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# Minimal residual disease assessment in multiple myeloma

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## Editorial

The introduction of novel compounds such as the second-generation proteasome inhibitors, new immunomodulatory agents and monoclonal antibodies (mAb) determined a consistent improvement in the depth of response in patients with Multiple Myeloma (MM) [1]. A three drugs combination as induction followed by Autologous Stem Cells Transplant (ASCT) determines Complete Remission (CR) in more than 50% of the patients and this may increase if consolidation and maintenance are included following ASCT [2].

Despite these improvements translating into prolonged Progression-Free Survival (PFS) and Overall Survival (OS), most patients achieving CR eventually relapse, thus highlighting the need for a more accurate definition of response to treatment. The introduction of Minimal Residual Disease (MRD) analysis aimed to increase sensitivity in assessing treatment response by measuring directly the amount of cancer cells in the bone marrow [3]. Several studies reported patients achieving MRD negativity have better PFS and OS irrespectively from the technique used to test MRD (i.e. next generation sequencing or flow cytometry) or treatment received to achieve MRD negativity [4,5].

Bone marrow samples from Transplant Eligible (TE) patients in the intensive pathway of the Myeloma IX study were tested using Multipara meterFlow Cytometry (MFC) to assess MRD (assessing 500 000 cells incubated with 6-color antibody combinations CD138/CD38/CD45/CD19 and CD56/CD27 to depth of response to $10^{-5}$) at day 100 after ASCT [5]. MDR negative patients in intensive pathway had a highly predictive favourable

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outcome both as PFS and OS whilst the impact in the non-intensive group of patients was less clear. Interestingly, the advantage of patients achieving MRD negativity was observed irrespectively from the cytogenetic risk status, although the best outcome was seen for MRD negative patients with standard risk cytogenetic profile. Besides the MRD negativity, log reduction of tumour load correlates directly with survival (median OS was 1 year for ≥10% log, 4 years for 1% log to <10% log, 5.9 years for 0.1% log to <1% log, 6.8 years for 0.01% to <0.1% log, and more than 7.5 years for <0.01% log MRD. P < .001) [6].

A pooled analysis of the clinical trials PETHEMA/GEM2000, GEM2005MENOS65 study for transplant-eligible MM and the GEM2010MAS65 for elderly patients showed that the 47% of patient who achieved CR experienced significantly superior median PFS (49 months) versus patients achieving nCR, PR, or <PR (37, 34, and 11 months, respectively). Patients in CR also showed significantly longer median OS (128 months) compared to those in nCR (77 months), in PR (75 months) or <PR (28 months). Interestingly, achieving conventional CR but with MRD positive status did not convey improved PFS and OS: they had similar survival to MRD-positive patients in nCR and PR median PFS, 27, 27 and 29 months, respectively and median OS, 59, 64, and 65 months, respectively [7]. As per the previous trial, high-risk cytogenetics patients who are MRD-negative had prolonged median PFS compared to patients MRD positive (38 v 14 months, respectively, P<0.001) and superior median OS (128 v 26 months, P <0.001).

A recent meta-analysis, pooled together data from 14 publications, showed that MRD negativity reduce the risk of relapse or death by 59% and 43% compared to those patients who are MRD positive [8]. These publications reported data from 1273 patients enrolled in several trials, following different treatments, with samples analysed in different laboratories and with different techniques; this further confirms the MRD-negativity as strong prognostic factor and surrogate marker for PFS and OS.

In all trials investigating novel drugs the MRD assessment has been included. Two trials were based on the use of Daratumumab to standard of care (i.e. POLLUX [9]: Daratumumab-Rd and CASTOR [10]: Daratumumab-Vd) and assessed the ability of these triplets to determine not only a CR but also a MRD negativity. Bone marrow aspirate samples were analysed using Next Generation Sequencing (NGS) by ClonoSEQTM assay. In both studies adding Daratumumab consistently demonstrated a 3-fold increase in MRD negative rate compared to the control groups, showing unprecedented results in relapsed/refractory MM setting and translating into improved survival.

The utility of MRD assessment in identifying patients with better outcome is widely accepted whilst the best technique to be used to test MRD is under debate. The flow cytometry approach has the advantage of being available in many laboratories and can be included in routine sample process. However, it can only be performed on fresh bone marrow samples and the sensitivity is still lower than other molecular biology technique despite novel approaches such as Next-generation flow allows to detect 1 myeloma cells over 100.000 cells (sensitivity of $10^{-5}$) [9]. The other method to monitor MRD is the NGS that can be performed on stored sample, exhibits a higher sensitivity ($10^{-6}$) but data interpretation is complex and at the moment is mainly performed by private companies [10]. Both these approaches had been validated in prospective trials and in view of their characteristics, may be used according to local policies and available facilities.

The increase rate of CR and the evidence that within patients in CR the MRD status predicts a different outcome, a new definition of response has been published by the International Myeloma Working Group (IMWG). The assessment by MRD has been included in the definition of response consensus and MRD negativity requires a minimum sensitivity of 1 in $10^5$ nucleated cells or higher both for flow using the Euro flow standard operating procedure and sequencing technology by NGS on bone marrow aspirate.

Although MRD switch from negative to positive precedes the biochemical and clinical relapse, with the extensive use of MRD monitoring rare but recurrent episodes of relapse in MRD negative patients have been observed. These are usually characterised by localised plasmacytoma in patients with no disease in the bone marrow. To prevent this, the implementation of radiological monitoring and combination of bone marrow-based and radiological-based techniques have been suggested.

The technique used to monitor MRD radiologically is largely based on PET-CT: this test must be performed at diagnosis and repeated at different time points throughout treatment and follow-up to confirm sustained radiological CR and to detect early relapse. The combination on bone marrow-based analysis and radiological assessment to evaluate MRD is nowadays the most accurate way of monitoring patients with MM and patients achieving sustained MRD negativity with both approaches showed excellent outcome irrespectively from the treatment received.

In summary, achieving MRD negativity on bone marrow analysis and radiological assessment is a strong determinant independent prognostic factor. This is evident as novel agents are achieving deeper molecular response directly translating in improved survival data. The use of the convention definition for CR now must incorporate MRD to better stratify patients according to the different MRD status.

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