Competing risk survival analysis in patients with symptomatic Waldenström macroglobulinemia: the impact of disease unrelated mortality and of rituximab-based primary therapy

WM is a disease of the elderly with a protracted course in many patients and a median survival of 7 to 10 years,[1] however, in many patients, other factors rather than WM or its treatment may be the cause of death.[2] Non-WM-related mortality mainly affects outcomes of elderly patients and is a confounding factor in the assessment of the aggressiveness of the disease, the interpretation of survival data for the assessment of the efficacy of various therapies or prognostic models. Non-cancer-related and cancer-related death are competing failure events, and their analysis is recommended[3-4] in order to facilitate decision making, allocate health resources, understand the outcomes of chronic conditions and to inform patients of the risks associated with their disease and other concomitant conditions. Thus, we analyzed the survival of a large cohort of patients with symptomatic WM accounting for unrelated deaths as a competing factor in order to evaluate disease related survival, current prognostic tools and contemporary treatments.

The analysis included 408 consecutive patients with symptomatic WM who received therapy within 15 centers of the Greek Myeloma Study Group from April 1982 until February 2013; 23 patients were excluded from the analysis due to missing data. Symptomatic disease was defined based on the criteria published after the 2nd Workshop in WM,[5] which were also retrospectively applied to patients who started therapy before 2003.

The cause of death and the relation to WM was assessed by the treating physicians. WM-related causes of death were those occurring due to progressive disease, transformation (to MDS or DLBCL), infections or treatment-related complications. Patients who died while their disease was in remission, off treatment, due to causes such as stroke, myocardial infarction or a second cancer (prostate, lung, pancreas or colon cancer) and without evidence of disease progression or relapse during this period were rated as "unrelated deaths".

Survival was calculated from the date of initiation of therapy until date of death or last contact. Cumulative incidence function curves for related and unrelated deaths were plotted, and the statistical significance of a prognostic factor in the cumulative incidence analysis was assessed as previously proposed[6,7] using R (R: The R Project for Statistical Computing) and STATA-12 (StataCorp, TX, USA).

Patients' characteristics are depicted in Table 1. Median follow up is 5.5 years (range 2-20 years); 52% (n=211) of the patients have died and 23% (n=49) of deaths were unrelated to WM, mainly due to cardiovascular causes (coronary heart disease or stroke) or non-hematologic malignancies (lung, prostate, colon or pancreatic cancer). The 5-year and 8-year overall survival (OS) was 72% and 54% respectively and the median OS was 8.8 years. The 5-year WM-related death rate was 21.4% (95%CI 17-26%) and the non-WM-related death rate was 7.6% (95%CI 5-10.5%); the 8-year WM-related death rate was 32% (95%CI 27-37%) and the unrelated death rate was 11.5% (95%CI 8-15%) (Figure 1A).

The median crude survival of patients >75 years was 5.3 *vs.* 9.7 years for patients ≤75 years (P<0.001). The 5-

Table 1. Characteristics of the 408 patients included in the analysis.

N=408	All patients	Before 2000	After 2000	*P*
Age (Median)	68	65	70	<0.001
>75 years	21%	13%	25%	<0.001
<50 years	9%	11%	8%	0.215
Indication for therapy				
Cytopenias	43%	39%	45%	
Hyperviscosity	18%	16.5%	18.5%	
B-symptoms	8%	7%	9%	
Organomegaly	11%	16%	8%	0.340
Cryoglobulinemia	1.5%	1.5%	1.5%	
Neuropathy	6%	2.5%	7.5%	
Other	12.5%	14%	12%	
IPSS				
Low	22%	36.5%	17%	<0.001
Intermediate	41%	25.5%	41%	
High	37%	38%	42%	
Hemoglobin<11.5 gr/dl	75%	74%	76%	0.652
Platelets < 100 x 10^9/L	11.5%	11.5%	11.5%	0.998
β-2 m >3 mg/dl	54%	42%	57%	0.024
sAlbumin<3.5 gr/dl	52%	55%	50.5%	0.421
LDH> 250 IU/L	18%	21%	16.5%	0.274
Primary Tx Rituximab	55%	4%	79%	
Primary Tx Alkylators	43%	92%	20%	<0.001
Primary Tx NAs*	2%	4%	1%	
IgM reduction >50%	59%	63%	58%	0.361

**NAs: Nucleoside analogues.*

Table 2. Multivariable analysis for WM-related and non-WM-related death as competing events.

	WM-related			non-WM-related death		
	HR	95% CI	P	HR	95% CI	P
Rituximab-based Primary therapy (*vs.* Non-rituximab)	0.73	0.58-0.93	0.013	1.17	0.86-1.6	0.322
Age > 75 years (*vs.* age ≤ 75 years)	1.15	0.74-1.79	0.524	2.38	1.16-4.9	0.018
Initiation of therapy after 2000 (*vs.* before 2000)	0.958	0.59-1.53	0.859	0.77	0.33-1.83	0.563
ISSWM						
Low	1			1		
Intermediate	1.47	1 -2.6	0.05	2.32	0.7-7.7	0.169
High	2.45	1.47-3.89	0.001	3.08	0.89-10.8	0.077

year WM-related death rate was 22% (95%CI 13-32%) for patients >75 years *vs.* 21% (95%CI 16-26%) for patients ≤75 years (*P*=0.193) while the 5-year non-WM-related death rate was 17% (95%CI 10-27%) *vs.* 5.1% (3-8%) respectively (*P*<0.001) (Figure 1B).

ISSWM was formulated based on the overall survival of a cohort of patients with a median age of 67 years, but the cause of death was not assessed.[8] In our patients, ISSWM discriminated 3 groups with different 5-year WM-related mortality rates (10%, 19% and 27% for the three ISSWM risk groups, *P*=0.03), while the 5-year non-WM-related death rate was 1.5%, 5% and 14% respectively (*P*=0.003) (Figure 1C), probably due to the inclusion of older patients in the intermediate and high risk groups. The 5-year WM-related mortality rate was 31% for patients with serum albumin <3.5 gr/dl *vs.* 14% if ≥3.5 gr/dl (*P*<0.001), while the rates of unrelated deaths were 9% *vs.*6% respectively (*P*=0.81). WM-related mortality at 5-years was 40% for patients with LDH≥250 IU/L (ULN<225 IU/L) *vs.* 19% for LDH<250 IU/L (*P*<0.001), while the rates of unrelated deaths were 7% in both (*P*=0.44).

We also examined whether the survival of patients with WM has improved since 2000, when rituximab became widely available. Patients who started therapy after 2000 were older (median age 70 *vs.* 65 years, *P*<0.001) and thus, more often had ISSWM high and intermediate risk disease (*P*<0.001). Only 4% of patients before 2000 *vs.* 79% of patients after 2000 received primary therapy with rituximab (Table 1). The median crude survival rate for patients who started therapy before and after 2000 was similar (9 *vs.* 8.1 years, *P*=0.474). The 5-year WM-related death rate was 21% for both groups, but the 5-year unrelated death rate was 4.6% *vs.* 9.1% for patients before and after 2000 (*P*=0.026). However, additional follow up is needed in order to evaluate the WM-related risk of death at later time points (at 10 or 15 years).

We found no significant difference in the crude mortality between patients who received primary therapy with rituximab *vs.* those who did not (5-year OS was 72% *vs.* 67% respectively, *P*=0.68). However, the 5-year WM-related death rate was 28% for patients who did not receive primary therapy with rituximab *vs.* 19% for patients who received rituximab-based primary therapy (*P*=0.02), while the respective 5-year non-WM-related death rate was 5% *vs.* 9% (*P*=0.004)(Figure 1D). Because more elderly patients have received primary therapy with rituximab (24% *vs.* 14% were older than 75 in the two groups, *P*=0.01) we performed a multivariate analysis in which rituximab-based primary therapy was independently associated with a significant reduction of the risk of WM-related death (Table 2). There was no significant impact regarding the era of the initiation of therapy (before or after 2000). Age was the most important risk factor for unrelated death (*Online Supplementary Table S1*), while primary therapy with rituximab was not associated with an increased risk of unrelated death.

To our knowledge, this is the first competing risks survival analysis in patients with symptomatic WM, although such analyses have been performed in other types of cancer in which unrelated mortality is common.[9,10] Our analysis was performed in a large population of patients, with symptomatic disease and with complete clinical and treatment data, in contrast to registry-based studies,[11] which also included asymptomatic patients and excluded those with a history of prior malignancy. The impact of unrelated mortality is of clinical importance given the aging population and the increasing numbers of very elderly patients who are diagnosed and treated for WM. In our study, the 5-year unrelated mortality rate in patients >75 years was 17% while WM-related mortality was 22%, indicating that about 40% of patients >75 years do not die of WM. This finding may have implications in the treatments applied to elderly or frail patients. Therapies with low toxicity which aim to control the disease may be preferable, since the chance of unrelated death is significant, and is perhaps similar to the possibility of death from WM. The allocation of health care resources must be prudent: novel and very expensive therapies are becoming available and their potential benefits may not outweigh their cost in elderly or frail patients. In contrast, in younger patients the aim of the therapy may be the eradication of the disease, or at least the achievement of a prolonged remission, and such a strategy may necessitate aggressive therapies with a high probability of a complete response. Not surprisingly, the incidence of non-WM-related death has increased since 2000, due to the increasing numbers of elderly patients who are treated for symptomatic WM. Although the 5-year WM-related mortality rate seems to remain similar, a separation of the survival curves after 8-9 years is appearing, and further follow up is needed. Importantly, the use of rituximab-based primary treatment was associated with a reduction of WM-related mortality, even after adjustment for other factors, and despite the fact

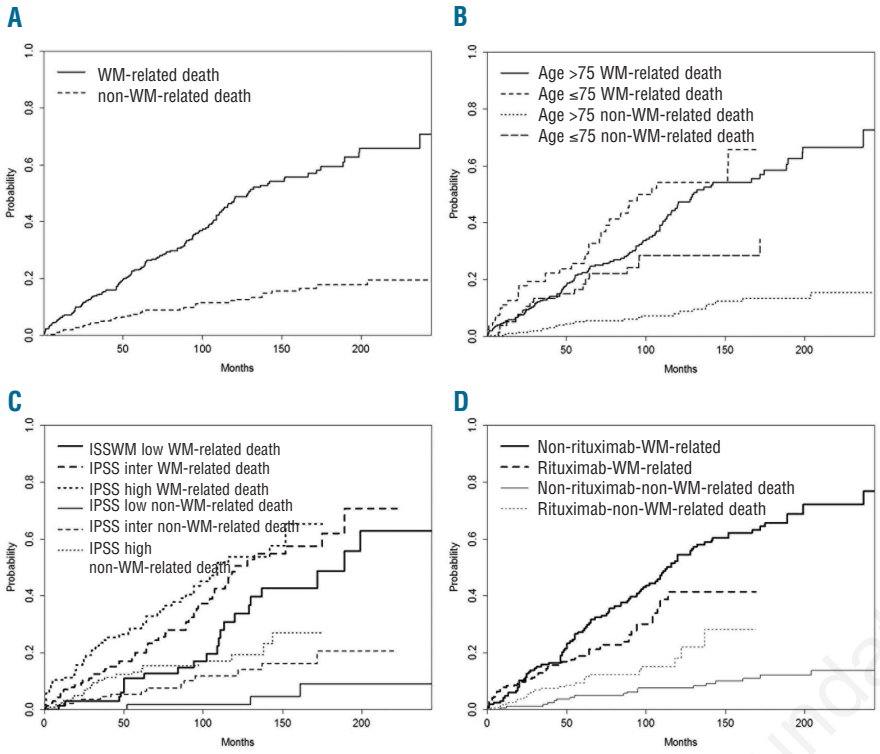

Figure 1. Survival curves (1-survival proportion) with WM-related and non-WM-related deaths as competing events (A) in all patients (B) in patients >75 *vs.* ≤75 years of age (C) per ISSWM risk group, (D) for patients who received primary therapy with rituximab *vs.* other agents (alkylators or NAs).

that it is also commonly given to frail patients because of its favorable safety profile. We also showed that ISSWM remains a robust prognostic system for WM-related mortality. Low serum albumin and elevated LDH levels were both associated with poor survival due to WM–related death, indicating that both are markers of advanced disease.

In our study the cause of death was prospectively assessed by the treating physicians and was not retrospectively collected from death certificates, which has inherent bias regarding causality. The latter is a major difference from other registry-based studies.[11,12] However, our analysis is not population-based and some selection bias may exist. Several authors have addressed the challenges in the definition and the identification of cause of death,[13] and the cause of death may not always be clearly linked (or not linked) to WM. Thus, although an increased risk of second malignancies in WM has been reported,[14,15] these are difficult to link with WM or therapy in our study, especially since many malignancies (prostate, lung and colon cancer) are common in elderly patients.

In conclusion, more patients of advanced age are diagnosed and treated for WM. Unrelated mortality is significant, and should be taken into account in the evaluation of long term outcomes and the design and analysis of clinical trials. Primary therapy with rituximab reduces WM-related mortality, independently of other prognostic factors.

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