blood®
Perspective

Requirements for operational cure in multiple myeloma

Mohamad Mohty,[1,2]* Hervé Avet-Loiseau,[3,4] and Jean-Luc Harousseau[5]

[1]Unite Mixte de Recherche en Sante 938 INSERM, Sorbonne University, Paris, France; [2]Hematology Department, Saint Antoine Hospital, Assistance Publique–Hôpitaux de Paris, Paris, France; [3]Myeloma Genomics Laboratory, Cancer Research Center of Toulouse, UMR 1037 INSERM, University Cancer Institute Toulouse Oncopole, Toulouse, France; [4]Unit for Genomics in Myeloma, Institut Universitaire du Cancer de Toulouse-Oncopole, University Hospital, Toulouse, France. Centre de Recherche en Cancérologie de Toulouse, INSERM U1037, Toulouse, France; and [5]Centre René Gauducheau, Institut de Cancérologie de l'Ouest, Nantes-St Herblain, France

Multiple myeloma is usually considered an incurable disease. However, with the therapeutic improvement observed in the past few years, achievement of an operational cure is increasingly becoming a realistic goal. The advent of novel agents, with or without high-dose chemotherapy or autologous transplantation, revealed a correlation between depth of response to treatment and outcome. Of note, minimal residual disease (MRD) negativity has been shown to be associated with improved progression-free survival (PFS), and MRD status is becoming a well-established and strong prognostic factor. Here, we discuss the impact of MRD negativity on PFS and long-term disease control, as a surrogate for potential cure in a significant proportion of patients. MRD value and impact should be examined by focusing on different parameters: (1) sensitivity or lower limit of detection level (method used), (2) timing of assessment and sustainability, (3) type and duration of treatment, (4) initial prognostic factors (most importantly cytogenetics), and (5) patient age. Currently, the highest probability of operational cure is in younger patients receiving the most active drugs, in combination with autologous transplantation followed by maintenance therapy. Older patients are also likely to achieve operational cure, especially if they are treated upfront with anti-CD38 antibody–based therapy but also with novel immunotherapies in future protocols. Incorporation of MRD as a surrogate end point in clinical trials would enable shorter trials, leading to more personalized management and achievement of long-term cure.

Introduction

Multiple myeloma (MM) is usually considered an incurable disease. However, with the therapeutic improvement observed in the past few years, achievement of an operational cure is becoming a more realistic goal. The phenomenon of the so-called operational cure, namely the persistence of a very low level of detectable cancer cells while either on or offtreatment but in deep disease response, differs from the state of cancer cell resistance. In such an operational cure, patients with minimal levels of residual disease remain in remission and symptom free over the long term, as previously described in chronic myeloid leukemia.[1] From a historical perspective, tribute must be paid to Barlogie,[2] who was the first to introduce the word cure in MM, as early as 1991. He devoted a great part of his career to developing a strategy aimed at a cure for MM. The only way to cure MM back in the 1990s was through allogeneic stem cell transplantation (allo-SCT), but this could be offered to only a limited number of patients and was associated with high rates of morbidity and mortality. However, with the introduction of high-dose therapy (HDT) followed by autologous SCT (ASCT), long complete remission (CR) could be observed. Powles et al[3] were the first to propose the term operational cure in 2000 for a small minority of patients who were in continuous first CR for ≥10 years after HDT and ASCT. In 2005, Fassas et al[4] published an article entitled "Cure of myeloma: hype or reality?" suggesting that adding novel agents like thalidomide to ASCT could improve the cure rate by improving the CR rate. However, around the same time, investigators from the Mayo Clinic questioned the curability of myeloma and developed new approaches incorporating novel drugs in an attempt to control MM progression and make MM a chronic disease. They discussed whether MM should be treated with an aggressive multidrug strategy targeting CR or with a sequential disease control approach emphasizing quality of life as well as overall survival (OS).[5] It was not until 2014 that Barlogie et al[6] published their contribution entitled "Curing myeloma at last: defining criteria and providing the evidence." This article addressed the curability of myeloma from the vantage point of having followed >1200 patients in the Total Therapy (TT) trials at the University of Arkansas for Medical Sciences. This program used an upfront approach involving standard ASCT and all myeloma-active drugs to target drug-resistant subclones during initial treatment to prevent later relapse. The authors concluded that MM was a curable malignancy. They saw an improvement in 10-year progression-free survival (PFS) and CR duration rates, especially in the TT3 clinical trial (33% and 49%, respectively). This trial of 303 patients with a median follow-up of 9 years added upfront bortezomib, thalidomide, and dexamethasone (VTD) to

conventional chemotherapy followed by tandem ASCT, consolidation, and maintenance. The 5-year PFS and CR estimates were 65% and 74%, respectively. These data enabled development of a gene expression profiling model based on a 70-gene classifier (GEP-70). Patients identified as low risk based on the GEP-70 model could achieve a high (~70%) PFS rate at 10 years, in comparison with those with GEP-70 high-risk status (<30% at 10 years).[6]

CR and cure

With the introduction of HDT, ASCT, and novel agents, it became possible to show a correlation between depth of response to treatment and outcome; achievement of CR was more frequent and was associated with longer PFS in the ASCT setting.[7] In 2011, Martinez-Lopez et al[8] showed the prognostic impact of CR on survival in 344 patients after HDT plus ASCT. Significant differences in OS and PFS were evident, with respective 12-year values of 28% and 35% for CR, 13% and 20% for near CR (nCR)/very good partial response (VGPR)/PR, and 4% and 4% for stable disease/progressive disease. The medians for PFS and OS were 47 and 91 months for CR, 26 and 51 months for nCR/VGPR/PR, and 4 and 6 months for stable disease/progressive disease. Important differences were found between the 3 groups in PFS and OS ($P < .0001$). A long-term analysis of an international cohort of 7291 patients included in different ASCT trials showed a statistical cure fraction rate at 14.3% and confirmed that CR at 1 year was associated with superior PFS and OS.[9]

Because it has been clearly shown that maintenance therapy prolongs CR duration,[10] more patients remained in first CR for ≥10 years, and 10 years ago, the requirement for operational cure was CR achievement.[11] However, CR achievement alone was not sufficient; as Barlogie et al[12] showed in 2008, some patients lost their CR within a few years, and such patients had poorer outcomes than those who responded but never attained CR. Barlogie et al used clinical outcome data from 668 patients in the TT2 clinical trial to determine whether sustained CR was a potentially superior surrogate for survival compared with attainment of CR status per se. Within 3 years of treatment initiation, sustained CR was associated with the highest probability of 10-year OS.

Measurable residual disease and cure

The level of CR or even stringent CR is not a satisfactory requirement in MM, because a vast majority of patients relapse in <10 years. Recently, it became possible to assess deeper levels of response and define molecular remission by allele-specific oligonucleotide quantitative polymerase chain reaction methods or phenotypic remissions by multiparameter flow cytometry (MFC).[13] MRD negativity assessed by MFC was shown to be associated with improved PFS, and MRD status was a strong prognostic factor, better even than achievement of CR.[13] This was shown by several groups in the field of ASCT. In a study by the Intergroupe Francophone du Myélome (IFM; 2009 study examining lenalidomide, bortezomib, and dexamethasone [RVD] therapy with or without ASCT), 700 patients were randomly assigned to receive induction therapy with 3 cycles of RVD and then consolidation therapy with either 5 additional cycles of RVD (350 patients) or high-dose melphalan (HDM) plus ASCT followed by 2 additional cycles of RVD (350 patients). Both groups received maintenance therapy with lenalidomide for 1 year. RVD plus ASCT was associated with prolonged PFS compared with RVD alone, and it was evident that PFS was also prolonged in patients who were MRD^- vs those who were MRD^+ (MFC lower limit of detection level, 10^{-4}), with an adjusted hazard ratio (HR) for disease progression or death of 0.30 (95% confidence interval [CI], 0.23-0.37; $P < .001$). In multivariate analysis, achievement of MRD negativity was one of the strongest prognostic factors (MFC: HR, 0.39; $P < .001$; fluorescence in situ hybridization [high risk/standard risk]: HR, 2.22; $P < .001$), even better than CR achievement (HR, 0.58; $P < .001$).[14]

The Spanish experience can be illustrated by the analysis of 3 pooled Programa de Estudio y Tratamiento de las Hemopatías Malignas (PETHEMA)/Grupo Español de Mieloma (GEM) clinical trials comprising >600 patients in total. This showed that MRD negativity in patients achieving CR was associated with much longer PFS (median, 63 months; $P < .001$) and OS (median not reached; $P < .001$) compared with patients achieving CR who were MRD^+, regardless of type of treatment or patient risk group. The prognostic value of CR is related to MRD negativity and outcome of patients in CR, but in patients with persistent MRD positivity, it is not better than in those in PR. MRD^+ patients in CR had similar survival to MRD^+ patients in nCR and PR (median PFS, 27, 27, and 29 months, respectively; median OS, 59, 64, and 65 months, respectively). An important point was that the impact of MRD negativity was shown for ASCT-ineligible patients as well. The authors concluded that MRD negativity should be considered as one of the most relevant end points for transplantation-eligible and elderly fit patients with MM.[15]

A meta-analysis comprising data from 14 studies and 1273 patients confirmed the impact of MRD negativity on PFS in patients achieving CR.[16] Compared with MRD^+ patients, the median PFS was 60 vs 36 months. Approximately 30% of MRD^- patients were progression free at 10 years (adjusted $\chi^2 = 35.85$; $P < .0001$). Therefore, MRD negativity was considered a new end point of myeloma therapy.[17] In addition, and although data are lacking and rather difficult to generate in this domain, one could speculate that negative MRD status might be linked (at least indirectly) to patient quality of life. Obviously, aspiration can be associated with some discomfort, but a very low or undetectable tumor mass is usually associated with good relief of MM symptoms and is likely to have a positive psychological impact.

However, the impact of MRD negativity on PFS should be examined by focusing on different parameters: (1) sensitivity or lower limit of detection level (method used), (2) timing of assessment and sustainability, (3) type and duration of treatment, (4) initial prognostic factors (most importantly cytogenetics), and (5) age.

In a more recent meta-analysis of 44 studies and >8900 patients, including studies using more sensitive methods of MRD assessment such as next-generation sequencing (NGS) and next-generation flow (NGF), Munshi et al[18] showed that in all circumstances across disease settings, achieving MRD negativity was associated with improved PFS (HR, 0.33; 95% CI, 0.29-0.37; $P < .001$) and OS (HR, 0.45; 95% CI, 0.39-0.51; $P < .001$). This improvement in survival was observed regardless of disease setting (newly diagnosed or relapsed/refractory MM), MRD lower limit of detection threshold, cytogenetic risk, method of MRD

assessment, depth of clinical response at the time of MRD measurement, and MRD assessment premaintenance and 12 months after start of maintenance therapy. This large sample size from a broad and heterogeneous MM population allowed confirmation that MRD negativity is a prognostic biomarker for PFS in MM. The impact on PFS, however, varied with different parameters. It was most marked with MRD negativity at the lower limit of detection threshold of 10^{-6} (HR, 0.22; 95% CI, 0.16-0.29; $P < .001$) and when assessed by NGF (HR, 0.22; 95% CI, 0.14-0.33). Finally, PFS estimates were more favorable in patients who achieved MRD negativity at 12 months after start of maintenance than in those who reached MRD negativity before maintenance therapy.

MRD sensitivity or lower limit of detection level

The findings of Perrot et al[19] in the IFM 2009 trial confirmed the value of NGS-determined MRD status as a prognostic biomarker in MM, with the best outcome observed when the lower limit of detection was $<10^{-6}$.

The Spanish group used NGF to assess MRD in the PETHEMA/GEM 2012 MENOS65 trial (registered at www.clinicaltrials.gov as #NCT01916252), in which 458 patients with newly diagnosed MM underwent longitudinal assessment of MRD after 6 induction cycles with RVD, ASCT, and 2 consolidation courses with RVD. The median lower limit of detection achieved by NGF was 2.9×10^{-6}. The estimated 36-month PFS rate was 87% in patients with undetectable MRD vs 50% in those with persistent MRD after consolidation (HR, 0.21; 95% CI, 0.12-0.36; $P < .001$). The probability of being progression free at 4 years was >80%. Patients with undetectable MRD had an 82% reduction in risk of progression or death (HR, 0.18; 95% CI, 0.11-0.30; $P < .001$) and an 88% reduction in risk of death (HR, 0.12; 95% CI, 0.05-0.29; $P < .001$). They also showed that the MRD negativity rate increased from 28% at postinduction (6 cycles of RVD) to 45% postconsolidation (2 cycles of RVD).[13] Their prospective analysis conducted in a large series of homogeneously treated patients validated the International Myeloma Working Group flow MRD^- response criterion[20] and supported its translation from trials into clinical practice.

MRD sustainability and timing of assessment

As with CR, the question of sustained negativity is important. Also, the timing of MRD assessment (ie, premaintenance or 1 or 2 years postmaintenance, as well as whether MRD should be tested only in patients in CR or in both CR and VGPR) is likely to be another key parameter for consideration. A minimum 6-month duration of sustained MRD negativity is necessary based on currently available evidence. In their exploratory analysis using data from the POLLUX and CASTOR trials of combination regimens including anti-CD38 monoclonal antibody daratumumab in relapsed/refractory MM, Avet-Loiseau et al[21] showed that even in this setting, patients who achieved MRD negativity at the lower limit of detection of 10^{-5} measured by NGS had a lower risk of disease progression or death compared with MRD^+ patients, consistent with previous findings. MRD was assessed via NGS (10^{-5}) at CR, 3 and 6 months after confirmed CR (POLLUX), 6 and 12 months after first dose (CASTOR), and every 12 months post-CR in both studies. Sustained MRD negativity (≥6 or ≥12 months) was evaluated in the intention-to-treat population and the population achieving CR or better. PFS was prolonged in patients who achieved sustained MRD negativity for ≥6 months compared with those with only 1 negative MRD assessment, regardless of treatment arm. Consistent with these findings, patients achieving sustained MRD negativity for ≥12 months demonstrated prolonged PFS with daratumumab combination regimens vs MRD^+ patients in the POLLUX trial.[21] However, despite the latter evidence, one must acknowledge that it is possible that a sustained very low level of disease burden (ie, low MRD positivity) or return after therapy to a monoclonal gammopathy of undetermined significance status could also be a pathway to long-term improved outcome in a chronic disease condition. This is different from the operational cure concept and might be analogous to the classical scenario of myeloma in a plateau phase after therapy, but with very low disease levels. Interestingly, the daratumumab arm of the MAIA trial[21] provides a possible example of the relevance of such scenario. In this trial, only 24% of patients reached MRD negativity vs the >60% rate usually seen in ASCT trials. The median PFS in the MAIA trial is projected to be likely ~60 months (T. Facon, University Hospital of Lille, Lille, France; 7 June 2021), which is at least comparable to what has been described with ASCT. The latter suggests that continuous therapy could control the persisting clone for a long period of time.

Finally, in the frontline setting, emerging data suggest that patients with sustained MRD negativity have improved outcomes. Prospective studies using MRD to inform treatment decisions have already shown feasibility and are slowly making their way into clinical practice.[22,23]

MRD and type of therapy

The benefit of ASCT in newly diagnosed MM was confirmed by follow-up of the IFM 2009 trial.[24] Focus was on MRD evaluation as assessed by NGS at a lower limit of detection level of 10^{-6}. As mentioned previously, this trial compared RVD plus ASCT vs RVD alone. All patients received lenalidomide maintenance for 12 months. After a median follow-up of 89.8 months, the median PFS was 47.2 months after ASCT and 35 months with RVD (HR, 0.70; 95% CI, 0.59-0.83). The MRD negativity rate was 29.8% with transplantation and 20% with RVD ($P = .01$). Transplantation was superior to RVD alone in terms of PFS, even in patients who achieved undetectable MRD at a lower limit of detection of 10^{-6}.

The question now is how to increase the proportion of transplantation-eligible patients achieving operational cure. Currently, >50% of patients with MRD negativity at a 10^{-6} lower limit of detection remain progression free at 8 years with standard ASCT strategies: standard triplet induction of 3 to 6 cycles of VTD or RVD, first or second ASCT, and maintenance with lenalidomide.[25] It is hoped that treatment with upfront daratumumab will increase the MRD negativity rate and by association the proportion of patients achieving operational cure. This was indeed the case with the addition of daratumumab to VTD in the CASSIOPEIA trial[26]; at day 100 after transplantation, 211 patients (39%) in the daratumumab plus VTD group vs 141 (26%) in the VTD group achieved complete response or better, and 346 (64%) of 543 vs 236 (44%) of 542 achieved MRD negativity (10^{-5} lower limit of detection threshold assessed by MFC; both $P < .0001$). However, longer follow-up is still needed to assess the true value of MRD negativity in these patients. In the GRIFFIN trial, the addition of daratumumab to RVD also increased the MRD negativity rate at

lower limit of detection thresholds of both 10^{-5} and 10^{-6}, before and after maintenance. MRD negativity (10^{-5}) rates favored daratumumab plus RVD vs RVD (62.5% vs 27.2%; $P < .0001$. Similarly, MRD negativity (10^{-6}) rates favored daratumumab plus RVD vs RVD (26.9% vs 12.6%; $P = .014$). After a median follow-up of 26.7 months, addition of daratumumab to RVD induction and consolidation followed by daratumumab plus lenalidomide maintenance in transplantation-eligible patients with newly diagnosed MM continued to demonstrate deep and improved responses, including MRD negativity rates, compared with lenalidomide alone. Maintenance therapy increased stringent CR and MRD negativity rates, compared with postconsolidation rates.[27]

The objective of the upcoming IFM trial for transplantation-eligible patients is to achieve the highest possible proportion of patients with MRD negativity (lower limit of detection level, 10^{-6}). Treatment will start with an induction of 6 cycles of isatuximab plus carfilzomib, lenalidomide, and dexamethasone (KRD), after which treatment will depend on achievement of MRD negativity at the 10^{-5} lower limit of detection. Patients achieving MRD negativity will be randomly assigned to proceed to HDM/ASCT or KRD treatment. MRD^+ patients will be randomly assigned to proceed to single or double HDM/ASCT. Maintenance will be different for MRD^- and MRD^+ patients, with a new regimen (combination of isatuximab and iberdomide) for the latter group to increase the rate of MRD negativity. In the mid and long term, incorporation of novel immunotherapies in the frontline or early disease treatment setting, such as chimeric antigen receptor T cells[28,29] and/or bispecific antibodies,[30] may also allow further improvement in the rates of MRD negativity and could become a key to sustained MRD negativity.

Another possibility for increasing the proportion of transplantation-eligible patients achieving operational cure would be to treat at an earlier stage of disease. The Quiredex phase 3 trial published by the Spanish PETHEMA/GEM group examined this scenario by randomly assigning 119 patients with high-risk smoldering MM (sMM) to either treatment or observation. Patients with sMM are not usually treated until development of symptomatic disease. The authors concluded that early treatment with lenalidomide and dexamethasone (RD), followed by maintenance therapy with lenalidomide, significantly delayed the time to progression to symptomatic disease and resulted in an OS benefit.[31] However, the objective of that trial, which started in 2007, was not operational cure, and MRD was not assessed. More recently, the same group initiated a more ambitious trial with the objective of achieving MRD negativity and curing patients. In 2019, results were published from this multicenter phase 2 clinical trial designed to evaluate the efficacy and toxicity of an intensive therapeutic approach in 90 patients age <70 years with asymptomatic high-risk sMM, eligible for transplantation between June 2015 and June 2017. Patients received induction treatment consisting of 6 4-week cycles of KRD. After induction, patients received IV HDT-based treatment followed by peripheral blood ASCT. Consolidation treatment consisted of 2 cycles of KRD. All patients without progression to symptomatic MM or toxicity requiring discontinuation of the trial received maintenance treatment (RD) for up to 2 years. The primary end point was sustained MRD negativity (assessed by NGF) at 5 years after HDT and ASCT. Seventy-seven patients completed induction, HDT and ASCT, consolidation, and 1 year of maintenance. The primary end point of the trial was met, and 56% of the patients who completed induction and HDT and ASCT achieved MRD negativity. This curative strategy for high-risk sMM continues to be encouraging, with a 35-month PFS of 92% and OS of 96%.[32] Although this treatment yielded very good MRD negativity rates and PFS, there were adverse events and a few fatalities in this nonrandomized trial. The question of the use of this aggressive approach in patients with asymptomatic sMM must be addressed. A better definition of high-risk sMM is therefore needed.

MRD negativity and initial prognostic factors

The previously mentioned IFM study by Perrot et al[12] defined high-risk patients at diagnosis as those with the presence of 17p deletion [del(17p)] or either t(4;14) or t(14;16) translocation. That study also showed improved PFS in those achieving MRD negativity (NGS lower limit of detection, 10^{-6}), irrespective of cytogenetic risk group. These results were from 366 patients with known MRD status at the start of maintenance therapy. Among patients with high-risk cytogenetics, MRD negativity was achieved in 17 (40%) of 42 patients with t(4;14), a rate comparable to standard risk, but in only 3 (11%) of 28 patients with del(17p). With respect to PFS, MRD negativity was associated with better outcome compared with MRD^+ patients in both standard- and high-risk groups, although results were slightly better for the former group.

The experience from the PETHEMA/GEM 2012 MENOS65 trial also showed that undetectable MRD (negativity at lower limit of detection, 2×10^{-6} to $<10^{-5}$) is more frequent in patients at standard compared with high risk (49% vs 37%). Interestingly, they showed that among patients with undetectable MRD, 36-month PFS was similar in those at standard (n = 300) and high risk (n = 90) at >90% in each group. The PFS results for high risk with persisting MRD, standard risk with persisting MRD, high risk with MRD negativity, and standard risk with MRD negativity were 37%, 60%, 91%, and 97%, respectively ($P < .0001$).[33] These studies confirm that it is possible to achieve MRD negativity in high-risk patients, and because this translates into better PFS, the objective of treatment of high-risk patients with MM is to achieve MRD negativity and overcome the dismal prognosis of transplantation-eligible patients with MM and high-risk cytogenetics.

MRD negativity and age

Until now, the impact of MRD negativity has mostly been seen in transplantation-eligible patients. However, the recent meta-analysis published by Munshi et al[18] confirmed that older patients can also achieve MRD negativity, which is also associated with dramatically improved PFS. Three-year PFS rates for transplantation-ineligible patients were 76.3% and 37.1% for MRD^- and MRD^+ patients, respectively ($P < .001$). In the open-label phase 3 MAIA trial, 737 patients with newly diagnosed MM (median time since diagnosis, 0.9 months [range, 0-14.5]) ineligible for ASCT because of older age (≥65 years or preexisting conditions likely to result in unacceptable adverse effects associated with ASCT) were randomly assigned (1:1) to receive either daratumumab in combination with standard treatment for older patients (daratumumab plus RD) or RD alone (control arm). The median age was 73 years (range, 45-90). Treatment continued until the occurrence of disease progression or unacceptable adverse effects. It was hoped that daratumumab would further increase the MRD negativity rate. At an NGS lower limit of detection level of 10^{-5}, 24% of patients treated with daratumumab plus RD compared with 7% of those treated with RD alone

achieved MRD negativity ($P < .001$).[34] Patients reaching this milestone (assessed in participants who achieved CR or better) experienced durable PFS.

Pitfalls of MRD assessment

When using a lower limit of detection for MRD of 10^{-4}, a majority of patients will relapse before 10 years.[18] However, a lower limit of detection of 10^{-6} may prove to be a more robust indicator. One would expect that patients who are still MRD$^-$ at the level of 10^{-6} at 10 years will enjoy very long PFS and OS and thus could be considered as having reached the status of operational cure. However, we still do not know what proportion of patients who achieve MRD negativity at this level of 10^{-6} will remain MRD$^-$ at 10 years. Also, the minimum duration of MRD negativity associated with the highest probability of remaining MRD$^-$ at 10 years is still unknown. Therefore, more follow-up is needed before confirming that operational cure is defined by 10-year MRD negativity at the level of detection of 10^{-6}. In addition to NGF and NGS techniques, imaging modalities such as magnetic resonance imaging and [^{18}F]flourodeoxyglucose positron emission tomography (PET) have emerged as significant tools to measure MRD and could provide additional information regarding disease eradication over the long term. These methods provide information on disease involvement of the bones and patterns of bone marrow (BM) involvement, as well as disease outside the marrow (extramedullary disease). Extramedullary disease, patchy involvement, and diluted samples can give rise to falsely negative MRD. Looking at the subanalysis of the IFM 2009 trial, Moreau et al[35] showed that posttreatment negative PET–computed tomography (CT; normalization) before maintenance had a prognostic impact on PFS (72% vs 56.8%; $P = .011$). Also, PFS was higher for patients with both normalized PET-CT and MRD negativity before maintenance compared with those with either PET positivity and/or MRD positivity before maintenance (3-year PFS, 86.8% vs 52.9%, respectively; $P = .05$). These results allowed the International Myeloma Working Group to define new criteria for MRD negativity,[20] as follows: in patients in CR, MRD negativity is present only if phenotypically aberrant clonal plasma cells are not detected in BM aspirate samples at a minimum lower limit of detection of 1 in 10^5 nucleated cells or higher (assessed by either NGF, NGS, or both) and if a negative PET-CT scan demonstrates a lack of disease outside the BM (ie, disappearance of every area of increased tracer uptake found at baseline or preceding PET-CT scan or decrease to lower mediastinal blood pool standardized uptake value, or decrease to lower standardized uptake value than that of surrounding normal tissue). Finally, it is worth emphasizing the importance of appropriate statistical methods in studies assessing the impact of MRD on outcome (ie, landmark analysis or similar techniques). This is of the utmost importance for accurate assessment.

Conclusion

Despite major advances, patients with MM continue to die prematurely as a result of their cancer. The requirement for long-term remission in MM is likely sustained MRD negativity (at a lower limit of detection of at least 10^{-5}). Different international consensus efforts have provided important guidance on how to implement MRD measurements in clinical trials to obtain solid data on sustained MRD negativity in different treatment and disease settings.[36,37] The best probability of long-term PFS is at the 10^{-6} level. MRD negativity should be sustained for at least 1 year. Achievement of MRD negativity is less frequent in those with high-risk MM, especially in patients with del(17p). However, when achieved, it can still be associated with long PFS. PET-CT scan negativity is also an important requirement (at least for the 10^{-5} threshold). Currently, the highest probability of operational cure is in younger patients receiving standard treatment with proteasome inhibitors and immunomodulatory drug–based triplet regimens, HDT/ASCT, and lenalidomide maintenance. It is hoped that daratumumab will increase the MRD negativity rate and the proportion of patients achieving operational cure and that older patients can also achieve operational cure, especially if they are treated upfront with daratumumab. Furthermore, incorporation of novel immunotherapies early in the treatment algorithm could also become a key factor for a favorable long-term outcome.

Efforts investigating the impact of MRD and refining its role in MM outcome will prove beneficial to different stakeholders, including practicing clinicians, clinical trialists, and regulatory authorities. Patients and physicians would be able to rely on a dynamic prognostic marker during the course of therapy. From the standpoint of trialists and regulatory agencies,[38] with the development of more sensitive techniques and the approval of novel drug therapies, it will be possible to perform shorter clinical trials. Such trials are currently ongoing (eg, PERSEUS; registered at www.clinicaltrials.gov as #NCT03710603), and it is hoped they will lead to more personalized management of patients with MM, potential avoidance of prolonged treatments with their associated toxicities (including cost), and achievement of long-term cure.

Acknowledgments

The authors acknowledge the support and work of the Intergroupe Francophone du Myelome (IFM) and thank the patients and families for their contribution to the different myeloma and IFM research protocols. M.M. thanks Junia Melo (University of Adelaide, Adelaide, SA, Australia) for critical reading of the manuscript.

Authorship

Contribution: M.M. and J.-L.H. performed the bibliographic search and wrote the first version of the manuscript; and all authors contributed to the design and writing, editing, and revision of this manuscript.

Conflict-of-interest disclosure: M.M. has received research support and lecture honoraria from Adaptive, Amgen, Astellas, Celgene, GlaxoSmithKline, Janssen, Jazz, Novartis, Pfizer, Takeda, and Sanofi, all outside the scope of this work. The remaining authors declare no competing financial interests.

ORCID profile: H.A.-L., 0000-0002-3050-0140.

Correspondence: Mohamad Mohty, Service d'Hématologie Clinique et Thérapie Cellulaire, Hôpital Saint-Antoine, 75012 Paris, France; e-mail: mohamad.mohty@inserm.fr.

Footnote

Submitted 7 June 2021; accepted 26 July 2021; prepublished online on Blood First Edition 29 July 2021. DOI 10.1182/blood.2021012854.

REFERENCES

1. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia*. 2020;34(4):966-984.
2. Barlogie B. Toward a cure for multiple myeloma? *N Engl J Med*. 1991;325(18):1304-1306.
3. Powles R, Sirohi B, Treleaven J, et al. Continued first complete remission in multiple myeloma for over 10 years: a series of 'operationally cured' patients [abstract]. *Blood*. 2000;96(suppl 1). Abstract 515a.
4. Fassas A, Shaughnessy J, Barlogie B. Cure of myeloma: hype or reality? *Bone Marrow Transplant*. 2005;35(3):215-224.
5. Rajkumar SV. Treatment of myeloma: cure vs control. *Mayo Clin Proc*. 2008;83(10):1142-1145.
6. Barlogie B, Mitchell A, van Rhee F, Epstein J, Morgan GJ, Crowley J. Curing myeloma at last: defining criteria and providing the evidence. *Blood*. 2014;124(20):3043-3051.
7. Harousseau JL, Attal M, Avet-Loiseau H. The role of complete response in multiple myeloma. *Blood*. 2009;114(15):3139-3146.
8. Martinez-Lopez J, Blade J, Mateos MV, et al; Programa para el Estudio de la Terapé utica en Hemopatía Maligna. Long-term prognostic significance of response in multiple myeloma after stem cell transplantation. *Blood*. 2011;118(3):529-534.
9. Usmani SZ, Hoering A, Cavo M, et al. Clinical predictors of long-term survival in newly diagnosed transplant eligible multiple myeloma – an IMWG Research Project. *Blood Cancer J*. 2018;8(12):123.
10. Diamond B, Korde N, Lesokhin AM, et al. Dynamics of minimal residual disease in patients with multiple myeloma on continuous lenalidomide maintenance: a single-arm, single-centre, phase 2 trial. *Lancet Haematol*. 2021;8(6):e422-e432.
11. San-Miguel JF, Mateos MV. Can multiple myeloma become a curable disease? *Haematologica*. 2011;96(9):1246-1248.
12. Barlogie B, Anaissie E, Haessler J, et al. Complete remission sustained 3 years from treatment initiation is a powerful surrogate for extended survival in multiple myeloma. *Cancer*. 2008;113(2):355-359.
13. Paiva B, Puig N, Cedena MT, et al; GEM (Grupo Español de Mieloma)/PETHEMA (Programa Para el Estudio de la Terapéutica en Hemopatías Malignas) Cooperative Study Group. Measurable residual disease by next-generation flow cytometry in multiple myeloma. *J Clin Oncol*. 2020;38(8):784-792.
14. Attal M, Lauwers-Cances V, Hulin C, et al; IFM 2009 Study. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med*. 2017;376(14):1311-1320.
15. Lahuerta JJ, Paiva B, Vidriales MB, et al; GEM (Grupo Español de Mieloma)/PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) Cooperative Study Group. Depth of response in multiple myeloma: a pooled analysis of three PETHEMA/GEM clinical trials. *J Clin Oncol*. 2017;35(25):2900-2910.
16. Munshi NC, Avet-Loiseau H, Rawstron AC, et al. Association of minimal residual disease with superior survival outcomes in patients with multiple myeloma: a meta-analysis. *JAMA Oncol*. 2017;3(1):28-35.
17. Harousseau JL, Avet-Loiseau H. Minimal residual disease negativity is a new end point of myeloma therapy. *J Clin Oncol*. 2017;35(25):2863-2865.
18. Munshi NC, Avet-Loiseau H, Anderson KC, et al. A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma. *Blood Adv*. 2020;4(23):5988-5999.
19. Perrot A, Lauwers-Cances V, Corre J, et al. Minimal residual disease negativity using deep sequencing is a major prognostic factor in multiple myeloma. *Blood*. 2018;132(23):2456-2464.
20. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol*. 2016;17(8):e328-e346.
21. Avet-Loiseau H, San-Miguel J, Casneuf T, et al. Evaluation of sustained minimal residual disease negativity with daratumumab-combination regimens in relapsed and/or refractory multiple myeloma: analysis of POLLUX and CASTOR. *J Clin Oncol*. 2021;39(10):1139-1149.
22. Costa LJ, Chhabra S, Godby KN, et al. Daratumumab, carfilzomib, lenalidomide and dexamethasone (Dara-KRd) induction, autologous transplantation and post-transplant, response-adapted, measurable residual disease (MRD)-based Dara-Krd consolidation in patients with newly diagnosed multiple myeloma (NDMM) [abstract]. *Blood*. 2019;134(suppl 1). Abstract 860.
23. Jasielec JK, Kubicki T, Raje N, et al. Carfilzomib, lenalidomide, and dexamethasone plus transplant in newly diagnosed multiple myeloma. *Blood*. 2020;136(22):2513-2523.
24. Perrot A, Lauwers-Cances V, Cazaubiel T, et al. Early versus late autologous stem cell transplant in newly diagnosed multiple myeloma: long-term follow-up analysis of the IFM 2009 trial [abstract]. *Blood*. 2020;136(suppl 1). Abstract 39.
25. Bal S, Costa LJ. Maintaining the minimal: dynamics of measurable residual disease with continuous lenalidomide therapy. *Lancet Haematol*. 2021;8(6):e386-e387.
26. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. *Lancet*. 2019;394(10192):29-38.
27. Kaufman JL, Laubach JP, Sborov D, et al. Daratumumab (DARA) plus lenalidomide, bortezomib, and dexamethasone (RVd) in patients with transplant-eligible newly diagnosed multiple myeloma (NDMM): updated analysis of Griffin after 12 months of maintenance therapy [abstract]. *Blood*. 2020;136(suppl 1). Abstract 45.
28. Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *N Engl J Med*. 2021;384(8):705-716.
29. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *Lancet*. 2021;398(10297):314-324.
30. Maples KT, Johnson C, Lonial S. Antibody treatment in multiple myeloma. *Clin Adv Hematol Oncol*. 2021;19(3):166-174.
31. Mateos MV, Hernández MT, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. *N Engl J Med*. 2013;369(5):438-447.
32. Mateos M-V, Martinez-Lopez J, Rodriguez Otero P, et al. Curative strategy (GEM-CESAR) for high-risk smoldering myeloma (SMM): carfilzomib, lenalidomide and dexamethasone (KRd) as induction followed by HDT-ASCT, consolidation with Krd and maintenance with Rd [abstract]. *Blood*. 2019;134(suppl 1). Abstract 781.
33. Goicoechea I, Puig N, Cedena MT, et al. Deep MRD profiling defines outcome and unveils different modes of treatment resistance in standard- and high-risk myeloma. *Blood*. 2021;137(1):49-60.
34. Facon T, Kumar S, Plesner T, et al; MAIA Trial Investigators. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med*. 2019;380(22):2104-2115.
35. Moreau P, Attal M, Caillot D, et al. Prospective evaluation of magnetic resonance imaging and [^{18}F]fluorodeoxyglucose positron emission tomography-computed tomography at diagnosis and before maintenance therapy in symptomatic patients with multiple myeloma included in the IFM/DFCI 2009 trial: results of the IMAJEM study. *J Clin Oncol*. 2017;35(25):2911-2918.
36. Holstein SA, Bahlis N, Bergsagel PL, et al. The 2020 BMT CTN myeloma intergroup workshop on immune profiling and minimal residual disease testing in multiple myeloma [published online ahead of print 6 June 2021]. *Transplant Cell Ther*. doi:10.1016/j.jtct.2021.05.027.
37. Costa LJ, Derman BA, Bal S, et al. International harmonization in performing and reporting minimal residual disease assessment in multiple myeloma trials. *Leukemia*. 2021;35(1):18-30.
38. Gormley NJ, Turley DM, Dickey JS, et al. Regulatory perspective on minimal residual disease flow cytometry testing in multiple myeloma. *Cytometry B Clin Cytom*. 2016;90(1):73-80.