

Failure to achieve very good partial or complete response (CR/VGPR) at 12 months is associated with short PFS and time to second treatment after first-line treatment with Dexamethasone Rituximab Cyclophosphamide (DRC) +/- Bortezomib in Waldenström macroglobulinemia in the prospective ECWM-1 trial

Background

It is one of the major goals to develop early surrogate markers for treatment outcome in the management of Waldenström's Macroglobulinemia (WM). We recently reported the final analysis of the ECWM-1 trial, which is one of the largest prospectively randomized clinical trials performed in WM (M (Blood 2025; 146 Suppl 1: 223). The DRC regimen with or without Bortezomib was associated with an excellent treatment outcome in the majority of patients with a median progression-free survival (PFS) of 50.1 and 55.9 months, respectively and with 15% overall death in the patient population after a median follow-up of 68.8 months. On the other hand a limited number of patients showed early progression indicating a limited number of high-risk patients identifiable at baseline.

Aim

We took advantage of the prespecified follow-up monitoring prospectively performed in 195 patients of the study to assess the prognostic role of the depth of response and progression.

Methods,

Response was assessed with PFS and subsequent PFS (SPFS, starting from response assessment) as endpoints. We also fitted a 4 states model of survival (OS, treatment initiation, response, progression, final status). These analyses were repeated with time to 2nd treatment (T2T) and subsequent T2T (ST2T, starting from response assessment) as endpoint and a similar 4 states model (2nd treatment instead of progression). The endpoints for assessing progression were OS and survival after the first progression (SA1P). We also fitted a 3 states model of OS.

Results

In Cox models of PFS and T2T with response coded by three time dependent covariates, only attainment of a CR/VGPR retained a significant prognostic value. Dynamic landmarking analysis over the first 36 months, identified a significant favorable effect only for achieving CR/VGPR for SPFS for nearly all time points after 7 months. Similar results were observed for ST2T.

The four states model provided fixed horizon prediction of being progression-free at 5 years after treatment initiation. In agreement with previous results, it showed higher probability of being progression-free only in case of achieving CR/VGPR. Once again, similar results were observed in fixed horizon prediction analyses of T2T at 5 years. Thus, the 36 patients who achieved CR/VGPR at 12 months had a median SPFS of 62 months (95% confidence interval [95CI]:56; n.a.) vs. 37 months (95CI: 26; 48, $p=0.0022$, Figure 1) for the 126 patients that did not achieve CR/VGPR.

There was no significant difference in survival after 24 months between patients being progression-free at this time point or not ($p=0.20$). SA1P was shorter only for the 38 patients who progressed before 22 months. In agreement with these results, only this limited subset of patients had reduced fixed horizon prediction of being alive at 5 years after treatment initiation.

Conclusion

In patients with WM receiving first-line chemoimmunotherapy, failure to achieve CR/VGPR at 12 months, is associated with significantly shorter PFS and time to 2nd treatment. This endpoint should be considered as an endpoint of interest for future trials, providing a potential early surrogate for PFS in clinical trials in WM.

Figure 1: Progression-free survival after 12 months according to CR/VGPR status at this time point

