Can WM ISS be used to make treatment decisions?

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Using the combination of 5 characteristics routinely evaluated in Waldenstrôm macroglobulinemia (WM) patients: age >65 years, hemoglobin <11.5 g/dL, platelet count <100 x109/L, β2-microglobulin >3 mg/L, and M-protein >7.0 g/dL, the international scoring system for WM (ISSWM) has been designed for predicting overall survival after initiation of first-line therapy. Low risk (27% of patients) was defined by the presence of <1 adverse characteristic except age, high risk (35% of patients) by the presence of >2 adverse characteristics; the remaining patients with 2 adverse characteristics or age >65years had intermediate risk (38% of patients). Five-year survival rates were 87%, 36% and 68% respectively ($p<0.0001$). ISSWM was effective in patients treated with alkylating agent or fludarabine. ISSWM has been validated in patients who received rituximab alone or in combination with dexamethasone and cyclophosphamide, as first line therapy. Since its publication, ISSWM has been used to describe the characteristics of patients enrolled in 3 phase II trials or treated with high-dose therapy and autologous stem cell transplantation. An update of the follow-up of 51 patients with advanced WM who received fludarabine and cyclophosphamide or fludarabine, cyclophosphamide and rituximab or fludarabine and rituximab showed that high-risk patients had a significantly shorter subsequent survival than low- or intermediate-risk patients (66% vs. 96% at 2 years, $p=0.019$). These findings support the use of ISSWM for stratifying the allocation of treatment in first-line randomized trial and for identifying high-risk patients with advanced WM. Other characteristics, including high concentration of lactate dehydrogenase, cytogenetic and molecular markers may enhance ISSWM. Estimating the separation parameter should be useful to assess the improvement in prognostic value. In patients with advanced WM, the prognostic significance of previous treatment, the quality or the duration of previous response should also be evaluated. Statistical tools used in international prognostic studies inadequately address some important issues for choosing therapy, namely the influence of long-term effects of therapy and the prognostic role of achieving a response, especially after a long period of time elapsed since treatment initiation. For these purposes, competing risk analyses, and proportional hazard model with time dependent covariates may be useful. We conclude that ISSWM should be used in the design of prospective first-line trials. Currently, few prognostic systems have been reported for patients with advanced phase WM. Additional prognostic studies may assess the relationship between initial ISSWM and response duration.