

Changes in the Overall Survival of Patients with Waldenstrom's Macroglobulinemia After the Introduction of Modern Targeted Therapies

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Over the last 25 years there have been significant advances in the treatment of Waldenstrom's macroglobulinemia (WM). Since 2016, BTK inhibitors have been added to the therapeutic armamentarium for WM which included anti-CD20 monoclonal antibodies, proteasome inhibitors and bendamustine. However, WM patients are mostly elderly and often frail due to age-related comorbidities, hence the benefit from the introduction of new therapies may not be evident in real-world practice. We sought to investigate the impact of newer therapies and particularly BTK inhibitors on WM outcomes.

The current analysis included 711 consecutive patients with WM who were divided into two groups: those who started therapy before and those after 2016. The 2016 cutoff was chosen based on the availability of BTK inhibitors in clinical practice in Greece.

The characteristics of the two groups were similar; including gender, bone marrow infiltration with lymphoplasmacytic cells, IgM and other immunoglobulin levels, hemoglobin and platelet counts as well as the prevalence of MYD88 mutations (among those with available data). However, patients after 2016 were older (median 71 versus 69 years of age, $p=0.01$). The main reason to initiate treatment among patients in the most recent era was anemia and less often due to hyperviscosity-associated symptoms when compared to the pre-2016 group. As expected, primary therapies differed significantly. Before 2016, 60% of patients were treated with rituximab-based therapy and a smaller percentage with alkylators/antimetabolites only. After 2016, among newly diagnosed patients 64% were treated with rituximab-based combinations and 31% with BTK inhibitors-based regimens, mainly BTKi monotherapy. However, major response rates to first line treatment were very similar between the two groups ($p=0.970$).

The median follow-up of the pre-2016 cohort was 7.9 years and of the post-2016 cohort was 2.5 years. The median OS of the pre-2016 group was 9.76 years (95% CI 9.08-11.05), it has not been reached for the post-2016 group and the corresponding hazard ratio was 1.134 (95% CI 0.758-1.697; $p=0.541$) (Figure 1). Even after adjusting for differences in the baseline characteristics there was no difference in the overall survival of the two groups.

According to our analysis, despite the advances in the treatment of WM and their increased efficacy compared to previous available therapeutic options, a significant survival benefit has not observed thus far. This lack of overt OS benefit may be due to the shorter follow up of the most recent cohort and the more advanced age. Older patients

may benefit less from the contemporary salvage therapies compared to those who failed previous chemoimmunotherapy in the pre-2016 era. Our data suggest that the evaluation of the benefit of new treatments should not be restricted only to traditional endpoints such as PFS, OS and response rates, but should evaluate other patient oriented metrics including QOL and toxicity burden.

Figure 1: OS curves of patients that started therapy before and after 2016

