Topic: 14. Myeloma and other monoclonal gammopathies - Clinical

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Challenging the concept of functional high-risk myeloma through advanced transcriptional and genetic profiling.

Type: Oral Presentation

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Background
Functional high-risk (FHR) multiple myeloma (MM) has been defined as an unexpected, early relapse (ER) of the disease, often within 24 months of diagnosis, despite a seeming absence of molecular or clinical high-risk (HR) markers. FHR has been reported to make up to a third to half of patients experiencing ER, questioning the ability to diagnose HR newly diagnosed MM (NDMM) patients early, and challenging feasibility of effective, early intervention as reported in the OPTIMUM/MUKnine or GMMG-CONCEPT trials. However, some FHR estimates have been derived from studies in which patients were not uniformly treated, or genetic profiling was incomplete.

Aims
To estimate the true rate of FHR, we investigated a sub-group of consistently treated and comprehensively molecularly profiled patients from the UK NCRI Myeloma XI (MyXI) trial, including high-risk cytogenetic aberrations (HRCA) as per updated IMS-IMWG HR criteria (IMWG-HR) and diagnostic risk gene expression profiling (GEP-HR).

Methods
A sub-group of transplant eligible (TE) MyXI patients treated with autologous stem cell transplantation (ASCT) and randomised to lenalidomide maintenance was selected, based on availability of complete molecular profiling data for HRCA t(4;14), t(14;16), t(14;20), del(17p), del(1p), and gain(1q), and GEP-HR as per diagnostic SKY-92 platform. ER was defined as relapse <18 months after maintenance randomisation post-ASCT, equivalent to relapse within 24 months of diagnosis. PFS and OS were calculated from timepoint of post-ASCT maintenance randomisation. Median follow-up was 50.1 months. Survival outcomes were evaluated with Kaplan-Meier estimates and log-rank tests. Cox proportional hazards regression analysis was performed, where indicated.

Results

135 TE NDMM patients with complete molecular profiling were included in the analysis. Of these, n=25 (18.5%) experienced ER, while n=110 (81.5%) did not. Patient age and gender were not different between groups. In the ER group, IMWG-HR identified n=14 patients, including n=12 by co-occurrence of ³2 HRCA and n=2 based on elevated b2 microglobulin. Of these 14 patients, n=8 also classified as GEP-HR, of which all had a gain(1q), n=6 (75%) had del(1p) and n=4 (50%) showed ³ 3 HRCA. Six patients were only identified

by GEP-HR. Of the remaining 5 patients, 3 had HR features: one isolated t(4;14), one isolated gain(1q), and one elevated LDH (ISS stage 3). Only n=2 (8% of ER; 1.5% of total) had no HR marker, both carried t(11;14); plasma cell leukaemia status was not recorded in MyXI.

To further elucidate association with outcome, four groups were defined, based on IMWG and GEP risk: At 36 months, virtually all (91.9%) patients with IMWG-HR & GEP-HR had progressed or died, as well as the majority (61.5%) of GEP-HR, opposed to less than half (41.1%) of IMWG-HR and 14.7% of standard risk patients (**Figure 1**). OS results were consistent, with hazard ratios of 29.2 (95% CI: 9.6–89) for IMWG-HR & GEP-HR, 11.1 (95% CI: 3.1–39.5) for GEP-HR, and 6.7 (95% CI: 2.1–21.3) for IMWG-HR only, compared to standard risk (all $P < 0.01$).

Summary/Conclusion

Combined diagnostic profiling by GEP and updated IMWG risk criteria can reduce functional HRMM to a very rare entity and enable stratified treatment for most patients. Furthermore, combined profiling can refine individual prognostication. Our results strongly support improved access to these diagnostic technologies for MM patients.

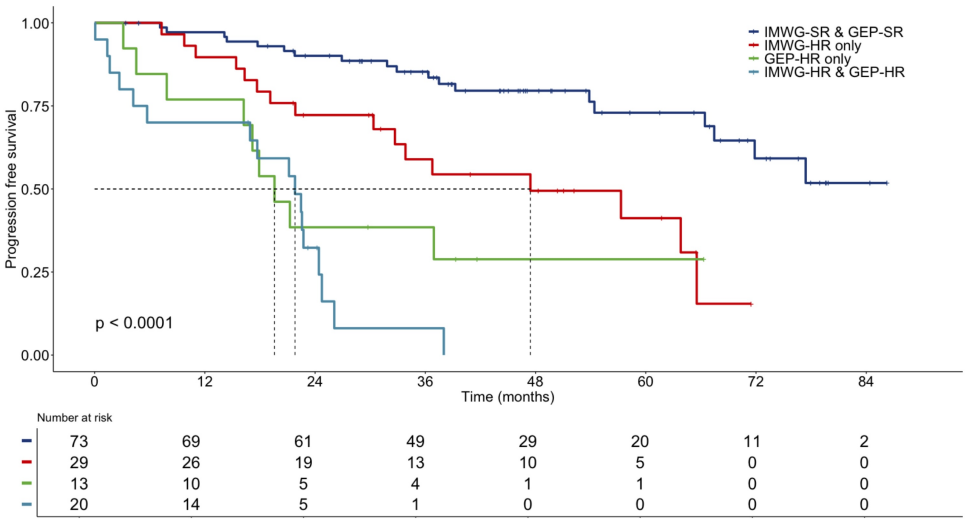

Figure 1: **Progression-free survival (PFS) by risk group**. PFS for patients with IMWG-SR & GEP-SR (blue), IMWG-HR only (red), GEP-HR only (green), and IMWG-HR & GEP-HR (light blue) in relation to Len maintenance randomization. *P*-value: log-rank test. SR = standard risk, HR = high risk, GEP = gene expression profile.

Keywords: Multiple myeloma, Molecular markers, Survival prediction, Gene expression profile