact of familial status in rituximab-naïve patients receiving a rituximab containing regimen.

Baseline patient characteristics by familial disease status

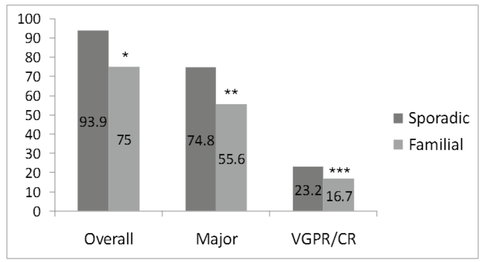
	Familial WM (n=36)	Sporadic WM (n=99)
Age (yrs)	63 (47-83)	62 (32-86)
Serum IgM (mg/dL)	3,230 (458-10,500)	3,690 (551-12,400)
Hemoglobin (g/dL)	10.1 (8-15.1)	10.7 (7.1-17.1)
Platelet count (x10^9/L)	233 (65-568)	239 (42-597)
Serum B_2M (mg/L)	3.0 (1.0-13.7)	3.2 (1.2-8.8)
WM IPSS	2 (1-3)	2 (1-3)

WM IPSS= WM International Prognostic System Score.
p=NS for all comparisons.

Categorical Responses in WM

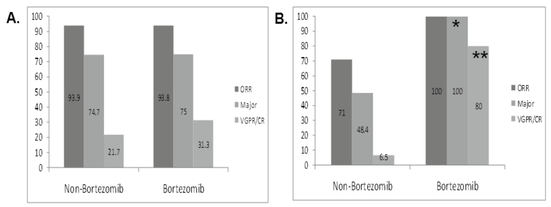
- **Complete response (CR)** was defined as having resolution of all symptoms, normalization of serum IgM levels with complete disappearance of IgM paraprotein by immunofixation, a bone marrow biopsy demonstrating no evidence of disease, and resolution of any adenopathy or splenomegaly.
- **Very good partial (VGPR) responses** were defined as achieving a ≥ 90% reduction in serum IgM levels.
- **Partial (PR) responses** were defined as achieving a 50-89% reduction in serum IgM levels.
- **Minor (MR) responses** were defined as achieving and 25-49% reduction in serum IgM levels.
- **Major response** was defined as PR or better.
- **Progressive disease** occurred with ≥ 25% increase in serum IgM level from the lowest attained response value or progression of clinically significant disease related symptom(s).

Overall, major, and VGPR/CR responses for 135 rituximab naïve WM patients with sporadic or familial disease who received a rituximab containing regimen.



**p=0.03; **p=0.03; ***p<0.001 for differences in categorical responses between familial and sporadic WM patients.*

Overall, major, and VGPR/CR responses for 135 WM patients with sporadic (A) or familial (B) disease who received either bortezomib or a non-bortezomib containing regimen.



**p=0.05; and **p=0.0006 among familial WM patients who received bortezomib versus non-bortezomib containing therapy.*

RESULTS

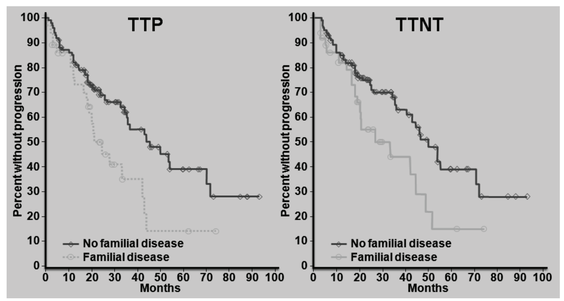
Patients received combination therapy including rituximab with either cyclophosphamide (n=58; 43.0%); fludarabine (n=21; 15.6%); an immunomodulatory agent (n=35; 25.9%); or bortezomib (n=21; 15.6%). The median follow-up for all patients was 33.2 months, and did not differ between familial and sporadic patients (p=0.63).

Impact of Familial Disease Status on Treatment Response: Median TTP was 45.5 and 21.0 months (p=0.01), and TTNT was 50.0 and 33.0 months (p=0.02) for patients with sporadic and familial disease. There were insufficient events to permit for an informative overall survival analysis. Eight and 4 deaths were recorded among sporadic and familial patients during the follow-up period of this study (p=0.89).

Predictive markers for disease progression: We examined previously established predictive markers along with familial disease status for impact on disease progression by multivariate analysis. Neither advanced age, serum IgM, hemoglobin, platelet count, serum B2M, or WM IPSS score predicted for disease progression. In contrast, familial disease status served as an independent marker for disease progression.

Impact of treatment type on clinical outcome in familial WM patients: We assessed if the type of treatment used impacted therapeutic outcome in familial WM patients. For patients with familial disease, the median TTP was estimated at >33 versus 20.6 months for bortezomib and non-bortezomib containing therapy, respectively (p=0.08). For sporadic WM patients, the median TTP was estimated at >35 versus 45.5 months for bortezomib and non-bortezomib containing therapy, respectively (p=0.68).

Time to progression (TTP) and to next therapy (TTNT) for 135 rituximab naïve WM patients with sporadic or familial disease who received a rituximab containing regimen.



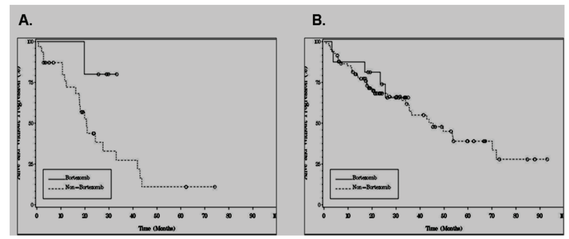
p=0.02 and p=0.01 for differences between familial and sporadic WM patients for TTP and TTNT, respectively.

Familial Disease Status in WM is an Independent Prognostic for PFS.

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Fam Disease	1	-0.59016	0.27386	4.6438	0.0312	0.554
Age	1	-0.02276	0.01320	2.9712	0.0848	0.977
sIgM	1	0.0000498	0.0000573	0.7538	0.3853	1.000
sB_2M	1	0.13171	0.05077	6.7293	0.0095	1.141
Hgb	1	0.08309	0.07579	1.2018	0.2730	1.087

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Fam Disease	1	-0.66490	0.26764	6.1717	0.0130	0.514
IPSS	1	0.20736	0.15232	1.8531	0.1734	1.230

Time to progression (TTP) for patients with familial (A) and sporadic (B) WM who received bortezomib (straight line) or non-bortezomib (dotted line) combination therapy.



p=0.08 (A) and p=0.68 (B) for differences between familial and sporadic WM patients for TTP, respectively.

CONCLUSIONS

- Familial predisposition is common in patients with WM, with 26.7% of patients in this series having a first/second degree relative with a B-cell lymphoproliferative disorder.
- Familial predisposition is associated with inferior response rates, TTP and TTNT in rituximab naïve WM patients who received a rituximab containing regimen.
- By multivariate analysis, familial predisposition was an independent prognostic marker.
- Patients with familial predisposition who received a bortezomib containing regimen had better responses, including attainment of CR/VGPR, and a trend for longer TTP.
- The results of this study suggest that patients with familial disease may have better therapeutic outcomes with a bortezomib containing rituximab regimen.

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