MSR45

The Prognostic Factors of Survival Outcomes in Newly Diagnosed Multiple Myeloma Who Are Not Transplant Eligible

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Key Takeaway

Results from this study can be informative for future indirect treatment comparisons (ITCs) in newly diagnosed multiple myeloma (NDMM) patients who are transplant-ineligible (TIE).

Conclusions

Baseline age, gender, ISS, cytogenetic risk, type of MM, ECOG performance score, frailty, EMD, eGFR, hemoglobin, LDH, serum calcium levels, ALT, and AST values are associated with survival outcomes in the NDMM TIE population.

Results are consistent with variables selected by traditional population-adjusted indirect comparisons (PAICs). Variables such as EMD and lab values should be considered in future ITCs for this population.

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Introduction

Drug development in multiple myeloma (MM) has advanced rapidly in recent years. As treatment options have increased, clinical experience has shown the importance of key patient characteristics as potential prognostic factors (PFs) and/or treatment effect modifiers (TEMs). Ensuring a systematic and up-to-date understanding of these factors is critical for protocol and statistical analysis plans for new clinical trials, as well as for cross-trial comparisons using population-adjusted indirect comparisons (PAICs).

Based on a recent literature review identifying prognostic factors and treatment effect modifiers in PAICs for MM, the International Staging System (ISS/R-ISS) stage, age, sex, creatinine clearance, cytogenetic risk, and type of MM were commonly adjusted baseline variables for newly diagnosed multiple myeloma (NDMM) patients who are transplant-ineligible (TIE). [1]However, whether a variable is a PF or TEM was not disclosed in these PAICs. In addition, empirical evidence of PFs based on randomized clinical trial (RCT) data analysis is lacking, especially in the NDMM TIE population..

Objectives

This study aims to identify PFs based on individual patient level data (IPD) from RCTs.

Methods

The pooled individual patient-level data (IPD) from three large head-to-head randomized clinical trials (MAIA, CEPHEUS, and ALCYONE) were included. A comparison of these trials is provided in Table 1. A frailty Cox model was used to examine the relationship between each potential prognostic factor (PF) with outcomes one at a time; [9] PFs were included as categorical variables. The following variables are considered: age, gender, ISS, cytogenetic risk, type of MM, ECOG performance score, frailty based on the simplified frailty score, [10] extramedullary disease (EMD), race, time from diagnosis, estimated Glomerular Filtration Rate (eGFR), hemoglobin, lactate dehydrogenase (LDH), serum calcium levels, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). The model considered each RCT study as a random effect and the potential PF as a fixed effect. We also repeated the analysis within each RCT.

Limitation: Other potential risk factors, such as CRAB-SLIM status, were not included in this study due to data availability.

Results

A total of 1,732 NDMM patients from ALCYONE (N=706), MAIA (N=737) and CEPHEUS (N=289, transplant-ineligible subgroup only) were analyzed.

Table 1) Brief description of clinical trials

	CEPHEUS [2]	MAIA [3]	ALCYONE [4]
Clinical Trial ID	NCT03652064	NCT02252172	NCT02195479
N	Total: 395 DVRd: 197 VRd: 198	Total: 737 DRd: 368 Rd: 369	Total: 706 DVMP: 350 VMP: 356
Phase	Phase 3, open label, international, multicenter		
Key Inclusion	≥18 years, transplant not intended (transplant ineligible or transplant deferred), measurable disease, ECOG 0-2	≥18 years, transplant-ineligible due to age ≥65 years or coexisting conditions, measurable disease, ECOG 0-2	
Key Exclusion	Frailty score ≥2 according to Myeloma Geriatric Assessment score		
	Prior therapy for multiple myeloma other than a short course of corticosteroids		
Enrollment period	Oct/18- Oct/19	Mar/15- Jan/17	Feb/15- Jul/16
Data cut used in this project	Median follow up 39 months	Median follow up PFS 64.5 months, [5,§] OS 7.5 years [7]	Median follow up PFS 40.1 month, [6,§] OS 86.7 months [8]
Endpoint	Primary: MRD Secondary: PFS, MRD negativity rate at 1 year, ORR, VGPR+, CR+, OS	Primary: PFS Secondary: MRD, MRD negativity rate at 1 year, ORR, VGPR+, CR+, OS	Primary: PFS Secondary: MRD, MRD negativity rate at 1 year, ORR, VGPR+, CR+, OS

Abbreviation: DVRd: Daratumumab, bortezomib, lenalidomide and dexamethasone, DRd: Daratumumab, lenalidomide and dexamethasone, DRd: Daratumumab, lenalidomide and dexamethasone; Rd: lenalidomide and dexamethasone, DVMP: Daratumumab, bortezomib, melphalan and prednisone, VMP: bortezomib, melphalan and prednisone, ECOG: Eastern Cooperative Oncology Group Performance Status, MRD: minimal residue disease, ORR: overall response rate, VGPR very good partial response, CR complete response, OS overall survival

§ The most extended PFS follow up with central lab assessment

There are minor missing values in a few variables, including type of multiple myeloma, race, LDH, and AST at baseline. Across trials, approximately 12% of baseline cytogenetic risk factors are missing (Table 2).

ISS III, EMD, as well as high cytogenetic risk, are considered indicators of aggressive disease. In this cohort, patients with EMD vary from 3.3% to 5.2%, high cytogenetic risk patients vary from 12.5% to 13.9%, and ISS category III varies from 27.8% to 38.4%.

Age, sex, ECOG performance status, ISS, type of multiple myeloma, cytogenetic risk, frailty, EMD, hemoglobin, LDH, calcium, and AST are strong predictors of PFS (Figure 1).

Age, sex, ECOG performance status, ISS, type of multiple myeloma, cytogenetic risk, frailty, EMD, hemoglobin, LDH, calcium, eGFR, ALT, and AST are strong predictors of OS (Figure 2).

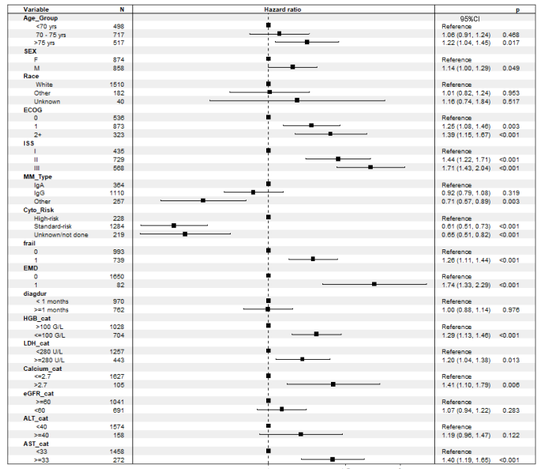
Race and duration of diagnosis are not predictive for both PFS and OS. It may be worth revisiting these variables in relapsed/refractory MM patients.

Results of the same set of baseline characteristic variables by individual RCT study remain consistent with the overall group.

Table 2) Baseline patient characteristics across trials

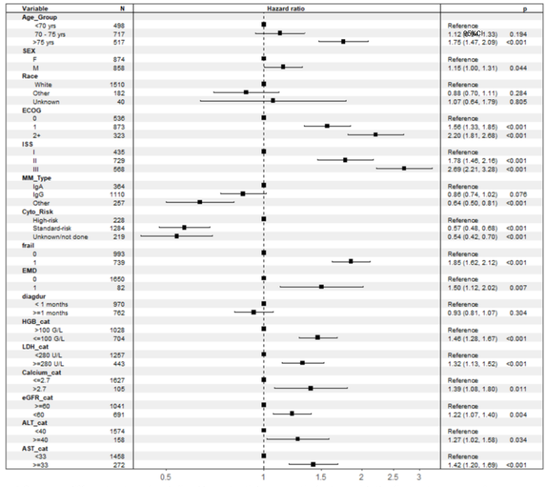
	ALCYONE (N=706)	CEPHEUS (N=289)	MAIA (N=737)
Age Group			
<70 yrs	273 (38.7%)	70 (24.2%)	155 (21.0%)
70 - 75 yrs	262 (37.1%)	158 (54.7%)	297 (40.3%)
>75 yrs	171 (24.2%)	61 (21.1%)	285 (38.7%)
Gender			
F	379 (53.7%)	142 (49.1%)	353 (47.9%)
M	327 (46.3%)	147 (50.9%)	384 (52.1%)
Race			
White	601 (85.1%)	234 (81.0%)	675 (91.6%)
Other	102 (14.4%)	34 (11.8%)	46 (6.2%)
Unknown	3 (0.4%)	21 (7.3%)	16 (2.2%)
ECOG			
0	177 (25.1%)	109 (37.7%)	250 (33.9%)
1	355 (50.3%)	153 (52.9%)	365 (49.5%)
2+	174 (24.6%)	27 (9.3%)	122 (16.6%)
ISS			
I	136 (19.3%)	98 (33.9%)	201 (27.3%)
II	299 (42.4%)	111 (38.4%)	319 (43.3%)
III	271 (38.4%)	80 (27.7%)	217 (29.4%)
Type of MM			
IgA	155 (22.0%)	68 (23.5%)	141 (19.1%)
IgG	453 (64.2%)	170 (58.8%)	487 (66.1%)
Other	98 (13.9%)	50 (17.3%)	109 (14.8%)
Missing	0 (0%)	1 (0.3%)	0 (0%)
Cytogenetic Risk			
High-risk	98 (13.9%)	38 (13.1%)	92 (12.5%)
Standard-risk	518 (73.4%)	216 (74.7%)	550 (74.6%)
Unknown/not done	90 (12.7%)	35 (12..%)	95 (12.9%)
Frailty			
0	391 (55.4%)	206 (71.3%)	396 (53.7%)
1	315 (44.6%)	83 (28.7%)	341 (46.3%)
Extramedullary Disease			
0	669 (94.8%)	268 (92.7%)	713 (96.7%)
1	37 (5.2%)	21 (7.3%)	24 (3.3%)
Diagnosis duration			
<1 months	456 (64.6%)	119 (41.2%)	395 (53.6%)
≥1 months	250 (35.4%)	170 (58.8%)	342 (46.4%)
Hemoglobin			
>100 G/L	375 (53.1%)	190 (65.7%)	463 (62.8%)
≤100 G/L	331 (46.9%)	99 (34.3%)	274 (37.2%)
LDH			
<280 U/L	489 (69.3%)	237 (82.0%)	531 (72.0%)
≥280 U/L	213 (30.2%)	52 (18.0%)	178 (24.2%)
Missing	4 (0.6%)	0 (0%)	28 (3.8%)
Serum Calcium(mmol/L)			
≤2.7	656 (92.9%)	272 (94.1%)	699 (94.8%)
>2.7	50 (7.1%)	17 (5.9%)	38 (5.2%)
eGFR(mL/min/1.73m^2)			
≥60	411 (58.2%)	197 (68.2%)	433 (58.8%)
<60	295 (41.8%)	92 (31.8%)	304 (41.2%)
ALT (IU/L)			
<40	645 (91.4%)	265 (91.7%)	664 (90.1%)
≥40	61 (8.6%)	24 (8.3%)	73 (9.9%)
AST (U/L)			
<33	583 (82.6%)	245 (84.8%)	630 (85.5%)
≥33	123 (17.4%)	44 (15.2%)	105 (14.2%)
Missing	0 (0%)	0 (0%)	2 (0.3%)

Figure 1: Forest plot of the hazard ratio of PFS *



* Compare different categories defined by potential prognostic factors with the first category as reference MM_Type: Type of multiple myeloma, Cyto_risk= cytogenetic risk, EMD=extramedullary disease, diagdur=diagnosis duration, HGB_Cat=hemoglobin category, LDH_cat=lactate dehydrogenase category, CI= confidence interval

Figure 2: Forest plot of the hazard ratio of OS*



* Compare different categories defined by potential prognostic factors with the first category as reference MM_Type: Type of multiple myeloma, Cyto_risk= cytogenetic risk, EMD=extramedullary disease, diagdur=diagnosis duration, HGB_Cat=hemoglobin category, LDH_cat=lactate dehydrogenase category, CI= confidence interval

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Multiple Myeloma