# Innovations in treatment and response evaluation in multiple myeloma

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Multiple myeloma (MM) is still an incurable disease. Recently, overall survival (OS) and progression-free survival (PFS) have improved with the introduction of immunomodulatory agents (IMIDs) and proteasome inhibitors (PI). Overall, an increase in 5-year relative survival from 28.8% to 34.7% was reported between 1990-1992 and 2002-2004 by Brenner *et al.*[1] Palumbo *et al.* reported a 10-year OS of 30% in transplant eligible patients.[2] Innovative agents (i.e. monoclonal antibodies) may further increase response rates and the quality of responses. Consequently, there will be a need for a more sensitive response assessment and risk-adapted treatment schedules.

In this editorial we will discuss the role of two innovative approaches to evaluate response in MM, minimal residual disease (MRD) and response evaluation with positron emission tomography-computed tomography (PET-CT), in the context of recent treatment innovations.

## Prognostic factors

The International Staging System (ISS) has recently been revised (R-ISS)[3] to facilitate stratification of patients with different clinical outcome. The R-ISS is a combination of ISS with chromosomal abnormalities (CA) and serum lactate dehydrogenase (LDH). CA t(4;14), t(14;16), del(17p), and potentially del(1p) and gain(1q), are associated with an adverse outcome.[4]

At present, a dichotomy arises between patients with poor CA and patients with potential long PFS and OS. Reliable, sensitive techniques for response assessment are needed to identify patients who require additional therapy.

The International Myeloma Working Group (IMWG) defined uniform response criteria for MM in 2006. In 2011, two new categories, stringent complete response (sCR) and very good partial response (VGPR) were added.[5] However, the current definition of complete response (CR) fails to predict a distinct overall outcome. Using MRD for response evaluation may give a better prediction of OS.[6,7] With multiparameter flow cytometry (FCM) or next generation sequencing (NGS) it is possible to detect a tumor load of $10^{-5}$ (Figure 1).[5,6,8-10] This is clinically relevant since time to progression (TTP) in patients with MRD below $10^{-5}$ is significantly better than in patients with MRD between $10^{-5}$ to $10^{-3}$ or above $10^{-3}$ (80 *vs.* 48 *vs.* 27 months).[11] MRD combined with cytogenetics gives a better prediction of outcome than standard CR.[7] Therefore, MRD has now been incorporated into several clinical trials.

## Evaluation by PET-CT

Bone marrow infiltration in patients with MM can be patchy. This implies that because of sampling error, MRD may be negative even in the presence of extramedullary disease (EMD). Therefore imaging techniques are increasingly applied to assess EMD.[12] Magnetic resonance imaging (MRI) seems the most sensitive imaging technique for detection of bone involvement in the spine;[6] however, EMD may not be visualized with this technique. PET-CT can detect bone involvement as well as EMD. Patients with persistence of abnormal 18F-fluorodeoxyglucose (FDG) uptake following high-dose therapy and stem cell trans-

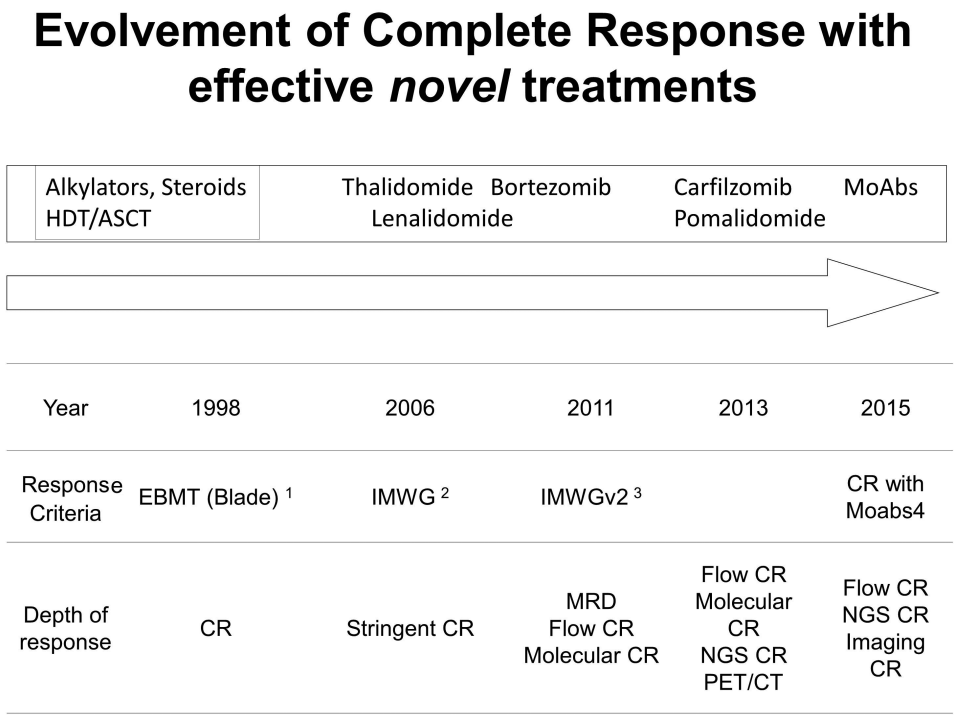


**Figure 1. In the last two decades, response criteria have changed because novel treatments have improved the quality of response.**

plantation (SCT) have a poor prognosis.[13] While small defects may be missed because of low spatial resolution, the use of PET-CT in detection of MRD seems promising enough to warrant further evaluation in clinical trials.

### Novel agents and treatment strategies

Treatment modalities have greatly expanded in the last two decades and we will discuss some of the novel agents in the context of new treatment strategies. IMIDs such as lenalidomide and thalidomide have increased OS and PFS in newly diagnosed multiple myeloma (NDMM).[14,15] Pomalidomide is a next generation IMID. It has direct antiproliferative, pro-apoptotic, and antiangiogenic effects, as well as modulatory effects on bone resorption, the immune system and the bone marrow microenvironment.[16-18] The pivotal phase III trial assessed the efficacy and safety of pomalidomide with/without low-dose dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM). At a follow up of 14.2 months, median PFS was 4.2 *versus* 2.7 months (HR=0.68; *P*=0.003), overall response rates (ORRs) were 33% and 18% (*P*=0.013), median response duration was 8.3 and 10.7 months, and OS was 16.5 and 13.6 months, respectively.[19,20]

The other class of novel agents is made up of proteasome inhibitors (PI). Bortezomib has improved CR rate, PFS and OS in elderly patients (VMP, VD) and in transplant eligible MM (PAD, VCD, VTD); as an example, in the HOVON65/GMMG-HD4 trial, addition of bortezomib increased CR from 25% in controls to 36% (*P*<0.001) and PFS was also superior (28 *vs*. 35 months; *P*=0.002).[21]

Novel PIs have emerged: carfilzomib, oprozomib, marizomib and ixazomib. Carfilzomib is an epoxyketone proteasome inhibitor that binds selectively and irreversibly to the constitutive proteasome and immunoproteasome. The ASPIRE trial evaluated safety and efficacy of adding carfilzomib to lenalidomide/dexamethasone (RD) *versus* RD alone in patients with relapsed MM. PFS was significantly better with carfilzomib *versus* control group (26.3 *vs.* 17.6 months, respectively).[22] The ENDEAVOR trial compared carfilzomib with bortezomib in patients with RRMM; PFS was 18.7 months with carfilzomib *versus* 9.4 months with bortezomib (*P*<0.0001).[23]

Ixazomib is a reversible boronic ester prodrug PI. Preclinical studies have shown activity in myeloma cells resistent to bortezomib. Combination of ixazomib with RD gave good responses also in unfavorable CA.[24,25]

Monoclonal antibodies [daratumumab, SAR650984 (SAR) and elotuzumab] have set the stage for a new treatment modality in MM. Elotuzumab is a monoclonal antibody targeting signaling lymphocytic activation molecule F7 (SLAMF7). This is a cell surface glycoprotein highly expressed on MM cells and normal plasma cells. A phase III trial was recently performed in patients with RRMM. Patients were randomized between treatment with RD with/without elotuzumab. Median PFS was 19.4 months in the elotuzumab group *versus* 14.9 months in the control group (*P*<0.001). OS in the elotuzumab group was 79% *versus* 66% in the control group (*P*<0.001).[26]

Daratumumab is an anti-CD 38 monoclonal antibody. It induces cell killing by multiple mechanisms: complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis through activation of complement proteins, natural killer cells, and macrophages, respectively.[27,28] A phase I/II study in heavily pre-treated patients with RRMM induced response in 42% of patients.[29] Daratumumab is currently under investigation in several phase III trials, including the IFM2015/HOVON131 randomized phase III trial in NDMM who are transplant eligible. This study investigates the efficacy of the combination of daratumumab with VTD for induction and consolidation followed by daratumumab maintenance treatment. During this trial, assessment of MRD will be performed using NGS on bone marrow and peripheral blood samples collected from subjects who achieve at least VGPR (Figure 2).

Histone deacetylase inhibitors (panobinostat, vorinostat and ricolinostat) inhibit cell growth and induce apoptosis. In the PANORAMA-1 trial, treatment with bortezomib, dexamethasone plus panobinostat resulted in significantly longer PFS (12 months *vs.* 8 months; *P*<0.0001).[30]

### Conclusions

During the last two decades, diagnostic methods and treatment modalities in MM have greatly improved. In deciding how to treat a particular patient, prognostic factors such as cytogenetic abnormalities are becoming more important.

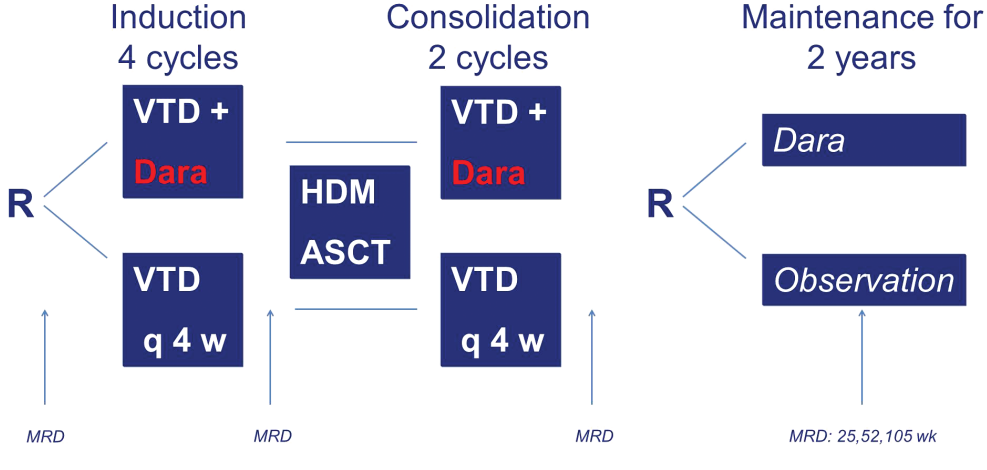


**Figure 2. IFM2015/HOVON 131.** Patients are randomized between treatment with VTD with/without daratumumab followed by high-dose melphalan (HDM) and autologous stem cell transplantation (ASCT). After ASCT, patients receive two consolidation cycles. Patients with at least a partial response (PR) will be randomized after determination of response at approximately day 100 after ASCT, and will enter the Maintenance Phase. Minimal residual disease (MRD) assessment will be performed before the first induction cycle, before ASCT, at day 100 after ASCT, and during maintenance in patients who achieve at least a very good partial response (VGPR).

Treatment schedules should be adapted to these prognostic factors. This requires further evaluation in clinical trials.

Novel agents induce deeper responses. This implies the need for a more sensitive response assessment such as determination of MRD by FCM or NGS. Therefore, clinical trials with novel agents should include standard panels for cytogenetics, MRD, and optimal imaging.

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