Survival in Monoclonal Gammopathy of Undetermined Significance and Waldenström Macroglobulinemia

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Clinical Lymphoma, Myeloma & Leukemia, Vol. 13, No. 2, 187-90 © 2013 Elsevier Inc. All rights reserved.

Keywords: Bortezomib, Fludarabine, Lymphoplasmacytic lymphoma survival, MGUS, Prognosis, Rituximab, Thalidomide, Treatment, Waldenström macroglobulinemia

Abstract
Monoclonal gammopathy of undetermined significance (MGUS) of IgM type is the strongest risk factor for the development of Waldenström macroglobulinemia (WM). The clinical management of WM has changed considerably over recent years, which is reflected in the use of new therapeutic agents (eg, purine analogues, monoclonal antibodies, and thalidomide- and bortezomib-based therapies), risk-and-response–adjusted stratification of treatments, and improvement in supportive care measures. However, because of the rarity of WM, there are few phase III randomized clinical studies to guide therapy and evaluate overall survival. In this review, we discuss the current knowledge on prognosis, survival patterns, and causes of death in individuals with MGUS. In addition, we discuss clinical studies as well as recent population-based studies on WM, with a focus on treatment, prognostic factors, and survival. Finally, new agents and future perspectives in these disorders are reviewed.

Introduction
Lymphoplasmacytic lymphoma (LPL) is characterized by small B lymphocytes, plasmacytoid lymphocytes, and plasma cells and usually involves bone marrow and sometimes lymph nodes and spleen. Waldenström macroglobulinemia (WM) is found in a large subset of patients with LPL and is defined as LPL in the bone marrow with a detectable IgM monoclonal gammopathy.1-3 Recently, Treon et al4 identified MYD88 L265P as a commonly recurring somatic mutation in patients with WM. Based on long-term follow-up by the Mayo Clinic, the strongest risk factor for WM is the presence of monoclonal gammopathy of undetermined significance (MGUS) of type IgM.5

Survival of Patients With MGUS
There are many published studies on the risk for the development of lymphoproliferative tumors after a diagnosis of MGUS; however, limited data are available on survival patterns among patients with MGUS.5-7 Data from the Mayo Clinic showed that the median survival of patients with MGUS was about 45% lower at 15 years of follow-up than that of a comparable population.6 In a study of 1324 patients with MGUS diagnosed in Denmark from 1978 to 1993, a 2-fold higher mortality rate was observed when compared with the general population.6 In addition, a single-center study from the Netherlands that included 1464 patients with MGUS reported survival inferior to that of a matched cohort.7 We conducted a large population-based study in Sweden based on 4259 patients with MGUS (diagnosed 1986-2005) and 16,151 matched controls.9 After a median follow-up of 5.6 years, there were 1565 (37%) deaths observed among the patients with MGUS. We found MGUS to be associated with inferior survival, which was reflected in cumulative relative survival rates for patients with MGUS of 0.93 after 5 years and 0.82 after 10 years (Figure 1). The major causes of excess mortality were multiple myeloma (MM), WM, amyloidosis, and other lymphoproliferative diseases.9 Furthermore, compared with controls, we found patients with MGUS to have an increased risk of death from ischemic heart disease, other heart disorders, liver diseases, bacterial infections, and benign hematologic disorders. Previous studies have reported the dominant causes of death among patients with MGUS to be hematologic malignancies, cardiovascular diseases, infections, and solid tumors.8,10

Age is an important predictor of prognosis, with younger age at MGUS diagnosis associated with significantly lower excess mortality in most but not all studies.7,9 The main causes of death in the younger patients in our study were lymphoproliferative malignancies, liver disorders, and amyloidosis, whereas cardiovascular diseases dominated in elderly patients with MGUS.9 It should be pointed out that the majority
of patients with MGUS are diagnosed as a result of a clinical investigation for various symptoms; thus the underlying mechanisms for the observed mortality and cause of death pattern may be causally related to the MGUS or explained by an underlying disease.

We found IgM (vs. IgG/IgA) MGUS to be associated with superior survival (P = .038). In the Dutch study, however, no difference in survival by MGUS subtype was observed. Contraindicatory to our findings, IgM MGUS has been reported to have a higher risk of malignant transformation compared with IgG MGUS. In our study, we found similar cause of death patterns by MGUS subtype, except that most patients with WM as a cause of death had IgM MGUS and those who died from MM typically had IgG/IgA MGUS. High M-protein concentration at MGUS diagnosis has been reported to predict a poor outcome in MM and MGUS; however, we did not observe differences in survival by concentration of the M-protein, in accordance with another MGUS study.

### Survival of Patients with WM

Asymptomatic patients with WM can be followed clinically without specific therapy. Based on a study of 48 patients at the Mayo Clinic, the overall survival of asymptomatic patients with WM was 83% at 5 years and 50% at 9.6 years. Recently, the International Scoring System for WM identified older age, low hemoglobin value, low platelet count, high β₂-microglobulin level, and high M-protein concentration as 5 adverse variables in patients with WM, with clearly defined criteria for initiation of treatment and 5-year survival rates of 87%, 68%, and 36% in patients with low-risk, intermediate-risk, and high-risk disease, respectively.

There is no standard of care for WM because of the lack of randomized phase III clinical trials to guide therapy; therefore, treatment decisions are based mainly on results from phase II trials and expert recommendations. The clinical management of WM has changed considerably over recent years, which is reflected in the use of new therapeutic agents (eg, purine analogues, monoclonal antibodies, and thalidomide- and bortezomib-based therapies), risk-and-response stratification of patients, as well as improvement in supportive care measures. Treatment should be initiated only in the presence of symptoms related to the disease, and therapy is directed toward prevention and/or symptomatic treatment of the associated clinical symptoms. First-line treatment of patients with symptomatic WM has traditionally been based on single-agent therapy with alkylating agents (chlorambucil, cyclophosphamide) or purine analogues (fludarabine, cladribine). These agents can be used in older individuals and have response rates of 30% to 80%, depending on whether they are used as primary treatment or in relapsed disease. Rituximab has been shown to have single-agent activity and induces responses in 44% of patients with WM. During recent years, combination therapies have resulted in good overall response rates but low complete response rates. Also, treatment with novel agents such as thalidomide and bortezomib, both as single agents and in combination with other drugs, is effective in WM.

Median overall survival has varied in different series, ranging from 60 to 120 months. We conducted a large population-based cohort study including 1555 patients with LPL and WM diagnosed in Sweden from 1980 to 2005 (with follow-up through 2007) and found that 1- and 5-year relative survival rates improved significantly during the study period in all age groups (Figure 2). Patients diagnosed in the last (2001-2005) calendar period had significantly lower excess mortality compared with patients diagnosed in the preceding periods. A trend toward an improvement in survival was found in patients with WM treated with rituximab-containing first-line therapy in a study comparing patients with WM treated in private oncology practices and patients treated in a university hospital in Germany. In contrast, in a study from Greece in symptomatic patients with WM, no improvement in survival was observed when survival of 130 patients with WM diagnosed from 1985 to 1999 was compared with survival of 215 patients with WM diagnosed after 2000. Although one cannot exclude lead-time bias (increase in asymptomatic cases being diagnosed) as a contributing factor, our findings suggest that the increase in available agents in the treatment of patients with LPL and WM, and possibly improvement in supportive care, contributed to the improvement in survival in our study.
As has been observed in other studies, older age at diagnosis was associated with higher excess mortality in our study. The underlying factors are probably a combination of contributing factors such as comorbidity, more advanced disease at diagnosis, and the fact that elderly patients are not able to tolerate aggressive treatment. Importantly, even patients in the oldest category had improved survival over time, indicating that despite having poorer survival than younger patients, the improvement in management of patients with LPL and WM has also been beneficial for these elderly patients. This has not been observed, eg, in population-based studies of patients with MM.

**Future Directions**

With recent advances in our understanding regarding the biological characteristics of MGUS and WM, we will hopefully use molecular diagnostics and prognostics, together with more targeted designed drugs and integrated molecular monitoring, in the management of these diseases. In WM, an important clinical challenge is to define the optimal sequence and combinations of available drugs. New drugs with novel mechanisms of action, such as PI3K/AKT/mTOR inhibitors (everolimus and perifosine), bendamustine, monoclonal antibodies such as alemtuzumab and epratuzumab, and histone deacetylase inhibitors, are currently being evaluated for the treatment of WM. Based on the recent discovery by Treon et al that MYD88 L265P is a commonly recurring somatic mutation in patients with WM, an exciting and rational future strategy could be to develop WM treatment trials using inhibitors of IRAK4 kinase and other components of the same pathway.

**Disclosure**

The authors have stated that they have no conflicts of interest.

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