Clinical Therapeutics/Volume ▮, Number ▮, 2018

Comparative Efficacy of Treatments for Previously Treated Multiple Myeloma: A Systematic Literature Review and Network Meta-analysis

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ABSTRACT

Purpose: New therapies, including daratumumab plus lenalidomide plus dexamethasone (DRd) and daratumumab plus bortezomib plus dexamethasone (DVd), have recently been approved in the United States for patients with multiple myeloma (MM) who have received at least 1 prior line of therapy. However, few treatments have been compared in head-to-head clinical trials to determine the most efficacious therapy. In an update of the POLLUX (Phase 3 Study Comparing DRd Versus Rd in Subjects with Relapsed or Refractory Multiple Myeloma [RRMM]) trial, median progression-free survival (PFS) for DRd was not reached; the hazard ratio compared with Rd was 0.41. In an update of the CASTOR (Phase 3 Study Comparing DVd Versus Vd in Subjects with RRMM) trial, median PFS for DVd was 16.7 months, compared with 7.1 months for Vd with a PFS hazard ratio of 0.31. A systematic literature review and network meta-analysis (NMA) was performed to estimate the relative efficacy of treatments for previously treated patients with MM.

Methods: A systematic search of MEDLINE, EMBASE, BioSciences Information Service, and the Cochrane Library databases was conducted from initiation to September 2016. Abstracts published by international congresses (2014–2016) and bibliographies of pertinent systematic reviews and meta-analyses were also searched. Eligible studies consisted of randomized controlled trials (RCTs) or long-term follow-up studies with >1 treatment arm assessing the efficacy or safety of MM therapies. An NMA was conducted by using Bayesian fixed effect mixed-treatment comparisons. Outcomes considered were hazard ratios for PFS and odds ratios for overall response rate (ORR).

Findings: In total, 108 articles reporting 27 RCTs were included in the NMA. Data formed 2 evidence networks: RCTs with DRd and RCTs with DVd. Primary analysis of PFS found that DRd and DVd had a higher probability of being the best treatments (probability, 0.997 and 0.999, respectively) and had the lowest risk of progression or death than other treatments approved by the US Food and Drug Administration for the treatment of MM. Results from sensitivity analyses using time to progression as a proxy for missing PFS data were consistent. DRd and DVd also showed improved ORR compared with other treatments. Subgroup analyses of PFS in patients treated with only 1 prior therapy were like the results of the primary analyses.

Implications: This NMA provides comparative efficacy for MM treatments not studied in head-to-head RCTs. The NMA suggests that, compared with other approved MM treatments in the United States, DRd and DVd have a higher probability of providing the longest PFS in patients who have received at least 1 prior therapy and in patients who have received only 1 prior therapy. (*Clin Ther*. 2018;▮:▮▮▮–▮▮▮) © 2018 The Authors. Published by Elsevier HS Journals, Inc.

Key words: antibodies, monoclonal, deacetylase inhibitors, histone, inhibitors, proteasome, meta-analysis as topic, multiple myeloma, therapies, immunomodulatory.

Accepted for publication January 25, 2018.
https://doi.org/10.1016/j.clinthera.2018.01.014
0149-2918/$ - see front matter

INTRODUCTION

Multiple myeloma (MM) is an incurable cancer of the monoclonal plasma cells located in bone marrow, resulting in the accumulation of abnormal plasma cells and the eventual destruction of normal architecture of the bone marrow and disruption of proper physiological bone function.[1,2] MM is the third most-frequent blood cancer, after lymphoma and leukemia, in the United States.[3] Despite increasing survival rates, MM remains incurable, and most patients tend to undergo disease progression after treatment.[4,5] Therefore, treatments aim to achieve a considerable amount of cancer cell clearance[6] and prolong the period of remission.

There are multiple treatment options for previously treated MM, but no uniform standard treatment exists.[4] Traditional options have been proteasome inhibitors, such as bortezomib, and immunomodulatory drugs, such as thalidomide and lenalidomide. In the last 5 years, several novel therapies have been developed and approved for the treatment of MM, including daratumumab, a monoclonal antibody, approved in November 2016 by the US Food and Drug Administration (FDA) for treatment in patients with MM who have received at least 1 prior line of therapy.[7] This approval was based on 2 randomized, Phase III clinical trials, CASTOR (daratumumab plus bortezomib plus dexamethasone vs bortezomib plus dexamethasone [Phase 3 Study Comparing Daratumumab, Bortezomib and Dexamethasone Versus Bortezomib and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma) and POLLUX (daratumumab plus lenalidomide plus dexamethasone vs lenalidomide plus dexamethasone [A Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma]). Daratumumab induces tumor cell death through multiple mechanisms, including antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent cellular phagocytosis.[8] In the latest POLLUX study data cut available at the time of writing, the median progression-free survival (PFS) for daratumumab plus lenalidomide plus dexamethasone was not reached. For lenalidomide plus dexamethasone, median PFS was 17.5 months; the hazard ratio for the PFS of daratumumab plus lenalidomide plus dexamethasone compared with lenalidomide plus dexamethasone was 0.41.[9] In the CASTOR study, median PFS survival for daratumumab plus bortezomib plus dexamethasone was 16.7 months, compared with 7.1 months for bortezomib plus dexamethasone with a PFS hazard ratio of 0.31.[10]

Physicians and patients must consider the efficacy of therapeutic options when making treatment decisions. However, with few head-to-head trials having been conducted comparing MM therapies, such evidence remains scant, although indirect comparisons may be made by using network meta-analysis methods.[11]

A systematic literature review was conducted to identify all available clinical evidence for treatment of patients with previously treated MM (ie, relapsed/refractory multiple myeloma [RRMM]). Results were synthesized by using network meta-analysis methods to assess the relative efficacy, including PFS and overall response rate (ORR), of daratumumab in combination with lenalidomide and dexamethasone and daratumumab in combination with bortezomib and dexamethasone versus other RRMM therapies.

MATERIALS AND METHODS

We conducted a systematic literature review in line with Cochrane methods[12] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations[13,14] (see **Supplemental Table I** in the online version at https://doi.org/10.1016/j.clinthera.2018.01.014), according to a protocol developed in August 2016. The meta-analysis was conducted according to the framework of Dias et al.[11]

Data Sources and Searches

MEDLINE, EMBASE, BioSciences Information Service, and the Cochrane Library were systematically searched from inception to September 1, 2016. Search terms included combinations of free text and Medical Subject Headings; term groupings were used for the population, intervention, and study type of interest, and searches were restricted to studies in humans (see **Supplemental Table II** in the online version at https://doi.org/10.1016/j.clinthera.2018.01.014). No geographical or language limitations were applied.

Abstracts published from 2014 to 2016 by selected conference proceedings (American Society of Hematology, American Society of Clinical Oncology, European Hematology Association, and European Society for Medical Oncology) were also reviewed for any