Survival in WM: Are we making Progress

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For several decades the treatment of Waldenström's Macroglobulinemia (WM) was based mainly on alkylating agents; nucleoside analogs were introduced in the early 90s, but a major change was the introduction of rituximab in the late 90s; rituximab-based regimens are increasingly used in WM especially over the past decade (1). Novel agents such as bortezomib and IMiDs, either alone or in combination with rituximab, have also been evaluated in WM. The introduction of novel agents as well as improvements in supportive care improved survival in malignancies such as multiple myeloma (2) and in follicular lymphoma, in the later, mainly as a result of the rituximab-based immunochemotherapy (3-5). In patients with WM, it is not clear if a significant improvement in survival has been achieved. In a registry report from Sweden in a large number of patients with the diagnosis of LPL or WM a significant improvement in the survival over 5-year intervals from 1980 to 2005 was observed. However, the later study had not examined whether this improvement was due to an earlier diagnosis and /or the inclusion of asymptomatic patients (6). In an analysis from the Greek Myeloma Study Group which included 345 patients with symptomatic WM, the survival of patients who started treatment before 1/1/2000 was compared to that of patients who started after 1/1/2000, on the basis of the availability of rituximab for patients with WM in Greece(7). Patients in the more recent era were older (median 70 vs. 65 years, $p=0.001$), more often at intermediate or high risk per the IPSSWM ($p<0.001$) but in both groups the reasons to initiate therapy were similar. However, 92% of patients who started treatment before 1/1/2000 were treated upfront with alkylating agents while 78% of the more recent patients received upfront rituximab-based therapy ($p<0.001$). A similar proportion of patients achieved ≥50% IgM reduction (59% vs 63%,$p=0.438$) after frontline treatment**,** while 46% of patients who started treatment before 1/1/2000 received rituximab or other new agents (thalidomide, bortezomib) during later phases of their disease. The median OS for patients who started treatment before 1/1/2000 was 106.5 months (95% CI 94-119 months) and it was estimated at 94 months (95% CI 72-116 months) for patients who started therapy after 1/1/2000 ($p=0.327$). There was also no difference between the two time periods in the cause specific survival or within patients >70 years or ≤70 years or for each risk category of IPSSWM, even after adjustment for risk factors including IPSSWM. The above observations however need further investigation. The lack of a clear survival improvement for WM patients could be due to a significantly shorter follow up of patients treated after 1/1/2000 since WM is an indolent disease with a median survival approaching or exceeding 10 years. Also, even with the addition of rituximab, only a small number of patients achieve a complete response and the lack of significant cytoreduction

(as depicted by the lack of CRs) may not allow for significant survival differences, especially in patients with more aggressive disease while in patients with indolent disease even minimal reductions of tumor load with consecutive treatment may significantly prolong survival. It is also possible that the failure to show a difference in survival is related to the effective salvage therapies that patients who started therapy before 2000 could receive when these became available after 2000. However, possible differences in the 15- or 20-year survival rate between the two groups may be detected with further follow-up of these patients.

References

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