Minimal residual disease (MRD) in multiple myeloma

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Abstract

A large body of evidence exists in the autologous stem cell transplantation (ASCT) setting which shows a clear association between optimal response –very good partial response (VGPR) and complete remission (CR)- and long-term outcome –progression free survival (PFS) and overall survival (OS)- of multiple myeloma patients. In parallel, it has also been shown by multiple prospective studies at distinct centres, that MRD levels measured by flow cytometry (flow-MRD) and molecular techniques (PCR-MRD) show a significant and tight correlation with the quality of response of multiple myeloma patients treated with high-dose therapy (HDT)/ASCT, and both patient PFS and OS. This also holds true for flow-MRD in the non-transplant settings among older (>65years) patients who have been treated with novel agents. Moreover, flow-based MRD provides additional prognostic information among patients who achieve CR and stringent CR (sCR), as independently demonstrated and confirmed in large series of myeloma patients in the ASCT by both the Spanish GEM and the UK MRC cooperative Groups. In line with this, the flow-based MRD status of multiple myeloma patients assessed 3 months after ASCT has emerged as the strongest independent prognostic factor for PFS and OS, particularly when combined with tumor cytogenetics and patient age, respectively. Noteworthy, a few discrepant cases exist when minimal residual disease is assessed by flow cytometry immunophenotyping versus immunofixation (IF). Interestingly, follow-up of such discrepant cases shows that almost all MRD-/IF+ patients become IF- at later time points, whereas patients with persistence of MRD by flow cytometry, but who are IF-, correspond to early responders that will not be able to sustain their CR status and which are associated with a poor outcome. In line with these observations, flow-based MRD together with tumor cytogenetics emerged as the most powerful combination of prognostic factors to predict for early relapses: every patient who presented with adverse cytogenetic features and was MRD+, showed an early relapse during the first year after ASCT, independently of his IF status. In conclusion, flow cytometric assessment of the MRD status provides essential information for optimal management of multiple myeloma patients who follow currently used therapeutic strategies.

Regarding the different methods which are currently available for MRD detecvtion, flow-based MRD, compared to molecular methods, shows a clear higher applicability (e.g. it can currently be applied to >95% vs 70-75% of all myeloma patients) and specificity, with a sensitivity of between 10-4 and 10-5 (slightly lower than that of PCR-based molecular methods (10-4 to 10-6); in addition, it is a fast and easy to perform test which is widely available in most clinical diagnostic laboratories where myeloma patients are treated and it provides information not only about the myeloma plasma cell compartment but also about the other cellular compartments in the sample. The new EuroFlow myeloma plasma cell-specific single 8-color combination of monoclonal antibodies and automated data analysis strategies aimed at full-standardized identification and quantification of MRD levels in multiple myeloma after therapy will contribute in the very near future to assure the intra- and inter-laboratory reproducibility of the assay and its robustness. New approaches for MRD detection, such as those based on next generation sequencing are also promising, but they have to be evaluated in large prospective studies against the established flow-MRD techniques.