The Prognostic Role and Utility of Highly Sensitive Minimal Residual Disease Assay in Multiple Myeloma: Is There Really a Difference?

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Poster Number: MM-361

BACKGROUND

- Complete response (CR) rates in multiple myeloma (MM) have significantly increased since the advent of novel treatment regimens combined with autologous stem cell transplant (ASCT), yet a significant proportion of patients still experience relapse.
- The International Myeloma Working Group criteria were updated in 2016 to further categorize patients who achieved CR utilizing minimal residual disease (MRD) and functional imaging (1).
- Recent meta-analysis have shown that achieving MRD negativity has been associated with improved progression free survival (PFS) and overall survival (OS), regardless of treatment or disease risk (2,3). Deeper responses, detected only with higher sensitivity assays, are associated with increased survival benefit (4). Depending on the total of number of nucleated cells analyzed, modern next generation sequencing (NGS) assays offer a sensitivity of up to 10^{-6} (1 clonal cell per million cells evaluated).
- Only a small number of researchers have examined the practical applicability of NGS MRD assays in a real-life settings.

OBJECTIVES

- Determine the predictive and prognostic significance of high sensitivity NGS MRD assay in patients diagnosed with multiple myeloma undergoing frontline ASCT.
- Evaluate the role of sequential MRD measurements after ASCT.

METHODS

- Retrospective analysis
- **Study Population:** patients diagnosed with MM between 2015 and 2020, treated with frontline ASCT, regardless of induction regimen.
- Patients underwent bone marrow evaluation with ClonoSeq® Assay 100 days after ASCT. Assay tracks and quantifies disease-associated immunoglobulin gene sequence rearrangements, identified as “dominant” in a bone marrow at time of diagnosis.
- Patients with two or more MRD measurements were included in the sequential MRD analysis.
- Given the retrospective nature of the study, time to next treatment (TTNT) was used as a surrogate marker for PFS.

RESULTS

TABLE 1. Demographic Characteristics and Response Status at Day 100 post-ASCT

	Overall (N=186)
SEX	
Male	121 (65.1%)
AGE	
Median	62.5
R-ISS STAGE	
I	68 (42.8%)
II	73 (45.9%)
III	18 (11.3%)
Missing	27
HIGH-RISK CYTOGENETICS	
No	143 (80.8%)
Yes	34 (19.2%)
Missing	11
IMWG Response Criteria (at day 100)	
Stringent Complete Response	101 (54.3%)
Complete Response	18 (9.7%)
Very Good Partial Response	48 (25.8%)
Partial Response	16 (8.6%)
Minimal Response	1 (0.5%)
Progressive Disease	2 (1.1%)
MRD Negativity by Sensitivity	
Positive	70 (37.6%)
10^{-4}	33 (17.7%)
10^{-5}	38 (20.4%)
10^{-6}	45 (24.2%)
10^{-6} SENSITIVITY THRESHOLD	
Negative	45 (24.2%)
Positive	141 (75.8%)

- MRD negativity rates did not differ according to MM subtype, R-ISS stage, or cytogenetic risk group.
- When compared to patients who achieved MRD negativity at 10^{-5} or lower thresholds, negativity at 10^{-6} was associated with prolonged TTNT (HR: 0.289, 95% CI: 0.110-0.758, p = 0.0116).
- MRD negativity at 10-6 was the strongest prognostic factor for longer TTNT on multivariable analysis correcting for R-ISS stage, IMWG response category and cytogenetic risk status.
- Sustained MRD negativity, defined as negative MRD at 10^{-5} confirmed one year apart, had significant longer TTNT in both univariate (HR: 0.07, 95% CI: 0.01-0.63, p=0.0175) and multivariable (HR: 0.0109, CI: 0.0003-0.4199, p=0.0153) models.

Figure 1. Time to next treatment according to MRD status at day 100 post-ASCT

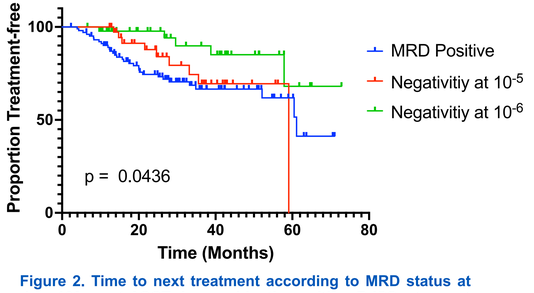


Figure 2. Time to next treatment according to MRD status at day 100 post-ASCT in combination with R-ISS stage at diagnosis

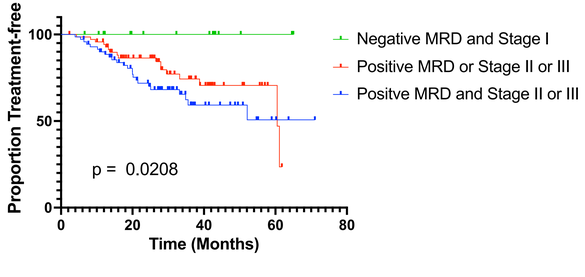
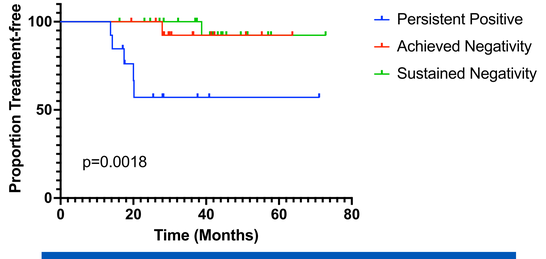


Figure 3. Time to next treatment by sequential MRD measurement status (taken at least ≥12 months apart)



CONCLUSIONS

- With current treatment regimens, high-risk patients do not have lower MRD negativity rates.
- Deeper response measurements enable more accurate identification of patients with superior outcomes.
- Sustained MRD negativity may overcome worse prognosis associated with high-risk features

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