Evidence-Based Minireview: Does achieving MRD negativity after initial therapy improve prognosis for high-risk myeloma patients?

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You are evaluating a 47-year-old man with revised international staging system stage III myeloma who recently underwent an autologous stem cell transplant after receiving 6 cycles of carfilzomib, lenalidomide, and dexamethasone for newly diagnosed disease. Fluorescence in situ hybridization testing at initial presentation also revealed t(4;14). On day 100 evaluation after transplant, he has achieved a stringent complete response. Two-tube, 8-color advanced flow cytometry with a sensitivity of 10^{-5} shows no minimal residual disease. Whole-body positron emission tomography/computed tomography scan shows resolution of all fluorodeoxyglucose avid uptake seen at diagnosis. The patient asks you how these test results impact his prognosis and whether this overcomes his baseline high risk from t(4;14)?

Learning Objectives

- Evaluate the rates of minimal residual disease (MRD) negativity in patients with high-risk (HR) multiple myeloma
- Determine the impact of MRD status on prognosis in HR myeloma and whether MRD negativity abrogates the adverse impact of HR cytogenetics

Introduction

Multiple myeloma (MM) patients with high-risk (HR) fluorescence in situ hybridization (FISH) abnormalities [t(4;14), t(14;16), t(14;20), and deletion 17p] or HR gene expression profiling have inferior outcomes. Amplification (≥4 copies) of CKS1B (1q21) also portends a poor prognosis. Although survival has improved for patients with HR myeloma, outcomes still remain inferior compared with those of patients who have standard-risk (SR) disease.[1] Achievement of bone marrow minimal residual disease (MRD) negativity results in improved progression-free survival (PFS) and overall survival (OS) in MM.[2] It remains unclear whether the benefit of achieving MRD negativity extends to HR patients and if it mitigates the adverse impact of HR cytogenetics. Here, we review data on the rates of MRD negativity in patients with HR MM and the impact of MRD status on prognosis in this population. Table 1 describes data from recent studies evaluating outcomes with MRD negativity in patients with HR cytogenetics.

The commonly used techniques for MRD assessment in MM are multiparametric flow cytometry, including next generation flow cytometry (NGF) and next generation sequencing (NGS).[3] The sensitivity of MRD detection can vary and should be carefully considered when interpreting the results of MRD studies in MM. Each method also has its advantages and disadvantages. NGS requires a baseline sample to determine the clonotype (tumor-specific sequences), which may not be identifiable in all cases. The advantages of NGS are that it is generally more sensitive (10^{-6}) than flow cytometry, is less user dependent, requires fewer cells than NGF, and does not require a fresh sample. However, flow cytometry, including NGF, does not require a baseline sample. It is generally less sensitive (NGF usual sensitivity: 10^{-5}) than NGS, although higher sensitivity with NGF (10^{-6}) can be achieved with the analysis of more cells. It requires a fresh sample. Efforts to streamline NGF with EuroFlow have resulted in standardization of this technique to reduce interuser variability.[3]

Do patients with HR MM achieve MRD negativity at similar rates?

As shown in Table 1, the proportion of HR patients achieving MRD negativity was similar to that of SR patients in several large prospective studies, including the Intergroupe Francophone du Myélome (IFM) 2009 trial (HR: 31% and SR: 26%; 10^{-6}) and the Medical Research Council (MRC) IX trial (HR: 61.5% and SR: 59.8%; 10^{-4}).[4-6] However, this was not consistent across all studies. Paiva et al[7] reported that MRD negativity was seen in 27% of HR patients and 38% of SR patients in the GEM2010MAS65 trial, and Hu et al[8] observed MRD negativity rates (sensitivity: 10^{-4}) of 42% in HR patients vs 69% in SR patients ($P = .014$) in a retrospective analysis. Data on MRD negativity for individual HR abnormalities are more limited and suggest that, although patients with t(4;14) have similar rates of MRD negativity as SR patients, MRD negativity may be lower in patients with 17p deletion.[9-11] In the IFM 2009 study, MRD negativity rates by NGS (sensitivity: 10^{-6}) in patients with 17p deletion, t(4;14), and SR cytogenetics were 11%, 40%, and 26%, respectively. Using NGF (sensitivity: 10^{-5} to 10^{-6}), Goicoechea et al[11] reported MRD negativity rates of 24%, 43%, 60%, and 50% in 17p deletion,

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Table 1. Studies evaluating MRD negativity in MM patients with HR cytogenetics

	Study	Study design	Population	N (MRD data)	HR definition	MRD testing/ sensitivity	Proportion of MRD negativity	Survival outcomes (MRD− vs MRD+)
1	Perrot et al[4]	Prospective (IFM 2009 trial)	NDMM HR + SR Evaluation at multiple time points	ITT population: 509 HR: 74 End of maintenance: 239 HR: 27	t(4;14), t(14;16), deletion 17p	Next generation sequencing 1×10^{-6}	ITT population All: 25% HR: 31% t(4;14): 40% deletion 17p: 11% SR: 26%	ITT population and start of maintenance therapy: longer PFS in MRD− vs MRD+ both for HR and SR patients, although PFS in HR MRD− patients lower than that in SR MRD– patients End of maintenance therapy: longer PFS in MRD– vs MRD+ both for HR and SR; PFS benefit similar across HR and SR MRD– patients Hazard ratio for PFS in HR vs SR patients (adjusted for MRD status, treatment, ISS stage) Start of maintenance: 1.69, 1.14-2.48, $P = .008$ End of maintenance: 1.08, 0.61-1.91, $P = .785$
2	Lahuerta et al[10]	Prospective (3 PETHEMA/GEM trials: GEM2000; GEM2005MENOS65; GEM2010MAS65)	NDMM HR + SR Evaluation 9 mo after enrollment (postinduction in non-ASCT group or post-ASCT)	609 HR: 60 (of 370 with FISH data)	t(4;14) t(14;16), deletion 17p	Flow cytometry 1×10^{-4} to 1×10^{-5}	43% HR: data not available	PFS: HR: 38 vs 14 mo, $P < .001$ Hazard ratio for PFS (adjusted for ISS stage and transplant) HR: 0.30, 0.16-0.58, $P < .001$ SR: 0.44, 0.33-0.59, $P < .001$ OS: HR: 128 vs 26 mo, $P < .001$ Hazard ratio for OS (adjusted for ISS stage and transplant) HR: 0.21, 0.09-0.50, $P < .001$ SR: 0.40, 0.26-0.61, $P < .001$
3	Rawstron et al[5]	Prospective (MRC IX trial)	NDMM HR + SR Day 100 post-ASCT assessment reported here	Post ASCT 397 HR: 109	t(4;14), t(14;16), t(14;20), deletion 17p, gain1q, del1p	Flow cytometry 1×10^{-4}	All: 62.2% HR: 61.5% SR: 59.8%	PFS: HR: 15.7 vs 8.7 mo, $P < .001$ SR: 44.2 vs 33.7 mo, $P = .014$

ASCT, autologous stem cell transplant; BMT CTN, Blood and Marrow Transplant Clinical Trials Network; CR, complete response; GEM, Grupo Español de Mieloma; GEP, gene expression profiling; IFM, Intergroupe Francophone du Myélome; ITT, intention to treat MRC, Medical Research Council; NDMM, newly diagnosed multiple myeloma; NR, not reached; PETHEMA, Programa para el Estudio de la Terapéutica en Hemopatías Malignas; PRIMeR, Prognostic Immunophenotyping in Myeloma Response; TTP, time to progression.

Table 1. (continued)

	Study	Study design	Population	N (MRD data)	HR definition	MRD testing/ sensitivity	Proportion of MRD negativity	Survival outcomes (MRD− vs MRD+)
								Both HR cytogenetics and MRD status predictive of PFS and OS
4	Li et al[6]	Prospective (NCT02086942; NCT02248428)	NDMM HR + SR	123 HR: 72	t(4;14), t(14;16), deletion 17p, gain1q	Flow cytometry 1×10^{-4}	All: 25% HR: 25%	PFS: HR: PFS: 45 vs 22 mo, $P = .016$ SR: PFS: NR vs 34 mo, $P = .009$ PFS in MRD– HR vs SR: 45 mo vs NR, $P = .035$ 4 y OS: HR: 100% vs 54%, $P = -.012$ SR: 87.5% vs 83.6%, $P = .508$ OS in MRD– HR vs SR: 100% vs 87.5%, $P = .48$ MRD status and HR cytogenetics: independent prognostic factors for PFS and OS in multivariate analysis
5	Paiva et al[12]	Prospective (PETHEMA/ GEM 2000 and GEM2005)	NDMM (in CR) HR + SR Day 100 post-ASCT	241 HR: 16%	t(4;14), t(14;16), deletion 17p	Flow cytometry 1×10^{-4} to 1×10^{-5}	All: 64% HR: not available	TTP: SR and MRD–: 83 mo, HR or MRD+ SR: 26 mo, HR and MRD+: 6 mo; $P < .001$ OS HR and MRD–: NR, HR or MRD+ SR: 47 mo, HR and MRD+: 21 mo; $P < .001$ HR FISH and MRD+ were independent prognostic factors for unsustained CR (progression from CR within 1 y of ASCT)
6	Paiva et al[7]	Prospective (PETHEMA/ GEM2010MAS65)	NDMM, older adults HR + SR	162 HR: 26 (of 132 with FISH)	(4;14), t(14;16), deletion 17p	Flow cytometry 1×10^{-4} to 1×10^{-5}	HR: 27% SR: 38% All: 33% (22% of ITT population, N = 241)	TTP: HR: NR vs 12 mo SR: NR vs 15 mo TTP HR MRD– vs SR MRD–: $P = .70$ TTP HR MRD+ vs SR MRD+: $P = .02$ MRD status and HR FISH: independent prognostic factors for TTP and OS
7	Chakraborty et al[9]	Retrospective	NDMM HR only Day 100 post-ASCT	HR: 185	t(4;14), t(14;16), t(14;20), deletion 17p, gain1q	Flow cytometry 1×10^{-4}	HR: 56% t(4;14): 60% Deletion 17p: 48%	PFS: HR: 26 vs 17 mo, $P < .001$ t(4;14): 24 vs 12 mo, $P = .002$ Deletion 17p: 22.5 vs 22 mo, $P = .464$

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Table 1. (continued)

	Study	Study design	Population	N (MRD data)	HR definition	MRD testing/ sensitivity	Proportion of MRD negativity	Survival outcomes (MRD− vs MRD+)
								≥2 HR abnormalities: 12 vs 14 mo, $P = .293$ OS: HR: NR vs 50 mo, $P = .023$ t(4;14): NR vs 31 mo, $P = .039$ Deletion 17p: 52 vs 50 mo, $P = .774$ ≥2 HR abnormalities: 36 vs 31 mo, $P = .419$
8	Hu et al[8]	Retrospective	NDMM HR + SR (matched) Day 100 post-ASCT	96 HR: 31	t(4;14), t(14;16), deletion 17p, gain1q, del1p	Flow cytometry 1×10^{-4}	All: 60% HR: 42% HR vs SR MRD: 42% vs 69%, $P = .014$	PFS: HR: NR vs 19 mo SR: 45.6 vs 24.1 mo MRD status and HR FISH: independent prognostic factors for PFS
9	Goicoechea et al[11]	Prospective (GEM2012MENOS65; abstract)	NDMM HR + SR	419 HR: 90 (of 390 with FISH data)	t(4;14), deletion 17p, and t(14;16)	Flow cytometry 1×10^{-5} to 10^{-6}	del17p: 24% t(4;14): 43% t(14;16): 60% SR: 50%	PFS: HR: NR vs 25 mo del17p: NR vs 14 mo t(4;14): NR vs 28 mo SR: NR vs 46 mo
10	Kunacheewa et al[13]	Retrospective (abstract)	NDMM HR + SR End of initial therapy	136 HR: 29	t(4;14), t(14;16), deletion 17p, gain1q (≥4 copies) and HR GEP signature	Flow cytometry 1×10^{-5}	HR: 41% SR: 54%	PFS: At median follow-up of 14 mo, median PFS was NR in HR or SR group; proportion of patients who relapsed or died in each group were HR: 40% vs 45%, SR: 10% vs 20%, and PFS: HR vs SR; $P = .004$
11	Hahn et al[14]	Prospective (PRIMeR, BMT CTN 0702; abstract)	NDMM HR + SR Before transplant, post-ASCT before maintenance and 1 y post-ASCT	445 HR: not known	t(4;14), t(14;16), t(14;20), deletion 17p, deletion13, aneuploidy, β_2-microglobulin > 5.5 mg/L	Flow cytometry 2.5×10^{-5} to 1×10^{-6}	Post-ASCT All: 78% HR: not known 1 y post-ASCT: all: 84% HR: not known	PFS: MRD status and HR myeloma: independent prognostic factors for PFS in multivariate analysis Hazard ratio for PFS (adjusting for MRD status and treatment arm) HR vs SR: 3.29, 2.09-5.18

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t(4;14), t(14;16), and SR, respectively, among patients treated in the GEM2012MENOS65 trial. In a retrospective study, posttransplant MRD negativity by flow cytometry (sensitivity: 10^{-4}) was seen in 48% and 60% of patients with 17p deletion and t(4;14), respectively.[9]

Does MRD negativity result in improved prognosis in HR MM?

Achievement of MRD negativity has been associated with improved PFS in patients with HR cytogenetics in most studies described in Table 1[4-8,10-12] and a meta-analysis reported by Munshi et al.[2] Conversely, a retrospective analysis using flow cytometry evaluation (10^{-5}) did not show any difference in PFS among MRD-negative vs MRD-positive HR patients.[13] Data on outcomes with specific HR abnormalities are more limited. In patients with t(4;14), the achievement of MRD negativity has been associated with improved PFS.[9,11] In patients with deletion 17p, variable results have been seen across studies. Goicoechea et al[11] reported improved PFS with MRD-negative vs MRD-positive disease (PFS: not reached vs 14 months), but Chakraborty et al[9] did not observe any difference based on MRD status in patients with 17p deletion (PFS: 22.5 vs 20 months, $P = .464$) or ≥2 HR abnormalities (PFS: 12 vs 14 months, $P = .293$). Although there is some variation in the outcomes of MRD-negative HR patients as described above, data consistently show that MRD-positive HR patients have dismal outcomes, even those who are in complete remission (Table 1).

Does achieving MRD negativity mitigate the adverse effect of HR cytogenetics?

In the IFM 2009 trial, there was no difference in the PFS of HR and SR patients achieving MRD negativity at the end of maintenance therapy, with adjusted hazard ratio (covariates: MRD, treatment, and international staging system stage) of 1.08 (0.61-1.91; $P = .785$). In this trial, PFS in HR patients was inferior based on MRD results at the start of maintenance therapy, with adjusted hazard ratio of 1.69 (1.14-2.48; $P = .008$).[4] Paiva et al[7] demonstrated that there was no difference in the PFS of elderly patients in the GEM2010MAS65 trial with HR and SR disease who achieved MRD negativity ($P = .70$). Other studies demonstrate that, although patients with HR MRD-negative disease have better outcomes than HR MRD-positive patients, HR cytogenetics still remains an independent prognostic factor for PFS and OS.[2,6,12,14] Some of the differences observed across studies may be attributed to the timing of MRD evaluation as well as the sensitivity of the MRD assay. Future studies are needed to definitively answer this question.

Interpretation of MRD status and its impact on outcomes in HR disease is limited by the heterogeneity of studies, which include both prospective and retrospective studies and different evaluation time points as well as different techniques used for MRD assessment with varying sensitivity (10^{-4} to 10^{-6}). It is well described that survival improves with every log reduction in MRD in MM.[7] It is unclear whether there is a threshold effect in HR patients. Future studies with high-sensitivity MRD techniques ($\geq 10^{-5}$) and those that concurrently evaluate resolution of extramedullary disease (which is more common in HR patients and can impact outcomes in MRD-negative patients[15]) are needed to provide additional clarification. Studies are also needed to evaluate the achievement of sustained MRD negativity (MRD negative in bone marrow and by imaging on 2 occasions at least 1 year apart)[3] and its impact on outcomes in patients with HR MM. One would expect that HR patients with sustained MRD negativity would have superior outcomes than HR patients who achieve but do not sustain MRD negativity. However, whether sustained MRD negativity can overcome the impact of HR cytogenetics entirely remains to be determined.

In conclusion, there is high-quality evidence based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach suggesting that achievement of MRD negativity after initial therapy in HR MM is associated with improved PFS, with some studies also demonstrating longer OS in HR MRD-negative patients. The GRADE approach is a comprehensive system to rate the quality of evidence. High-quality evidence implies that additional research is very unlikely to change confidence in the estimate of effect. The question of whether MRD negativity abrogates HR is still unanswered, with some studies indicating that MRD-negative HR patients have similar outcomes as MRD-negative SR patients and others indicating that outcomes in HR MRD-negative patients may be similar or even inferior to those of SR MRD-positive patients. Based on available data, we can conclude that achievement of MRD negativity may partially abrogate the adverse prognosis of HR cytogenetics. HR patients with MRD-positive disease have poor outcomes, suggesting that eradicating MRD should remain the goal of treatment in HR patients.

Patient case (conclusion)

Based on the data available to date, achievement of MRD negativity and resolution of all fluorodeoxyglucose avid disease are favorable prognostic factors for this patient. There is insufficient evidence to determine whether this completely mitigates his adverse risk attributable to the HR cytogenetic abnormality [t(4;14)] noted at diagnosis.

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References

1. Nandakumar B, Binder M, Dispenzieri A, et al. Continued improvement in survival in multiple myeloma (MM) including high-risk patients. *J Clin Oncol*. 2019;37(15 suppl):8039.
2. 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.
3. 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.
4. 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.
5. Rawstron AC, Child JA, de Tute RM, et al. Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the Medical Research Council Myeloma IX Study. *J Clin Oncol*. 2013;31(20):2540-2547.
6. Li H, Li F, Zhou X, et al. Achieving minimal residual disease-negative by multiparameter flow cytometry may ameliorate a poor prognosis in MM patients with high-risk cytogenetics: a retrospective single-center analysis. *Ann Hematol*. 2019;98(5):1185-1195.
7. Paiva B, Cedena MT, Puig N, et al; Grupo Español de Mieloma/Programa para el Estudio de la Terapéutica en Hemopatías Malignas (GEM/PETHEMA) Cooperative Study Groups. Minimal residual disease monitoring and immune profiling in multiple myeloma in elderly patients. *Blood*. 2016;127(25):3165-3174.
8. Hu B, Thall P, Milton DR, et al. High-risk myeloma and minimal residual disease postautologous-HSCT predict worse outcomes. *Leuk Lymphoma*. 2019;60(2):442-452.
9. Chakraborty R, Muchtar E, Kumar SK, et al. Impact of post-transplant response and minimal residual disease on survival in myeloma with high-risk cytogenetics. *Biol Blood Marrow Transplant*. 2017;23(4):598-605.
10. Lahuerta J-J, Paiva B, Vidriales M-B, 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.
11. Goicoechea I, Puig N, Cedena MT, et al. Clinical significance and transcriptional profiling of persistent minimal residual disease (MRD) in multiple myeloma (MM) patients with standard-risk (SR) and high-risk (HR) cytogenetics. *Blood*. 2018;132(suppl 1):112.
12. Paiva B, Gutiérrez NC, Rosiñol L, et al; PETHEMA/GEM (Programa para el Estudio de la Terapéutica en Hemopatías Malignas/Grupo Español de Mieloma) Cooperative Study Groups. High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma. *Blood*. 2012;119(3):687-691.
13. Kunacheewa C, Patel KK, Lee HC, et al. Correlation of minimal residual disease negativity (MRD-) with prognosis in high-risk myeloma (HRM). *J Clin Oncol*. 2019;37(15 suppl):8024.
14. Hahn TE, Wallace PK, Fraser R, et al. Minimal residual disease (MRD) assessment before and after autologous hematopoietic cell transplantation (AutoHCT) and maintenance for multiple myeloma (MM): results of the Prognostic Immunophenotyping for Myeloma Response (PRIMeR) study. *Biol Blood Marrow Transplant*. 2019; 25(3):S4-S6.
15. Alonso R, Cedena MT, Gómez-Grande A, et al. Imaging and bone marrow assessments improve minimal residual disease prediction in multiple myeloma. *Am J Hematol*. 2019;94(8):853-861.