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Does the Combination of a Proteasome Inhibitor, Lenalidomide, and Dexamethasone Reduce Fatigue in Patients with Relapsed or Refractory Multiple Myeloma?

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Does the Combination of a Proteasome Inhibitor, Lenalidomide, and Dexamethasone Reduce Fatigue in Patients with Relapsed or Refractory Multiple Myeloma?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not "the combination of a proteasome inhibitor, lenalidomide, and dexamethasone reduce fatigue in patients with relapsed or refractory multiple myeloma (RRMM)?"

STUDY DESIGN: A systematic review of three English language open-label clinical trials with one published in 2013 and two published in 2016.

DATA SOURCES: Two randomized open-label, phase 3 clinical trials and one open-label phase 2 cohort study found using PubMed and Cochrane Library. All sources were published in peer-reviewed journals.

OUTCOME MEASURED: Fatigue was the outcome measured in all three studies utilizing Common Terminology Criteria for AEs (version 3.0) or European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire core 30 module (EORTC QLQ-C30) and myeloma-specific module (QLQ-MY20).

RESULTS: In the cohort study conducted by Wang et al. (*Blood*. 2013;122(18):3122–3128. doi:10.1182/blood-2013-07-511170.), showed no reduction in fatigue in the maximum planned dose (MPD) of carfilzomib, lenalidomide, and dexamethasone group compared to the other cohorts. The MPD group reported fatigue 69.2% compared to 65.5% overall. The RCT performed by Stewart et al. (*J Clin Oncol*. 2016;34(32):3921–3930. doi:10.1200/JCO.2016.66.9648.) found no statistical significance in reduction of fatigue between the carfilzomib, lenalidomide, and dexamethasone (KRd) group and control group (-0.46 in favor of KRd, $p=0.71$); however, both groups had statistically significant mean change from baseline of worsening fatigue in multiple cycles ($p<0.05$). Lastly, in a double-blind RCT by Moreau et al. (*N Engl J Med*. 2016;374(17):1621–1634. doi:10.1056/NEJMoa1516282.), there was no significant difference in fatigue reduction between the ixazomib group and placebo group.

CONCLUSIONS: Based on analysis of these studies, the combination of a proteasome inhibitor, lenalidomide, and dexamethasone does not reduce fatigue in patients with relapsed or refractory multiple myeloma. Future studies need to be designed in order to evaluate the effectiveness in fatigue reduction in patient with relapsed or refractory multiple myeloma.

KEY WORDS: Multiple myeloma, quality of life, lenalidomide, dexamethasone, carfilzomib

INTRODUCTION

Multiple myeloma (MM) is a malignancy of plasma cells which accumulate in the bone marrow and produce abnormal proteins leading to complications. At diagnosis, patients are approximately 66-70 years old with 37% being younger than 65 years old.[1] Relapsed MM is a disease that previously responded to induction treatment and progressed beyond 60 days of the last therapy. Refractory MM is "disease that is nonresponsive while on primary or salvage therapy or progresses within 60 days of last therapy."[2]

Multiple myeloma is the second most common hematologic malignancy, accounts for 13% of hematologic cancers, and 1% of all cancers.[3] The total lifetime cost of treatment for the 30,000 patients diagnosed with MM in 2017 was $22.4 billion, which is disproportionately high compared to other cancers that metastasized to bone.[4] The average monthly cost per patient for two recommended triple therapies of carfilzomib plus lenalidomide plus dexamethasone (CAR/LEN/DEX), and ixazomib plus lenalidomide plus dexamethasone (IXA/LEN/DEX) is $27,432 and $22,231 respectively.[5] There is not an exact estimate available within the past few years; however, emergency room visits for patients with multiple myeloma increased from 0.14 per person per month (PPPM) in 2000 to 0.90 PPPM in 2014.[6] The number of healthcare visits a patient with multiple myeloma will require is dependent on the stage of the disease and the patient's goals for their care. PAs will play a vital role in all aspects of their care, whether that is hematology/oncology, primary care, or emergency medicine.

The exact cause of multiple myeloma is unknown; however, it is thought to be related to specific genomic alterations, with one significant abnormality in the frequency of IgH translocations.[3] Symptoms of MM include nausea, loss of appetite, constipation, fatigue, frequent infections, weight loss and myeloma-related organ dysfunction including hypercalcemia, renal

insufficiency, anemia, and bone disease (lytic lesions, osteopenia, or pathologic fractures).[1] Treatment aims at relieving symptoms, preventing complications, and prolonging patient's lives. Current treatment for multiple myeloma is a combination of these drug classes: Immunomodulators (ex. lenalidomide and thalidomide), Proteasome Inhibitors (ex. bortezomib, carfilzomib, ixazomib), Monoclonal antibodies (ex. elotuzumab, daratumumab), and Corticosteroids (ex. dexamethasone, prednisone).[5] To provide years of remission for most patients, the gold standard has been a stem cell transplant; however, it can be difficult to find compatible donors and the procedure is associated with a high morbidity and mortality rate.[5] There is currently no cure for MM and treatment is directed at delaying disease progression and improving symptoms in patients with MM. However, the use of triple therapy of a proteasome inhibitor (PI), lenalidomide, and dexamethasone has been shown to be effective in reducing disease progression. This paper evaluates one cohort study and two randomized controlled trails (RCTs) comparing the efficacy of a proteasome inhibitor, lenalidomide, and dexamethasone for reducing fatigue in patients with relapsed or refractory MM.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not the combination of a proteasome inhibitor, lenalidomide, and dexamethasone reduce fatigue in patients with relapsed or refractory multiple myeloma (RRMM).

METHODS

The studies chosen for this review involved adult patients (18 years old or older) with relapsed or refractory multiple myeloma (RRMM). The intervention evaluated in these articles was a combination of a PI, lenalidomide, and dexamethasone. Comparison groups included

varying dosages of carfilzomib plus lenalidomide and dexamethasone between cohorts, lenalidomide and dexamethasone (doublet therapy), and a visually matching placebo, oral lenalidomide, and oral dexamethasone. The outcomes measured in all these studies are the impact of a PI (carfilzomib or ixazomib), lenalidomide, and dexamethasone on health-related quality of life (HRQoL) measures and safety/adverse events. The types of studies included were two randomized, open-label, phase 3 clinical trials by Stewart, et al. and Moreau, et al. as well as one open-label phase 2 clinical trial written by Wang, et al.

All articles were selected via a detailed search using PubMed and Cochrane Library by utilizing five key words: multiple myeloma, quality of life, lenalidomide, dexamethasone, and carfilzomib. All articles were published in English and peer-reviewed journals. Articles were chosen based on relevance and inclusion of patient-oriented outcomes (POEM). Inclusion criteria included studies that were randomized controlled trial, English language only, published in 2009-2019, full text, and humans (species). Exclusion criteria included any article not published in peer-reviewed journals and non-patient-oriented outcomes. Table 1 provides more information on the demographics and criteria of the studies. Statistics used in the studies included p-values and confidence intervals (CI). Numbers needed to harm (NNH) was calculated by the author.

OUTCOMES

The outcomes measured in this selective EBM are efficacy assessed according to disease response defined by the International Myeloma Working Group (IMWG) criteria; grading of fatigue performed according to Common Terminology Criteria for AEs (version 3.0), and European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire core 30 module (EORTC QLQ-C30) and myeloma-specific module (QLQ-MY20) (patient-

reported HRQoL measure); all are patient reported and were measured on day 1 of each cycle, except for cycle 1 (on day 15) in Wang et al. [7,8,9]

Table 1 – Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Wang[7] (2013)	Cohort	84	43-86	Patients with relapsed or progressive disease (PD) MM after prior therapy; systemic therapies discontinued for at least 3-4 weeks; minimal reaction (MR) to prior therapy; ECOG performance status 0-2; life expectancy of 0.3 months; adequate hepatic, bone marrow and renal function	Patients previously treated with LEN or BOR who progressed during the first 6 months; durable MR on any prior therapy; neuropathy at baseline or within 14 days of study entry; h/o significant CVD	50	Varying doses of carfilzomib, plus lenalidomide and low-dose dexamethasone
Stewart[8] (2016)	RCT	792	31-91	Adults with relapsed MM and measurable disease after prior therapy; adequate hepatic, hematologic, and renal function	Patients with peripheral neuropathy within 14 days before randomization or NYHA class III or IV HF	79	Carfilzomib, lenalidomide, and dexamethasone or lenalidomide and dexamethasone
Moreau[9] (2016)	RCT	722	30-91	Adult patients with RRMM; ECOG performance status of 0-2; received prior therapy; adequate hematologic, hepatic, and renal function	Patients with peripheral neuropathy; refractory disease to prior LEN or proteasome inhibitor–based therapy	451	Oral ixazomib, lenalidomide, and dexamethasone or placebo plus oral lenalidomide and dexamethasone

RESULTS

Wang et al. conducted a single-arm, open-label phase 2 cohort study comparing dose escalations of carfilzomib, lenalidomide, and low dexamethasone (CRd) in relapsed or refractory multiple myeloma (RRMM). The overall study population was 84 patients, chosen based on the inclusion and exclusion criteria listed in Table 1, with 52 patients enrolled in the maximum planned dose (MPD) cohort of CRd.[7] The MPD of carfilzomib was 20 mg/m^2 days 1 and 2 of cycle 1 and 27 mg/m^2 days 8, 9, 15 and on subsequent days, lenalidomide 25 mg days 1 to 21, and low-dose dexamethasone 40 mg once weekly in 28-day cycles.[7] Due to various situations including but not limited to disease progression (50%), adverse reactions (19.2%), and compliance (1.9%), 50 patients discontinues treatment, however the rates and reasons between study populations were similar.[7] Fatigue was one of the most common adverse effects (AE) associated with study drug discontinuation (3.8%, 2 patients).[7] The overall response rate (ORR) in the MPD cohort was 76.9% with a median duration of response (DOR) of 22.1 months (95% CI = 9.5-38.0), which compared favorably to the ORR of the overall study population, 69.0%, and median DOR was 18.9 months (95% CI = 7.3-not estimable).[7] Overall, the most common non-hematological AE patients experienced was fatigue (65.5%).[7] No p-values or confidence intervals were reported for fatigue. Further subdivisions between the grading of fatigue can be seen in Table 2.

Table 2. Fatigue according to patient population (data from Wang et al.[7])

Cohort	Any Grade	Grade 3/4
MPD Cohort (n = 52)	36 (69.2%)	6 (11.5%)
Overall (n = 84)	55 (65.5%)	6 (7.1%)

Stewart et al. is an open-label, phase 3 randomized control trial evaluating carfilzomib, lenalidomide, and dexamethasone (KRd) compared to lenalidomide and dexamethasone (Rd) in patients with relapsed multiple myeloma (MM). Patients included in this study were adults (≥18

years old) with relapsed MM with measurable disease who received at least one or up to three prior treatments; did not have disease progression during previous treatment with bortezomib; did not discontinue Rd due to AE or have progression at any time if it was their most recent treatment; and have adequate hepatic, hematologic, and renal function at screening.[8] Refer to Table 1 for exclusion criteria. A total of 792 patients were randomly assigned 1:1 to receive KRd or Rd in 28-day cycles, but past cycle 18 both groups received only Rd until disease progression. Carfilzomib (starting dose of 20 mg/m^2; target dose of 27 mg/m^2) was administered on days 1, 2, 8, 9, 15, and 16 from cycles 1 through 12 and on days 1, 2, 15, and 16 from cycles 13 to 18, plus 25 mg of oral lenalidomide on days 1 through 21 and 40 mg of oral or intravenous dexamethasone on days 1, 8, 15, and 22.[8] Out of the 792 patients, 713 (KRd, n = 365; Rd, n = 348) completed at least one post-baseline patient reported outcome assessments and were included in the analyses.[8] The ORR were 87.1% (95% CI = 83.9 to 90.3) for the KRd group and 66.7% (95% CI = 61.8-71.3) for the Rd group.[8] Between the two groups, the mean difference in score based on the EORTC QLQ-C30 was -0.46 in favor of KRd overall.[8] The 95% CI = -2.92 to 1.99 and the p-value was 0.71 (see Table 3).[8] The mean change from baseline of both groups had worsening fatigue during cycles 3, 6, and 12 (95% CI, p-value <0.05).[8] Compliance, calculated using the intent-to-treat population and the alive and on study population, was 94.1% and similar across the two groups.[8]

Table 3. Mean treatment difference for fatigue (data from Stewart et al.)[8]

	Mean difference in score (KRd v Rd)	95% CI	KRd (# of pts)	Rd (# of pts)	P-value
Cycle 3	0.40	-2.58 to 3.39	357	338	0.79
Cycle 6	-0.04	-3.18 to 3.10	327	284	0.98
Cycle 12	-1.16	-4.64 to 2.31	256	212	0.51
Cycle 18	-1.05	-4.90 to 2.80	227	148	0.59
Overall	-0.46	-2.92 to 1.99	365	348	0.71

Moreau et al. is a double-blind, phase 3 randomized control trail comparing ixazomib plus lenalidomide–dexamethasone (ixazomib group) or placebo plus lenalidomide–dexamethasone (placebo group) in patients with RRMM. Patients were eligible for enrollment based on inclusion criteria listed in Table 1. Patients were not eligible to participate in the study if they had peripheral neuropathy of grade 1 with pain or greater than or equal to grade 2, or had disease that was refractory to previous lenalidomide therapy or proteasome inhibitor–based therapy.[9] After exclusion, 722 patients were randomly assigned in a 1:1 ratio to receive 4 mg of oral ixazomib or matching placebo group on days 1, 8, and 15, 25 mg of oral lenalidomide on days 1 to 21, and 40 mg of oral dexamethasone on days 1, 8, 15, and 22 in 28-day cycles.[9] The final group analysis included all eligible patients, however 451 patients withdrew from the study, after a median follow up of 23 months, mainly due to disease progression and AEs.[9] The ixazomib group ORR was 78.3% (95% CI = 74-83) and the placebo group ORR was 71.5% (95% CI = 67-76).[9] There was a trend of better fatigue scores in the ixazomib group compared to the placebo group; yet 29% and 28% of participants respectively reported fatigue of any grade.[9] No p-value or confidence interval was reports, however the calculated number needed to harm (NNH) was 100. The RRI was 0.4 and the ARI was 0.01, as recorded in Table 4. Compliance was not discussed in this study.

Table 4. Calculations for Harm from Moreau et al.

Study	CER	EER	RRI	ARI	NNH
Moreau et al.	0.28	0.29	0.4	0.01	100

DISCUSSION

Fatigue related to cancer and its treatment is persistent and more severe than normal fatigue. This systematic review investigated whether the combination of a proteasome inhibitor, lenalidomide, and dexamethasone can help reduce fatigue in patients with RRMM. All three

studies have demonstrated that this drug combination is not effective in reducing fatigue in patients with RRMM. Wang et al. did not confirm a statistically significant reduction in fatigue in the MPD cohort compared to the other cohorts; however, fatigue was generally graded 1 or 2 in severity in all cohorts.[7] Stewart et al. similarly did not reveal statistically significant differences in fatigue reduction between the KRd and Rd groups, but the results did show that the addition of a proteasome inhibitor to Rd improves quality of life (QoL) without adversely affecting patient-reported fatigue when compared to Rd.[8] Finally, Moreau et al. did not establish statistical significance for fatigue reduction in the treatment or placebo group.[9] However, the NNH was 100, supporting that adverse events, such as fatigue, are rare.[9] All three studies did reveal some decline in patient-reported fatigue with this drug combination; nonetheless, it is unclear whether or not it is statistically effective at fatigue reduction in patients with RRMM.

There were limitations noted in each of the studies, along within researching articles for this review. In Wang et al., the authors acknowledge that data reported and comparisons across the phases need to be confirmed in additional studies in a randomized matter due to the differences in study design, number of patients, and patient populations in this study series.[7] Stewart et al. listed their open-label design and differential attrition across group as limitations.[8] The authors discussed that although these are limiting factors to the study that both groups had similar baseline completion rates and baseline QoL scores along.[8] This shows little evidence of bias. The limitations listed for Moreau et al.'s study were those of the existing instruments used to measure quality of life outcomes and the tendency to overestimate the benefit on QoL in open label studies.[9] In searching for these articles, one limitation was that two of the three articles used the same proteasome inhibitor (carfilzomib) and one used a different one (ixazomib), which could lead to differences in results gathered due to administration routes and carfilzomib having

a slightly higher risk of associated neuropathy and cardiac effects.[7,8,9] Also, Wang et al. and Stewart et al. utilized the same treatment administration days within 28-day cycles, but Moreau et al. used different administration time frames in the same cycle.[7,8,9] Lastly, all articles were conducted in the United States, which could lead to limited generalizability into international populations.

The use of triplet therapy to treat relapsed and refractory multiple myeloma comes with its own issues. Although proteasome inhibitors, lenalidomide and dexamethasone are all FDA approved medications in the treatment of multiple myeloma (newly diagnosed or relapsed/refractory), proteasome inhibitors and lenalidomide are contraindicated in pregnancy and females of reproductive age should be on at least one method of contraception during treatment. Another limitation to use of these medications are if there is a prior hypersensitivity allergy to any one of the medications. Most new cancer treatments, including those for multiple myeloma, are expensive; however, patients with a commercial insurance can receive therapy and pay a very nominal copay but those with Medicare or without insurance must involve a third-party (i.e., manufacturer) in order to pay less out of pocket.[6] The availability of these drugs are not an issue in the United States, which allows for adequate access to those with a medical necessity.

CONCLUSION

Although there was some clinical reduction in fatigue in patients receiving this triple therapy, this review has demonstrated a proteasome inhibitor, lenalidomide, and dexamethasone in combination does not effectively reduce fatigue in patients with relapsed/refractory multiple myeloma with statistical significance. Further studies involving patients with newly diagnosed multiple myeloma should be evaluated for efficacy and reduction of fatigue from baseline with

this triplet therapy. Future studies that explore patients with specific previous treatments (i.e., previous lenalidomide treatment) can assist in determining the best treatment for these specific patients when relapse occurs. Another factor future studies should analyze are the patterns of other chronic diseases in patient-reported fatigue in those with MM. Additionally, these studies should expand to include international countries for a larger population size and demographics. Since MM is such a rapid and progressive disease, continued research into progression-free and symptom reduction should be investigated to improve survival and overall quality of life.

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