Minimal residual disease and imaging-guided consolidation strategies in newly diagnosed and relapsed refractory multiple myeloma

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Abstract
Measurement of minimal residual disease (MRD) by next-generation flow cytometry (NGF) is an important tool to define deep responses in multiple myeloma (MM). However, little is known about the value of combining NGF with functional imaging and its role for MRD-based consolidation strategies in clinical routine. In the present study, we report our experience investigating these issues with 102 patients with newly diagnosed ($n = 57$) and relapsed/refractory MM ($n = 45$). Imaging was performed using either positron emission tomography or diffusion-weighted magnetic resonance imaging. In all, 45% of patients achieved MRD-negativity on both NGF and imaging (double-negativity), and 8% and 40% of patients were negative on either NGF or imaging respectively. Thus, in a minority of patients imaging was the only technique to detect residual disease. Imaging-positivity despite negativity on NGF was more common in heavily pretreated disease (four or more previous lines) compared to newly diagnosed MM ($p < 0.01$). Among the 29 patients undergoing MRD-triggered consolidation, 51% responded with MRD conversion and 21% with improved serological response. MRD-triggered consolidation led to superior progression-free survival (PFS) when compared to standard treatment ($p = 0.04$). In conclusion, we show that combining NGF with imaging is helpful particularly in patients with heavily pretreated MM, and that MRD-based consolidation could lead to improved PFS.

KEYWORDS
consolidation, functional imaging, minimal residual disease, MRD-based decision-making, multiple myeloma
INTRODUCTION

In multiple myeloma (MM), minimal residual disease (MRD) status is gaining increasing importance as an end-point in clinical studies and, more recently, in clinical routine as an additional tool for response assessment. This development is mainly driven by the introduction of novel therapeutic agents that show long lasting and deep responses beyond complete response (CR). MRD status has been shown to constitute a good surrogate marker for progression-free survival (PFS) and overall survival (OS) in a number of trials and meta-analyses.1–7 Thus, there are efforts to implement MRD status as a new end-point for registration trials because MRD data mature far earlier when compared to traditional end-points like OS and PFS.8–11

If MRD negativity needs confirmation by functional imaging to rule out residual focal disease outside the iliac crest12–14 has yet to be determined. The CASSIOPEIT trial indicated minor relevance of imaging in addition to MRD diagnostics in front-line treatment.15 This is supported by published data from the University of Arkansas for Medical Sciences (UAMS). In patients with newly diagnosed MM (NDMM) enrolled on total therapy trials, the frequency of residual disease captured by imaging was only 12%.14,16 However, real-world data supporting this observation is missing.

While MRD data are clearly associated with outcome, the use of this information for clinical decision-making is still unclear. Recently, a first report suggests that MRD-based clinical decision-making during maintenance therapy could be beneficial for both MRD-negative and -positive patients in NDMM,17 and a number of trials are currently testing MRD-triggered maintenance strategies in a randomised fashion.18–21 A good example is the MASTER trial (ClinicalTrials.gov Identifier: NCT03224507) highlighting a MRD-guided approach to de-escalate treatment intensity.22

Here, we report on our institutions experience with implementing both functional imaging and next-generation flow cytometry (NGF)-guided MRD diagnostics in clinical practice. Furthermore, we report on our initial experience with using this information to guide consolidation strategies.

METHODS AND COHORT

We included patients with NDMM and relapsed/refractory (RR) MM achieving very good partial response (VGPR), CR or stringent CR (sCR) by International Myeloma Working Group 2016 criteria.23 Patients undergoing one or more anti-myeloma treatments and not responding or progressing to therapy after achieving a minimal response or better were considered as RR.

Bone marrow samples were collected between July 2019 and May 2021 and analysed using NGF at sensitivity level between $10^{-5}$ and $10^{-6}$ according to the Euroflow guidelines.23,24 For detailed NGF data see Table S6. We performed functional imaging by positron emission tomography (PET) and/or diffusion-weighted magnetic resonance imaging (DWMRI) independent from NGF results within median of 1 day of MRD measurement. However, in some of our patients, imaging in time was not available due to limited capacity of our imaging department and some patients declined. We classified deletion 1p7 detect by fluorescence in situ hybridisation with a cut-off of 20%, translocation (14;16) and (4;14) as high-risk disease features.

Whole-body MRI was assessed at a 1.5-T system (Magnetom Avanto16; Siemens Healthcare) acquiring a diffusion-weighted single-shot echo-planar imaging sequence, an axial T2-weighted half-Fourier single-shot turbo spin-echo (HASTE) and a coronal T1-weighted dual-echo volume-interpolated sequence with Dixon technique. MRI scans were performed and assessed for clinical purposes and not for study purposes.

We acquired PET-computed tomography (CT) scans on Siemens Biograph mCT 64 and mCT 128 PET-CT scanners (Siemens Medical Solutions). We considered focal lesions as a circumscribed focus with increased fluorodeoxyglucose (FDG) or methionine uptake compared to surrounding tissues.26–28 Increased diffuse background signals were not graded as signs of residual disease because of potential interference due to treatment-related reactive changes. Standardised uptake value limits are prone to intra- and inter-patient variability, which includes but are not limited to blood glucose levels, scanner calibration or injected activity. However, we have implemented a respective cut-off for $[18F]$FDG of 2.5 according to the publication by Fonti et al.29 For $[11C]$methionine, we have used the strategy by our group published in 2020.30

The PFS was defined as time to disease progression or death from date of MRD assessment. Number needed to screen was the number of patients that need to be screened to detect residual disease despite MRD negativity on NGF. In patients undergoing consolidation the reference mark for PFS was the date of first MRD assessment. Survival analysis was performed with the Kaplan–Meier method, log-rank test and Cox regression. For subgroup analysis regarding MRD we used chi-squared-test and Fisher’s exact test in case of a low number of observations. A $p \leq 0.05$ was deemed statistically significant. Analyses were undertaken with the Statistical Package for the Social Sciences (SPSS; IBM Corp.). Ethical approval for this study was obtained from local review board (# 8/21). Data sharing agreement: all data will be made available in an anonymised fashion upon request.

In transplant-eligible patients with NDMM, we assessed MRD status mainly after stem cell transplantation and/or after consolidation. In transplant-ineligible and patients with RRMM, we assessed MRD status when $\geq$VGPR was achieved. We identified 102 patients who underwent MRD sampling by NGF after achieving a serological response of $\geq$VGPR (Figure 1). Patients with NDMM ($n=57$) were treated with proteasome inhibitor-based (induction) therapy (93%) combined with at least a first-generation immunomodulatory imide drug (IMiD) (68%) or an alkylating agent (21%). Daratumumab- and elotuzumab-containing.
regimens were administered in 19% and 4% of patients with NDMM respectively. In all, 92% of patients with NDMM underwent high-dose melphalan therapy with autologous stem cells transplantation, of which 82% received tandem transplant. The patients with RRMM ($n = 47$) underwent a median (range) of three (two–13) treatment lines. Seven of them (15%) were penta-refractory toward bortezomib, carfilzomib, daratumumab, lenalidomide and pomalidomide. The majority of patients (51%) were pretreated with an anti-CD38$^+$ antibody prior to MRD assessment and 27% of relapsed patients received a salvage autologous stem cell transplantation before or after.

Detailed patients' characteristics are shown in Table S1.

**RESULTS**

**Response; focus on MRD by NGF data**

First, we addressed the question whether MRD-negativity rates correlated with serological response levels. In patients undergoing consolidation, we referred to serological remission status and NGF-based MRD after consolidation. Indeed, in CR and sCR patients we observed a significantly higher probability of achieving MRD-negativity versus VGPR on NGF (59% vs. 34%, $p = 0.01$, chi-squared; odds ratio [OR] 2.8, 95% confidence interval [CI] 1.2–6.5). Similarly, we found higher rates of double-negativity (negative on both NGF and
functional imaging) among CR and sCR patients (56% vs. 27%, \(p = 0.01\), chi-squared; OR 3.5, 95% CI 1.3–9.5). Despite these findings, a remarkable proportion of VGPR patients attained MRD-negativity, of which three of 11 were positive on functional imaging. Detailed NGF-based MRD data and functional imaging results are shown in Table 1.

In our study, we did not observe a relevant difference in achieving MRD negativity on NGF between high- and standard-risk patients and a similar proportion of patients with NDMM and RRMM achieved MRD-negativity on NGF. Detailed data and analyses are shown in Table S2.

Combining functional imaging and MRD results

Next, we interrogated the correlation of MRD results by NGF with results from functional imaging (available in 78 patients): 45% of patients achieved double-negativity, and 8% and 40% patients were exclusively negative on flow cytometry or imaging respectively (example given in Figure 2, and Table S3).

Double-negativity rates were similar between patients with NDMM and RRMM, yet we observed at least a trend to more imaging-only positive patients in the relapse setting (\(p = 0.10\), chi-squared test). In contrast, we observed both a significant lower proportion of double-negative patients (\(p = 0.03\), chi-squared test), and a higher rate of imaging-only positive (\(p = 0.001\), chi-squared test) patients in heavily pretreated RRMM, as defined by four or more lines of previous treatment. All analyses are shown in Tables S4 and S5. This resulted in a number needed to screen for imaging-only positive patients of 40, eight and three in NDMM, relapsed, and heavily pretreated RRMM, respectively.

Progression-free survival/OS

The median follow-up from NGF-based MRD measurement was 12 months. For both OS and PFS the median was not reached. The 1-year PFS was 87% and 1-year OS was 99%.

| Variable                      | Response | N (%) |
|-------------------------------|----------|-------|
| **Serological response at MRD**-measurement | VGPR     | 38 (37) |
|                               | CR       | 25 (25) |
|                               | sCR      | 39 (38) |
| **MRD status**                | Positive | 51 (50) |
|                               | Negative | 51 (50) |
| **Functional imaging results** | SD       | 3 (4)  |
|                               | PR       | 9 (11) |
|                               | CR       | 66 (85) |

Abbreviations: (s)CR, (stringent) complete response; (VG)PR, (very good) partial response; MRD, minimal residual disease; SD, stable disease.

We observed one death due to secondary acute myeloid leukaemia and 14 relapses. Subgroup analysis showed inferior PFS for patients with residual focal lesions and presence of extramedullary disease. PFS and OS plots are shown in Figures S1–S6.

Our approach of using MRD and imaging data to tailor consolidation

Patients not achieving optimal serological response or MRD negativity by NGF and imaging were offered an individual consolidation approach in line with the current European Society of Medical Oncology (ESMO) guidelines. Indeed, 72% of patients showed MRD conversion (51%) or deepening of serological response levels (21%) following consolidation therapy (Table 2).

To obtain a first impression of whether this deepening of response translated into improved outcome, we performed a survival analysis comparing patients with and without MRD-triggered consolidation. To account for the limited number of patients in both groups, we performed a combined analysis of patients with NDMM and RRMM. MRD-triggered consolidation resulted in a superior PFS (\(p = 0.04\); Figure 3). To account for the heterogeneity in our dataset, we performed a multivariate analysis for PFS including MRD-triggered consolidation, serological response, cytogenetic risk and treatment setting (NDMM/RRMM), which confirmed the impact of MRD-triggered consolidation as an independent variable (\(p = 0.05\)).

Finally, we compared survival of patients with MRD-triggered consolidation to a group of deep-responders who achieved double negative results after standard treatment without consolidation (\(n = 22\)). There was no difference in PFS between these two subgroups (\(p = 0.8\)), supporting consolidation therapy in patients with detectable residual disease (Figure 3).

DISCUSSION

In recent years, MRD negativity became a new end-point in clinical trials with regulatory intent for the NDMM and RRMM settings. Furthermore, MRD testing has entered the clinical routine, but real-world data supporting the use of MRD for decision-making is largely lacking. In the present study, we report our real-world experience with MRD assessment using NGF and functional imaging to guide consolidation approaches in MM.

First, we addressed the clinically highly relevant question of whether functional imaging is mandatory to complement NGF-based MRD testing. In the NDMM setting, we observed hardly any (3%) MRD-negative patients with residual lesions on imaging, resulting in a number needed to screen of 40, appreciating the limited sample size of our study. On the contrary, relapsed patients, and here particularly patients with four or more treatment lines, showed...
persistent focal lesions despite achieving MRD negativity on NGF with a number needed to screen of seven and three. This may be explained by surviving resistant MM clones in focal lesions apart from iliac crest due to a patchy disease pattern.\textsuperscript{14,32} Thus, functional imaging added to flow cytometry MRD assessment and, in our hands, was helpful to custom tailor treatment strategies with a higher impact on patients with RRMM compared to those with NDMM, supporting previous experience from the UAMS group\textsuperscript{14} and CASSIOPET.\textsuperscript{15}

FIGURE 2  Case of a patient with being positive on imaging only PET-CT of a 78-year-old patient progressing with new focal lesions after fourthline therapy. (A) Next-generation flow cytometry-based MRD assessment was negative, (B) no FDG-avid bone disease was detected by PET at the iliac crest – the traditional site for MRD assessment. (C) PET scan of the lower limb revealed multiple new FDG-avid focal bone lesions in line with progressive disease. CT, computed tomography; FDG, fluorodeoxyglucose; MRD, minimal residual disease; PET, positron emission tomography; SUV, standardised uptake value.

Recent studies reported superior outcome for patients achieving double-negativity on NGF and functional imaging.\textsuperscript{14,33} Because of these findings, double-negativity gains more attention as a new therapeutic goal in MM.\textsuperscript{15} However, it is still unclear of how to reach this goal, e.g., in patients who failed to achieve MRD negativity during standard treatment. Mohan et al.\textsuperscript{34} recently confirmed that persistent MRD positivity despite change in treatment is associated with inferior clinical outcome. Intensifying therapy may be a way to address this issue as carfilzomib/lenalidomide
maintenance resulted in a superior rate of MRD-negative patients compared to lenalidomide monotherapy in the FORTE trial (ClinicalTrials.gov Identifier: NCT02203643). To achieve the best possible response, we offered patients not achieving double negativity after standard therapy an individualised consolidation approach. Our practice led to an increased overall response rate and a MRD conversion rate of 51% with a superior PFS. This is in line with recently published data showing MRD-based treatment stratification to improve PFS in a retrospective multicentre analysis. At least in patients with double positivity, which is associated with dismal prognosis, we suggest changing the treatment, appreciating that prospective data are missing. Furthermore, we appreciate the limitations of our study, which include a heterogeneously treated patient population, the comparison of small subgroups, and lacking imaging data for some of our patients.

In conclusion, our data highlight functional imaging to complement MRD assessment in patients with RRMM. Our single-centre observation supports MRD-triggered consolidation, but prospective trials are warranted to confirm this strategy in the management of MM.

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CONFLICT OF INTEREST
All authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS
David Böckle and Leo Rasche designed research, analysed, collected and interpreted data, performed statistical analysis and wrote/reviewed the manuscript. Andreas K. Buck and Paula Tabares contributed to data collection and interpretation, performed research wrote/reviewed the manuscript. Xiang Zhou, Sven Schimanski, Elena Seebacher, Maria Ulbrich, Amy Wilnit contributed to data collection and analysis. Maximilian J Steinhardt, Max Bittrich, Corona Metz, Anke Heidemeier, Thorsten Bley, Rudolf Werner, Andreas Beilhack, Hermann Einsele, Martin Kortüm wrote and critically reviewed the manuscript.

DATA AVAILABILITY STATEMENT
The datasets used and/or analysed during the present study are available from the corresponding author on reasonable request. NGF data generated during this study are included in this published article and its supplementary information files.

**TABLE 2** Detailed individual consolidation data

| Variable                                | N (%) |
|----------------------------------------|-------|
| Total                                   | 29 (100) |
| NDMM                                    | 17 (59) |
| RRMM                                    | 12 (41) |
| Indication for consolidation therapy    |       |
| NGF MRD and/or imaging-positive         | 18 (62) |
| Other (mostly to improve serological response) | 11 (38) |
| Treatment prior to consolidation        |       |
| Stem cell transplantation               | 28 (97) |
| Multiagent chemotherapy                 | 1 (3) |
| Consolidation regimen                  |       |
| PI + anti-CD38 antibody + IMiD + chemotherapy | 11 (38) |
| PI + IMiD + chemotherapy                | 9 (31) |
| Anti-CD38 antibody + IMiD              | 2 (7) |
| Other (all PI-based combinations)      | 7 (24) |
| Results                                 |       |
| NGF + imaging conversion                | 1 (3) |
| NGF conversion only/or achieving double-neg | 9/9 (31/31) |
| Imaging conversion/or achieving double-neg | 5/1 (17/3) |
| Improved serological response only (CR or sCR) | 6 (21) |
| No measurable improvement               | 8 (28) |

Abbreviations: (s)CR, (stringent) complete response; double-neg, both NGF and functional imaging negative; IMiD, immunomodulatory imide drug; MM, multiple myeloma; ND, newly diagnosed; NGF, next-generation flow cytometry-based minimal residual disease status; PI, proteasome inhibitor; RR, relapsed/refractory.

**FIGURE 3** Impact of MRD-triggered consolidation. Left panel shows Kaplan–Meier estimate for progression-free survival (PFS). The right panel shows the comparison of patients undergoing consolidation versus patients achieving MRD negativity on NGF and functional imaging (double-neg) after standard of care (SoC) treatment. MRD, minimal residual disease; NGF, next-generation flow cytometry.
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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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