POINT-COUNTERPOINT

blood advances

POINT Should minimal residual disease negativity be the end point of myeloma therapy?

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This article has a companion Counterpoint by Sonneveld.

There has been remarkable progress in the treatment of multiple myeloma (MM), primarily based on the efficacy of high-dose melphalan and autologous stem cell transplantation, coupled with the more recent advent of novel therapies, including the immunomodulatory drugs (IMiDs) thalidomide, lenalidomide, and pomalidomide; the proteasome inhibitors (PIs) bortezomib, carfilzomib, and ixazomib; the monoclonal antibodies (mAbs) elotuzumab and daratumumab; and the histone deacetylase (HDAC) inhibitor panobinostat.[1-20] Although these agents were initially shown to be active in advanced MM, they have rapidly been tested earlier in the disease course to treat early relapse and as therapy of newly diagnosed disease. As initial therapy, they are most effective in combination, with triplets superior to doublets in both transplant-eligible and non–transplant-eligible patients.[21-23] Novel agent maintenance therapy posttransplant or continuous therapy in nontransplant patients can prolong progression-free survival (PFS) and in some studies overall survival (OS).[6,7] IMiDs, PIs, mAbs, and HDAC inhibitors are now used in combination to treat relapsed disease[5,8-11,13-20]; as in initial therapy, combinations of these agents achieve high rates of durable responses.[23] Indeed a three- to fourfold prolongation in OS in MM[24] is related not only to the increased extent, frequency, and duration of response to initial therapy, but also to the high rates of durable responses even in relapsed MM.

In order to assure that patients benefit optimally from this remarkable therapeutic progress, the MM community has recently redefined those patients who can benefit from therapy, developed revised prognostic systems, and most recently refined response criteria. Specifically, the International Myeloma Working Group (IMWG) now recommends therapy not only in patients with hypercalcemia, renal dysfunction, anemia, or bone disease (CRAB), but also in patients with >60% bone marrow (BM) plasma cells, $\kappa:\lambda > 100$ fold, and >1 bone lesion on magnetic resonance imaging, even in the absence of CRAB features.[25] The International Staging System based upon serum β2 microglobulin and albumin has also been refined to include fluorescence in situ hybridization analysis of BM plasma cells, as well as serum lactic dehydrogenase.[26] Since novel therapies are effective even in patients previously considered to have high-risk disease (ie, efficacy of bortezomib in t (4:14) MM or mAb therapy in del 17p MM),[27] prognostic staging of MM will continue to evolve with development of novel targeted and immune therapies. Most importantly, the evaluation of response in MM has similarly evolved to parallel advances in therapy and outcome.[28]

Traditionally, complete response (CR) in MM has required absence of monoclonal protein by sensitive immunofixation techniques and normalization of the BM. This definition was then refined by the IMWG to stringent CR, which also required a normal $\kappa:\lambda$ ratio. Importantly, due to the unprecedented depth of responses now achievable with novel therapies with or without high-dose therapy and transplantation, the IMWG has most recently further defined the consensus criteria for response and minimal residual disease (MRD) response assessment.[28] In the setting of conventional CR, absence of detectable MM using either next-generation flow cytometry or by next-generation sequencing (both with a sensitivity of detection of 1 in 10^5 nucleated cells or better) now defines flow or sequencing negative MRD, respectively. By IMWG criteria, sustained MRD negativity requires 2 such determinations 1 year apart. Finally, an imaging MRD-negative response in addition requires resolution of all areas of increased tracer uptake on positron emission tomography/computed tomography scan.

Until recently, MRD negativity was obtainable primarily in the context of allogeneic stem cell transplantation, where sustained MRD negativity due to a donor graft-versus-MM effect is associated with long-term disease-free survival and cure.[29-31] However, it is now urgent to define and incorporate MRD into our response criteria more generally, since combination novel therapies, with or without autologous stem cell transplant (ASCT), can now achieve MRD. For example, in the Inter-Groupe Francophone du Myelome and Dana-Farber Cancer Institute (IFM/DFCI) clinical trial of lenalidomide, bortezomib, and dexamethasone induction therapy with or without early ASCT followed by 1 year of lenalidomide

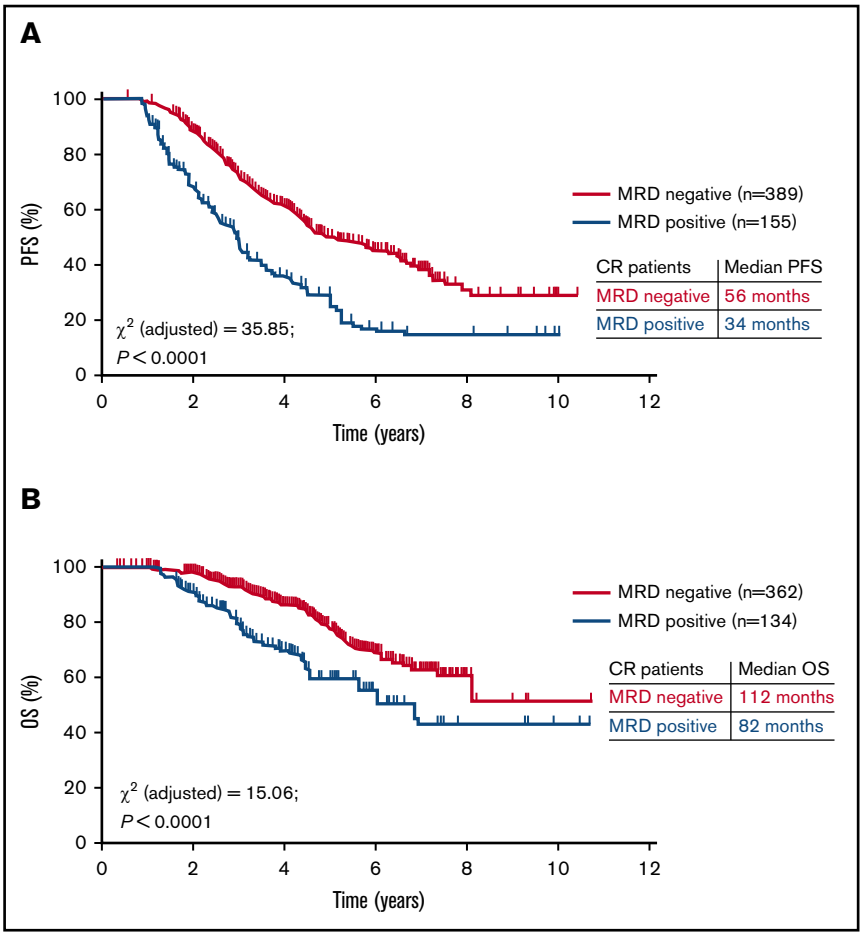

Figure 1. Impact of MRD on patient outcome in patients who have achieved conventional CR. Impact of MRD on PFS was evaluated in 14 studies (1273 patients) and on OS in 12 studies (1100 patients) overall, including the impact of MRD on PFS in 5 studies (574 patients) (A) and OS in 6 studies (616 patients) (B) in the setting of conventional CR. MRD negativity was associated with improved PFS and OS, both overall ($P < .001$) and in patients who were in CR ($P < .001$).[38] Modified from Munshi et al[38] with permission.

maintenance, 80% and 60% patients achieved MRD with or without early transplant, respectively.[32] Importantly, this study further showed that MRD status after maintenance therapy was associated with PFS and suggested a threshold of sensitivity of 10^{-6} to define MRD negativity. Excitingly, daratumumab in combination with either lenalidomide or bortezomib and dexamethasone can achieve MRD even in relapsed disease.[18,19]

Now that MRD is achievable, methodologies for its detection need to be validated and standardized to assure quality control. To date, multicolor flow cytometry and immunoglobulin gene sequencing to detect MRD have both achieved the 10^{-5} sensitivity included in the IMWG criteria,[33,34] and it will be essential for current and future novel MRD assays to at least meet this threshold. This is highlighted by the Medical Research Council Myeloma IX clinical trial, which used MRD assessment with lower sensitivity and did not demonstrate its clinical utility.[35] Multicolor flow cytometry is based upon the specific phenotype of the MM cell vs normal plasma cell and assumes that this phenotype is stable during disease evolution. Although it can be informative in all patients, there are many different panels used, fresh patient samples are required, and its sensitivity depends on the number of mAbs in the panel. Next-generation sequencing is based upon unique immunoglobulin gene rearrangements in MM that are stable during disease evolution. Although knowing the sequence is required, this methodology is highly sensitive and standardized and can be done using frozen samples. Importantly, the status of MRD and its duration is related to the frequency with which this assay is performed. Although there is no standardized recommendation, incorporation of uniform intervals for measuring MRD and its durability is required in order to compare the relative clinical efficacy of novel targeted and immune therapeutics. Finally, since MRD evaluates MM in 1 BM region, assays are now sampling peripheral blood (PB) in comparison with BM. For example, next-generation MRD assays, including single-cell sequencing[36] and cell-free DNA assays[37] comparing BM and PB, are now in exploratory phases and will determine whether PB sampling more accurately reflects BM tumor burden and if increased sensitivity of MRD detection confers additional clinical benefit.

What is the clinical data to date justifying the use of MRD? Two recent meta-analyses have examined all available data.[38,39] The first meta-analysis examined clinical studies in which MRD, PFS, and OS were reported in >20 patients.[38] The impact of MRD on PFS was evaluated in 14 studies (1273 patients) and on OS in 12 studies (1100 patients) overall, including the impact of MRD on PFS in 5 studies (574 patients) and OS in 6 studies (616 patients) in the setting of conventional CR. MRD negativity was associated with improved PFS and OS, both overall ($P < .001$) and in patients who were in CR ($P < .001$). Although there was some overlap in the clinical studies included in the second meta-analysis, Landgren et al[39] similarly found a statistically significant correlation between MRD negativity and both PFS ($P < .001$) and OS ($P < .001$). In

addition to these meta-analyses supporting the clinical utility of MRD for predicting outcome in MM, there are also multiple ongoing DFCI/IFM, Compass, Black Swan, industry-sponsored, and cooperative group trials that will provide additional clinically annotated data to further bolster this database. These studies will provide the framework for incorporation of MRD into clinical trials to determine whether achieving MRD status utilizing different therapies, at various stages of MM, or in genetically distinct MM subgroups has similar clinical implications.

A second urgent need for the development and incorporation of MRD into clinical trials is in new drug development and registration. As described above, the development and approval of novel agents both for initial therapy and treatment of relapsed MM has already extended both PFS and OS several-fold. Therefore, at present, it is no longer possible to examine the impact of a novel agent to treat newly diagnosed MM, alone or in combination, utilizing PFS and OS as end points, as these metrics would require clinical trials lasting well over a decade. Such a delayed determination of efficacy is unfair for patients and caregivers alike; moreover, it would slow drug development due to the prohibitive cost of such trials. There is therefore an urgent need for a parameter or surrogate marker, such as MRD, which can be examined earlier after treatment and predict subsequent PFS and OS. This need for a clinically significant parameter to make further progress is analogous to our predicament at the time of early development of the first PI, bortezomib, in the early 2000s. Up until that time, response in MM was of unclear clinical significance, since patients with stable disease after treatment with melphalan and prednisone had similar outcome to those who responded. However, high-dose therapy and ASCT for the first time achieved CRs associated with improved patient outcomes, which helped to establish the clinical benefit of response in MM. At that time, the expected PFS in MM patients with increasing numbers of relapses was determined using a retrospective analysis of the Mayo Clinic database. With these clinically annotated databases, the US Food and Drug Administration was able to incorporate response and PFS as metrics in clinical trials for new drug development in MM, and multiple subsequent studies have confirmed that these registration end points confer clinical benefit. None of the remarkable progress in MM over the past 10 to 15 years would have been possible without definition and incorporation of these end points into trial strategies. Most importantly, with a sufficiently large and growing database correlating MRD with clinical outcome, it should now become possible to similarly include MRD as a regulatory end point and in so doing fast-forward new drug development in MM.[40]

Finally, there is an urgent need to further define the utility of MRD in the clinical care of patients with MM. Should all patients be treated to achieve a goal of MRD? As ongoing studies bolster the association of improved outcome in patients with MRD negativity and novel therapies can achieve MRD without adverse effects, this issue can now be addressed. MRD negativity may not be an appropriate goal in all patient subsets (eg, frail patients). Can we inform the intensity or duration of therapy predicated upon MRD status? More widespread incorporation of MRD into clinical trials will allow us to determine whether patients should receive consolidation therapy to achieve MRD or if the duration of maintenance therapy can be defined by MRD status. Finally, the recent advent of immune therapies that can achieve MRD negativity in both newly diagnosed and relapsed MM is a major advance.[19,20,41,42] Particularly in this setting, we must define the kinetics of achieving MRD, which differ from those after targeted therapies. Moreover, it is possible that our therapeutic goal with immune therapies should include not only MRD negativity, but also restoration of host immune function to prevent relapse of disease. These and many other questions remain to be addressed and require that MRD be more generally incorporated into clinical trials both for new drug registration and to define clinical practice. Most importantly, our ability with modern therapies to achieve an unprecedented frequency and extent of response in MM, including MRD negativity, now provides the realistic framework for long-term survival and potential cure in MM.

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