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EDITORIAL

Risk factors for progression from smoldering into active myeloma: additional insights from a population-based study

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Smoldering multiple myeloma (MM) is defined by a monoclonal protein concentration (IgG or IgA) ≥30 g/L and/or presence of ≥10% monoclonal plasma cells in bone marrow biopsy, but without evidence of end-organ damage such as hypercalcemia, renal dysfunction, anemia, and lytic bone lesions or osteoporosis (1). More recently, a couple of studies have identified a group of very-high-risk smoldering MM patients based on ≥60% bone marrow infiltration by monoclonal plasma cells and/or serum free light chain (FLC) ratio ≥100 (2, 3). In the study by Kastritis and colleagues, the 2-yr progression rate in patients with serum FLC ratio ≥100 was approximately 80% compared with approximately 20% in patients with serum FLC ratio <100 (2). Additionally, patients with bone marrow infiltration ≥60% had a 2-yr progression rate of approximately 60% vs. 15% in patients with bone marrow infiltration <60%. The study by Larsen and colleagues showed a 72% 2-yr progression rate to symptomatic MM in patients with serum FLC ratio ≥100 compared with 28% in patients with serum FLC ratio <100, and a median time to progression of 15 and 55 months, respectively (3). Based on these single-center studies, the International Myeloma Working Group updated the definition of symptomatic MM to include patients with bone marrow infiltration ≥60% and/or serum FLC ratio ≥100 (4).

In this issue of the Journal, Sorrig and colleagues present the results of a population-based cohort study in patients with smoldering MM evaluating risk factors for progression to symptomatic MM (5). To the best of my knowledge, this is the first population-based study aiming at identifying risk factors for progression from smoldering to symptomatic MM. The study included 321 patients newly diagnosed with smoldering MM between 2005 and 2014. In a multivariate analysis, the researchers found that a monoclonal protein concentration ≥30 g/L and immunoparesis were independently associated with a threefold increase in the hazard ratio of progression into symptomatic MM. A serum FLC ratio ≥100 was associated with a trend toward a higher risk of progression (2.5-fold) but it was not included in the multivariate analysis. Overall, these results are in part confirmatory of previous findings but also shed additional light into important biological aspects of MM progression. Specifically, immunoparesis was defined as at least one uninvolved immunoglobulin (IgG, IgA or IgM) below reference level at diagnosis. Smaller studies have supported a prognostic role of immunoparesis in patients with MM (6, 7). Immunoparesis has also been identified as an adverse factor for progression from solitary plasmacytoma to symptomatic MM, for response to proteasome inhibitors in AL amyloidosis, and for survival in patients with newly diagnosed and relapsed/refractory MM (8–10).

The population-based study by Sorrig and colleagues carries a number of advantages over single-center studies. Population-based studies tend to be more representative of the population under study while single-center referral studies could be potentially biased toward younger, more robust patients that could have biological, if not truly physiological, differences than the older, less robust population. The study also carries a number of weaknesses, which include a relatively short follow-up of approximately 2 yrs, and that the results might not be generalizable to other racial and/or ethnic populations. In summary, the findings of the study by Sorrig and colleagues are valuable and should be evaluated, and hopefully confirmed, in larger studies and had into account for consideration of high-risk patients in whom early therapeutic intervention might be beneficial.

Disclosures

There is no conflict of interests to disclose.

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