editorials

Modern Myeloma Therapy + Sustained Minimal Residual Disease–Negative = (Functional) Cure!

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Over 35,000 individuals are diagnosed with multiple myeloma annually in the United States, and more than 120,000 people are living with the disease.[1] In the past decade, we have seen unprecedented advances in the treatment of multiple myeloma. Although we are still lacking established curative treatments, in the past decade, we have witnessed how modern, effective combination therapies have transformed multiple myeloma from a lethal disease (overall survival [OS] 1-3 years) to a chronic disease (OS over 10-20 years).[2] Using modern combination therapy in patients with newly diagnosed multiple myeloma, high proportions of patients with newly diagnosed multiple myeloma obtain minimal residual disease (MRD) negativity (eg, in the MANHATTAN study, 71% of patients were MRD-negative in the absence of high-dose melphalan chemotherapy followed by autologous stem-cell transplantation support [HDM-ASCT][3]), and consequently, MRD testing has rapidly become an integral part of clinical trials focusing on patients in this setting. Furthermore, MRD testing has been implemented in clinical trials focusing on patients with relapsed/refractory multiple myeloma. Recent data from clinical trials show that patients with relapsed/refractory multiple myeloma treated with 1-3 prior lines of therapy also have high rates of MRD negativity (over 30%).[4,5] The reason for the rapidly increased interest in MRD testing in all types of clinical trials is the fact that MRD negativity is closely correlated with longer progression-free survival (PFS) and OS, which has been documented in recent meta-analyses.[6-8] Because these meta-analyses include all published studies with information on MRD status and clinical outcomes, inherently, there is heterogeneity regarding variables related to MRD testing. For example, the applied MRD assays vary, and the time point for MRD testing is also different across studies. Emerging information from newer studies focusing on longitudinal MRD tracking of patients with multiple myeloma treated with maintenance therapy shows that sustained MRD negativity is associated with longer PFS and OS (compared with patients found to be MRD-negative at a single time point).[9]

To our knowledge, the Myeloma XI trial is one of the largest studies conducted to date (N = 2,568) focusing on transplant-eligible patients with newly diagnosed multiple myeloma.[10] In the current paper, the authors examined data from Myeloma XI to determine the relationship between MRD status, PFS, and OS in post–HDM-ASCT patients randomly assigned to lenalidomide maintenance or no maintenance at 3 months after HDM-ASCT (N = 1,248; Fig 1).[10] MRD status was assessed by flow cytometry (median sensitivity 0.004%) before maintenance random assignment (HDM-ASCT + 3) and 6 months later (HDM-ASCT + 9).

One of the key results from the main analysis is that lenalidomide maintenance therapy, when given after combination therapy HDM-ASCT, improved PFS from 30 to 57 months compared with observation (hazard ratio [HR] = 0.48; $P < .0001$) and OS at 3 years from 80.2% to 87.5% (HR = 0.69; $P = .014$). Here, de Tute et al[10] report on the impact of MRD status on PFS and OS in patients receiving lenalidomide maintenance or observation in the Myeloma XI trial and the interaction with molecular risk and the impact of sustained MRD negativity.

In their study, in accord with prior meta-analyses focusing on MRD status and clinical outcomes in patients with newly diagnosed multiple myeloma,[6-8] de Tute et al[10] found MRD negativity to be associated with improved PFS (HR = 0.21; $P < .0001$) and OS (HR = 0.33; $P = .0077$). Their findings were very similar when restricted to those patients in complete response or near complete response. In their longitudinal analysis, they found sustained MRD negativity (defined by MRD negativity at the 3-month and 9-month milestones after HDM-ASCT), or the conversion from MRD positivity to MRD negativity by 9 months after HDM-ASCT was associated with the longest PFS/OS. Patients randomly assigned to lenalidomide maintenance were more likely to convert from MRD positivity (before maintenance random assignment) to MRD negativity 6 months later (30% of patients treated with lenalidomide and 17% of patients on observation). Patients deemed to have high-risk multiple myeloma by fluorescent in situ hybridization (FISH)/cytogenetics had an adverse effect on PFS and OS even for those patients achieving MRD negativity; however, on multivariate analysis, they found that

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THE TAKEAWAY

In the article that accompanies this editorial, de Tute et al[10] show that minimal residual disease (MRD) negativity 3 months after high-dose melphalan chemotherapy followed by autologous stem-cell transplantation support is highly predictive of longer progression-free survival and longer overall survival in patients with newly diagnosed multiple myeloma. The observation that sustained MRD negativity predicts longer progression-free survival and overall survival in the setting of newly diagnosed multiple myeloma is clinically important for physicians treating patients with multiple myeloma, and it will have important impact on the design of future clinical trials for multiple myeloma (ie, it emphasizes the need to capture MRD status longitudinally).

MRD status, maintenance therapy, and risk status (high-risk versus standard risk) maintained independent prognostic impact at both 3 and 9 months after HDM-ASCT.[10]

The current study has many strengths including the large sample size and the fact that patients were treated and monitored uniformly on the study protocol. One of the main weaknesses is the utility of a flow cytometry–based MRD assay with a sensitivity level of 4×10^{-5} (ie, able to rule out four myeloma cells in 100,000), which is less stringent than current established guidelines for MRD negativity (requiring a sensitivity level of 10^{-5} or better for a patient to be considered MRD-negative, which means ability to rule out one myeloma cell in 100,000).[11] In this light, current consensus guidelines define sustained MRD negativity as two negative tests at least 1 year apart while the Myeloma XI trial used MRD negativity at the 3-month and 9-month milestones after HDM-ASCT.[11] These discrepancies reflect that the Myeloma XI clinical trial was initiated before current guidelines were developed. Another weakness of the Myeloma XI trial is the use of FISH/cytogenetics to determine adverse risk (including gain(1q), del(17p), t(4;14), t(14;16), or t(14;20)). Specifically, high-risk was defined as the presence of one of these lesions, and ultra-high-risk defined as the presence of more than one. Emerging data show that DNA-based sequencing data (compared with FISH/cytogenetics) allow more precise and accurate characterization of high-risk disease biology of multiple myeloma; however, the Myeloma XI trial did not include DNA-based sequencing data.[12,13]

Combination therapies (before maintenance therapy) have evolved since the Myeloma XI trial, with most patients now

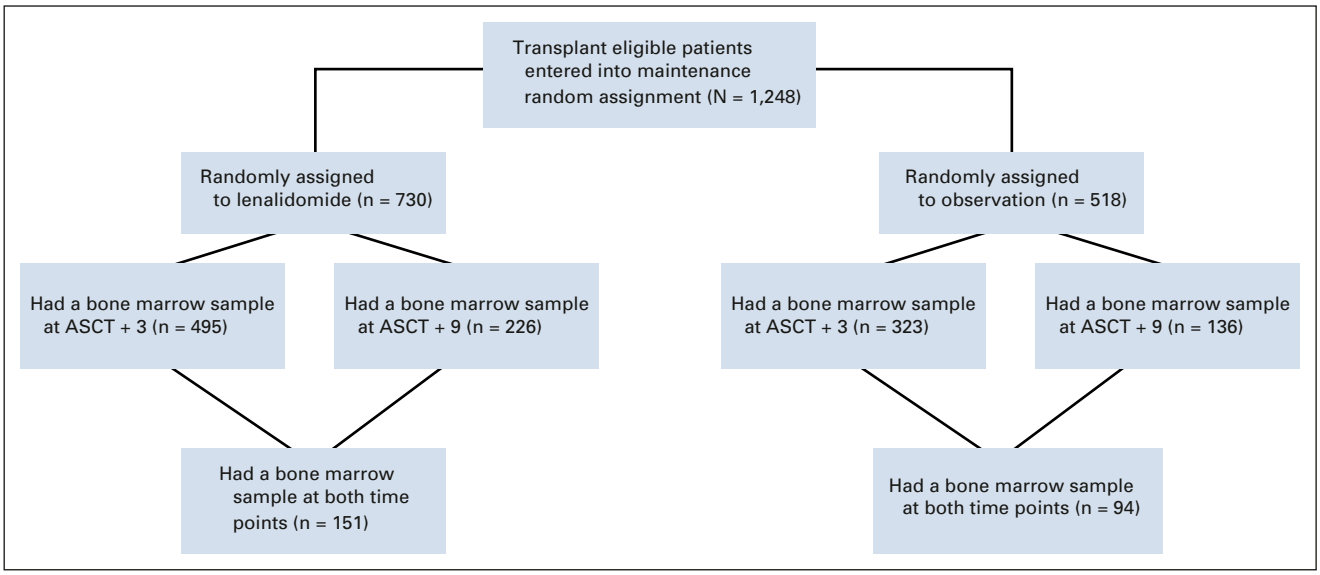

FIG 1. Distribution of patients in the current study. In the Myeloma XI trial, 1,248 transplant eligible patients were randomly assigned to lenalidomide (n = 730) or observation (n = 518) at 3 months after HDM-ASCT. A total of 818 patients had HDM-ASCT + 3 bone marrow samples sent to the central laboratory (lenalidomide, n = 495; observation, n = 323). Of the samples received, 750 of 818 (91.7%) were informative for MRD status (lenalidomide n = 452 of 495 [91.9%] and observation n = 298 of 323 [92.3%]). A comparison of those patients with and without informative MRD data showed no significant difference in overall survival or baseline characteristics. ASCT, autologous stem-cell transplantation; HDM-ASCT, high-dose melphalan chemotherapy followed by autologous stem-cell transplantation support; MRD, minimal residual disease.

receiving combinations with immunomodulatory drugs, proteasome inhibitors, and low-dose steroids as standard therapy, and that the addition of anti-CD38 antibodies (the so-called quadruplets) is becoming increasingly more common in parts of the world where available and reimbursed. Such quadruplet combinations are able to achieve very high rates of MRD negativity such as those seen in the GRIFFIN study (bortezomib, lenalidomide, and dexamethasone, with daratumumab) followed by HDM-ASCT[14] and even in combination therapies without subsequent HDM-ASCT such as in the MANHATTAN study (carfilzomib, lenalidomide, and dexamethasone, with daratumumab).[3] Moreover, these modern combination therapies may somewhat abrogate the poor-risk prognosis conferred by traditional high-risk FISH/cytogenetic characteristics and therefore making MRD status the most important prognostic biomarker. The bottom line is that an increasing proportion of patients with newly diagnosed multiple myeloma achieve MRD negativity, and many patients are MRD-negative after completing combination therapy (ie, in the absence of HDM-ASCT). As discussed in the literature, this will continue to challenge the role of HDM-ASCT in the near future.[15-17]

Data from the current study indicate that longitudinal MRD testing is a strong prognostic indicator that needs to be implemented in all clinical trials, and it should be considered in the standard-of-care setting. Indeed, the utility of longitudinal MRD testing is supported by the most recent version of the National Comprehensive Cancer Network guidelines for multiple myeloma.[18] Going forward, we need to develop new clinical trials to determine whether there is need to change therapy to achieve MRD negativity in every patient, and if it matters if the patient achieves MRD negativity earlier or later during the planned therapy. Indeed, several ongoing clinical trials are already investigating the utility of MRD-driven therapy in multiple myeloma (eg, delayed HDM-ASCT in patients who are MRD-negative after combination therapy, multidrug maintenance in patients who are MRD positive and single drug maintenance in patients who were MRD-negative, start of new therapy in patients who convert from MRD negativity to MRD positivity [molecular relapse], and more).

As extrapolated from the current study and our current knowledge, it seems reasonable to conjecture that the introduction of modern, effective combination therapies partnered with easily available, reliable MRD assays which can be performed longitudinally—ideally blood-based MRD tests—will serve as the engine for improved clinical outcomes and ultimately lead to a (functional) cure for multiple myeloma.[16,17,19] The future looks bright for patients diagnosed with multiple myeloma!

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