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CLINICAL TRIALS AND OBSERVATIONS

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MRD end point in myeloma: ready for prime time?

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In this issue of *Blood*, Cavo et al[1] confirm the prognostic value of minimal residual disease (MRD) negativity in multiple myeloma (MM) by conducting a robust analysis of pooled data of 2510 patients from 4 phase 3 registrational studies. This report is timely, as MRD is being explored as a potential surrogate end point in clinical trials to accelerate regulatory drug approval and guide future treatment strategies for patients with MM.

The achievement of MRD negativity is perhaps the most important prognostic factor in MM, as has been demonstrated in several meta-analyses.[2,3] One recent meta-analysis[2] of 44 studies in >8000 patients showed that the achievement of MRD negativity improved both progression-free survival (PFS; hazards ratio [HR], 0.33; $P < .001$) and overall survival (OS; HR, 0.45; $P < .001$) in patients with MM. The studies included in this meta-analysis were heterogeneous in MRD evaluation methods, MRD sensitivity thresholds, timing, and depth of clinical response at the time of MRD evaluation. Thus, the data presented by Cavo et al are particularly valuable in that they were derived from a sizable cohort of patients with uniform prospective MRD assessment, per the International Myeloma Working Group (IMWG) consensus statement.[4] Patients who achieved complete response (≥CR) and were MRD negative had a resounding 80% relative risk reduction in disease progression or death ($P < .001$). This benefit occurred irrespective of the assigned treatment and disease state (relapsed or newly diagnosed MM), reinforcing the notion that MRD status could serve as an independent surrogate end point for PFS.

In this study, daratumumab-based treatment increased the rate of MRD-negative CR compared with the control and caused prolonged PFS. Among the patients in CR who were MRD negative, daratumumab-based treatment resulted in a 45% risk reduction in progression or death compared with the controls ($P = .005$). This fact perhaps speaks to the impact of therapy on sustained MRD negativity, which has emerged as a more robust correlate to PFS, as was reported separately in 2 recent publications of the same studies.[5,6] Sustained MRD negativity of at least 6 or 12 months incrementally improved PFS, irrespective of the treatment arm for both newly diagnosed MM (NDMM)[6] and relapsed/refractory MM (RRMM).[5]

The longer MRD negativity is sustained, the stronger the positive impact on PFS,[5,6] whereas loss of MRD negativity predicts clinical relapse of MM.[7] However, the achievement of MRD negativity is not the be-all and end-all for everyone. Attaining MRD negativity is essential for patients with high-risk MM to overcome the poor prognostic impact of adverse cytogenetics.[8,9] In contrast, patients with an indolent MM phenotype or active immune reconstitution may not progress with long-term follow-up, despite persisting MRD positivity.[7] In this report,[1] among patients with poor cytogenetic risk factors, daratumumab-based therapy resulted in a sixfold higher rate of ≥CR with MRD negativity in patients than in controls. Whether this result translates to a PFS shift toward that of the standard-risk group, as occurred in other studies[8,9] was not reported.

To date, the biggest challenge for using this end point has been the lack of uniformity and standardization of different MRD assessment techniques, which has posed a problem in data interpretation and comparisons in clinical trials. The international consensus statement for harmonization of performing and reporting MRD in MM clinical trials,[10] developed in alignment with the IMWG consensus for response and MRD assessment in MM,[4] will unify and improve MRD assessment standards going forward. In many centers, next-generation sequencing (NGS) has superseded the traditional molecular methods of allele-specific oligonucleotide polymerase chain reaction (ASO PCR) or real-time PCR (ASO RQ-PCR). Next-generation flow (NGF) has replaced the conventional 8- or 10-color multiparameter flow cytometry. The IMWG response criteria[4] dictates that MRD assessment should be performed in patients who achieve ≥CR according to NGF or NGS, with a sensitivity threshold of at least 10^{-5}.

The data presented by Cavo and colleagues confirm the prognostic and predictive value of MRD status as measured by NGS (clonoSEQ®) with a sensitivity of 10^{-5} from the largest and relatively uniform set of prospective MRD data collected to date with a long follow-up. The data, together with meta-analyses, including 1 publication in which MRD status fulfilled the Prentice Criteria for PFS surrogacy,[3] support MRD status as a surrogate end point for survival in MM clinical trials. A more rapid end point is essential to moving toward effective

MRD-driven therapeutic strategies in multiple myeloma

Study	Official title	Phase	Patient population	Point of MRD-driven decisions	MRD-driven therapeutic strategies	MRD evaluation technique
IFM 2020-02 NCT04934475	Minimal Residual Disease Adapted Strategy (MIDAS)	3	NDMM, TE	Post–Isa-KRd induction.	Randomization to various consolidation pathways based on MRD status.	NGS at 10^{-6} sensitivity
PERSEUS NCT03710603	Daratumumab, VELCADE (Bortezomib), Lenalidomide, and Dexamethasone Compared with VELCADE, Lenalidomide, and Dexamethasone in Subjects With Previously Untreated Multiple Myeloma (Perseus)	3	NDMM, TE	Upon sustained MRD negativity for 12 mo and at MRD relapse.	Cessation of dara upon sustained 12-mo MRD negativity then reintroduction of dara upon MRD relapse.	NGS at 10^{-5} sensitivity
MASTER NCT03224507	Monoclonal Antibody–Based Sequential Therapy for Deep Remission in Multiple Myeloma (MASTER)	2	NDMM, TE	Upon achieving post-ASCT MRD negativity.	Entry into treatment-free observation and MRD surveillance phase upon achieving post–ASCT MRD negativity.	NGS at 10^{-5} sensitivity
REMNANT NCT04513639	Relapse From MRD Negativity as Indication for Treatment (REMNANT) Study	3	Patients with MRD negativity after VRd induction before and consolidation after ASCT.	Upon MRD relapse (loss of MRD negativity).	Randomization to receive second-line treatment (KRd) either at loss of MRD-negative CR or at progressive disease, per IMWG criteria.	NGF at 10^{-5} sensitivity
DRAMMATIC/ S1803 NCT04071457	S1803, Lenalidomide ± Daratumumab/rHuPh20 as Post–ASCT Maintenance for MM w/MRD to Direct Therapy Duration (DRAMMATIC)	3	TE	After 2 y of maintenance (R ± dara) post–ASCT.	Patients who are MRD positive continue assigned therapy. Those who are MRD negative are randomly assigned to continue or discontinue therapy.	NGS

Clinical trials were selected based on a search of http://clinicaltrials.gov, as of July 2021.

ASCT, autologous stem cell transplant; CT, computed tomography; D, dexamethasone; dara, daratumumab; isa, isatuximab; K, carfilzomib; KRd, carfilzomib-lenalidomide-dexamethasone; L, line; NDMM, newly diagnosed multiple myeloma; PET, positron emission tomography; R, lenalidomide; TE, transplant eligible; TIE, transplant ineligible; V, bortezomib; VRd; bortezomib-lenalidomide-dexamethasone.

MRD-driven therapeutic strategies in multiple myeloma (continued)

Study	Official title	Phase	Patient population	Point of MRD-driven decisions	MRD-driven therapeutic strategies	MRD evaluation technique
AURIGA NCT03901963	A Study of Daratumumab Plus Lenalidomide Versus Lenalidomide Alone as Maintenance Treatment in Participants With Newly Diagnosed Multiple Myeloma Who Are Minimal Residual Disease Positive After Frontline Autologous Stem Cell Transplant (AURIGA)	3	Patients who are MRD positive after ASCT ± consolidation.	After ASCT ± consolidation.	Patients who are MRD positive will be randomly assigned to receive R, with or without dara.	NGS at 10^{-5} sensitivity
PREDATOR - MRD NCT03697655	Pre-emptive Daratumumab Therapy of Minimal Residual Disease Reappearance or Biochemical Relapse in Multiple Myeloma (PREDATOR)	2	MRD-negativity patients after 1 or 2 prior lines of therapy.	At MRD relapse (loss of MRD-negativity).	Patients with MRD negativity who experience MRD relapse will be given dara.	NGF at 10^{-5} sensitivity
CONPET NCT03314636	Intensified Treatment With Carfilzomib in Myeloma Patients Still PET-positive After First Line Treatment. (CONPET)	2	TIE and TE patients after 1 L of therapy.	Post 1 L of therapy.	Patients who are PET negative will be excluded from treatment; those who are PET positive will be given KRd.	PET/CT NGF at 10^{-5} sensitivity.
NCT04221178	Stopping Maintenance Therapy in People With Multiple Myeloma in MRD-Negative Remission	—	Patients with NDMM or RRMM who have sustained MRD negativity for at least 3 y while receiving continuous maintenance therapy.	Upon sustained MRD negativity for 3 y.	Cessation of continuous maintenance therapy upon sustained MRD negativity for at least 3 y.	NGF at 10^{-5} sensitivity.

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immunotherapies and powerful triplet and quadruplet regimens in earlier lines of treatment, with the real prospect of operational cure. The time frame to demonstrate statistically significant PFS superiority of new therapies over existing ones will be too long for timely regulatory approval of new drugs.

The exciting challenge in the years ahead will be to unravel the appropriate use of MRD status to guide therapeutic decisions. For example, can we escalate therapy in the presence of MRD positivity or de-escalate therapy upon achieving MRD negativity, particularly in the context of maintenance? What duration of sustained MRD negativity is needed to consider de-escalation/cessation of continuous treatment? Will salvage therapy upon loss of MRD negativity be necessary in our quest for operational cures in MM? These MRD-driven therapeutic strategies are being explored in an increasing number of clinical trials (see table) and are gaining momentum. Undoubtedly, MRD assessment will serve as a gateway to better therapeutic strategies in the quest for an operational cure in MM. The data presented by Cavo et al are a firm step toward this quest, and at the very least, indicate that the use of MRD status as a surrogate end point for PFS in MM is ready for prime time.

Conflict-of-interest disclosure: H.Q. has received research funding from Amgen, GlaxoSmithKline, Celgene, Sanofi, and Karyopharm and has served on advisory boards for Amgen, GlaxoSmithKline, Bristol Myers Squibb, Celgene, Karyopharm, Sanofi, Takeda, Janssen, CSL, and Antengene. ■

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DOI 10.1182/blood.2021013363

HEMATOPOIESIS AND STEM CELLS

Comment on Yang et al, page 845

Renewing your HBO1 subscription

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In this issue of *Blood*, Yang et al[1] show that HBO1 (KAT7) promotes hematopoietic stem cell (HSC) quiescence and self-renewal through histone acetylation and transcription of HSC genes, revealing an important role for HBO1 in maintaining the blood system.

Acetylation, one of the oldest described histone modifications, involves the transfer of an acetyl group from acetyl-CoA to the ε-amino group of a lysine residue by histone acetyltransferases.[2] Histone acetylation acts to unfold chromatin to facilitate DNA access for replication or transcription. Histone H3 lysine 14 acetylation (H3K14ac) is found throughout gene bodies and promoters[3] and promotes processivity of RNA polymerase. H3K14ac is mainly established by HBO1, a conserved, widely expressed member of the MYST acetyltransferase family.[4] The MYST family includes 4 additional acetyltransferases: KAT6A, KAT6B, KAT8 (MOF), and KAT5 (TIP60). HBO1 acts as a core catalytic subunit in multimeric complexes along with a host of cofactors that includes MEAF6, ING4, ING5, BRPF1, BRPF2, BRPF3 (H3K14), JADE1, JADE2, and JADE3 (H4). HBO1 and its cofactors work in concert with other epigenetic regulators in various complexes, such as MLL, that promote epigenetic or transcriptional activation.[5]

Yang et al provide important new insights into the role of HBO1 in normal HSC function and blood replenishment (see figure). The investigators produced 2 mouse models that enabled inducible deletion of exon 1 of *Hbo1*. Deletion led to HSC loss and significantly decreased production of blood cells of all lineages, suggesting HSC exhaustion as a potential cause. Further experimentation suggested that depletions were apparent in the HSC compartment before losses in the differentiated populations. The authors strengthened these findings through experiments with competitive transplantation into lethally irradiated mice. *Hbo1*$^{fl/+}$*;CreER* (heterozygous) donor cells contributed 56% to 86% of peripheral blood cells in bone marrow chimeras whereas *Hbo1*$^{fl/fl}$*;CreER* (deletion) donor cells made no detectable contribution. Furthermore, lower