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A Systematic Literature Review and Network Meta-Analysis of Treatments for Patients With Transplant-Ineligible Newly Diagnosed Multiple Myeloma

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INTRODUCTION

- Commonly recommended standards of care for patients with transplant-ineligible newly diagnosed multiple myeloma (NDMM) include melphalan and prednisone (MP) combined with thalidomide (MPT) or bortezomib (VMP)[1-3]
- The randomized, controlled phase 3 FIRST trial demonstrated that continuous treatment with lenalidomide and low-dose dexamethasone (Rd continuous) significantly improved progression-free survival (PFS, the primary study endpoint) and overall survival (OS) vs MPT in patients with NDMM[4]
  - Randomized, controlled phase 3 trials of Rd continuous vs VMP or MP have not been performed
- In the absence of a head-to-head comparison, an indirect comparison of treatments across separate trials may provide additional information for consideration
- Mixed treatment comparisons (MTCs), a type of network meta-analysis, combine direct and indirect evidence of available pairwise comparisons, allowing synthesis of a greater amount of evidence than a traditional meta-analysis[5,6]

OBJECTIVE

- To evaluate the relative efficacy of Rd continuous compared with VMP on OS and PFS in patients with previously untreated multiple myeloma (MM) who are transplant ineligible using an MTC network meta-analysis

METHODS

Systematic Literature Review

- A systematic literature review was conducted in Embase, PubMed, and CENTRAL databases in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[7]
  - Scientific conference proceedings for ASCO, ASH, EHA, ESMO, and IMW meetings held from January 2012 through September 2014 were also reviewed to identify potential studies of interest
- The search used keywords for MM combined with the treatments of interest: lenalidomide, thalidomide, bortezomib, interferon, and bendamustine, as monotherapy or combination treatment, and melphalan plus prednisone combination therapy
- Search results were narrowed to English-language articles of clinical trials in treatment-naive patients published from January 1, 1988, through September 30, 2014

METHODS (cont)

Data Collection

- To avoid potential biases, quality assessments for each study were conducted using key questions derived from the *Cochrane Handbook for Systematic Reviews of Interventions*[8]
  - Assessments were validated by independent investigators
  - Discrepancies were resolved by a senior investigator through reaching a consensus
- Study comparability and treatment relevance were assessed to compare VMP with Rd continuous using MPT as the common comparator associating Rd to VMP
- Studies with treatment duration > 48 weeks were included in the analysis
- To reduce bias and better reflect the real-world practice, the analysis network was further limited to include only studies evaluating MPT on a fixed-dose thalidomide schedule (per the thalidomide summary of product characteristics and current clinical practice)

Statistical Methods

- Random- and fixed-effects Bayesian MTC meta-analyses were conducted comparing treatment hazard ratios (HRs) for OS and PFS
  - The analysis was based on HRs, not medians, in part to help account for the different patient populations and inclusion criteria for the various studies in the network

RESULTS

Systematic Literature Review

- The literature searches identified 1993 unique articles
  - 1799 were rejected during abstract screening
  - 113 were rejected during full-text review, most commonly for not evaluating a population of interest (n = 56)
  - 1 article was added through search of conferences
- 82 articles were selected for inclusion in the review representing 48 unique trials
- On the basis of clinical relevance and treatment schedule, the network meta-analysis was based on 5 trials evaluating Rd continuous, VMP, MP, and MPT (**Table 1**; **Figure 1**)
  - Direct meta-analysis determined that there was no heterogeneity among the three MPT vs MP studies in the network (I-squared = 0%), justifying a fixed-effects analysis

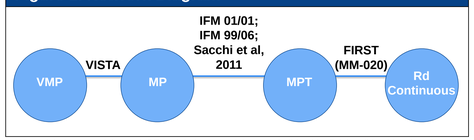
RESULTS (cont)

Table 1. MM Studies Included in the Primary Analysis Network

Trial	Treatment Arms	OS, HR (95% CI), *P* Value	PFS, HR (95% CI), *P* Value
IFM 01/01[9]	MPT (n = 113) vs MP (n = 116)	0.68 (0.48-0.96)[a] *P* = .028	0.62 (0.46-0.82)[a] *P* = .001
IFM 99/06[10]	MPT (n = 125) vs MP (n = 196)	0.59 (0.46-0.81) *P* = .0006	0.51 (0.39-0.66) *P* < .0001
Sacchi et al, 2011[11]	MPT (n = 64) vs MP (n = 54)	0.52 (0.28-0.97) *P* = .07	0.57 (0.35-0.94) *P* = .02
VISTA[12]	VMP (n = 344) vs MP (n = 338)	0.695 (0.567-0.852) *P* < .001	0.558 (0.43-0.72) *P* < .001
MM-020 (FIRST)[4]	Rd continuous (n = 535) vs MPT (n = 547)	0.78 (0.64-0.96) *P* = .02	0.72 (0.61-0.85) *P* < .001

[a] 95% CI imputed from the log standard error.
HR, hazard ratio; MM, multiple myeloma; MP, melphalan + prednisone; MPT, melphalan + prednisone + thalidomide; OS, overall survival; PFS, progression-free survival; Rd continuous, continuous lenalidomide + low-dose dexamethasone; VMP, bortezomib + melphalan + prednisone.

Figure 1. Network Diagram

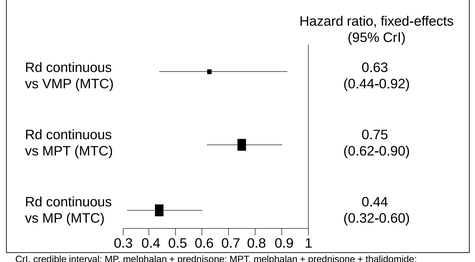


MP, melphalan + prednisone; MPT, melphalan + prednisone + thalidomide; Rd, lenalidomide + low-dose dexamethasone; VMP, bortezomib + melphalan + prednisone.

Overall Survival

- In the fixed-effects analysis, there was a significantly lower risk of death with Rd continuous than with all treatment regimens of interest (**Figure 2**)
  - Rd continuous vs VMP: HR 0.63 (95% credible interval [CrI)], 0.44-0.92)
  - Rd continuous vs MPT: HR 0.75 (95% CrI, 0.62-0.90)
  - Rd continuous vs MP: HR 0.44 (95% CrI, 0.32-0.60)

Figure 2. OS Fixed-Effects Analysis

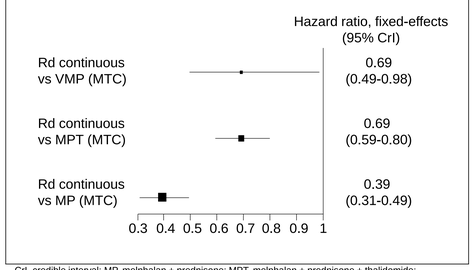


CrI, credible interval; MP, melphalan + prednisone; MPT, melphalan + prednisone + thalidomide; MTC, mixed treatment comparison; OS, overall survival; Rd continuous, continuous lenalidomide + low-dose dexamethasone; VMP, bortezomib + melphalan + prednisone.

Progression-Free Survival

- In the fixed-effects analysis, there was a significantly lower risk of progression or death with Rd continuous than with VMP, MPT, and MP (**Figure 3**)
  - Rd continuous vs VMP: HR 0.69 (95% CrI, 0.49-0.98)
  - Rd continuous vs MPT: HR 0.69 (95% CrI, 0.59-0.80)
  - Rd continuous vs MP: HR 0.39 (95% CrI, 0.31-0.49)

Figure 3. PFS Fixed-Effects Analysis



CrI, credible interval; MP, melphalan + prednisone; MPT, melphalan + prednisone + thalidomide; MTC, mixed treatment comparison; PFS, progression-free survival; Rd continuous, continuous lenalidomide + low-dose dexamethasone; VMP, bortezomib + melphalan + prednisone.

Sensitivity Analyses

- Treatment duration was 72 weeks in all MPT studies, except Sacchi et al, which had 6 to 12 four-week cycles[11]
  - When this study was removed from the network analysis, the point estimates for OS and PFS did not vary to a high degree (data not shown)
- A separate sensitivity analysis evaluated the effect of combining fixed-duration MPT studies with 6 studies that either included thalidomide maintenance or had a study comparator with a 1- to 2-degree linkage to either MPT or MPT with maintenance thalidomide treatment in the network
  - When these additional 6 studies were included, results were nearly identical in magnitude and direction
  - For PFS point estimates, Rd continuous demonstrated the lowest risk of progression or death when compared with all other treatments and was statistically significant for MP based on the random-effects analyses (HR 0.39 [95% CrI, 0.19-0.81])

CONCLUSIONS

- A significant advantage in OS was associated with Rd continuous compared with other first-line treatments (VMP, MPT, and MP)
- Patients treated with Rd continuous had a lower risk of a PFS event than those treated with VMP, MPT, or MP
- These conclusions are focused on efficacy and do not consider any potential differences in safety

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