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Is Pomalidomide Plus Low Dose Dexamethasone an Effective and Safe Treatment for 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 pomalidomide plus low dose Dexamethasone is an effective and safe treatment for patients with relapsed or refractory multiple myeloma (RRMM).

Study Design: Review of three open-label clinical trials with one published in 2012 and two published in 2013.

Data sources: Two randomized, open-label, phase 2 clinical trials and one open-label phase 3 clinical trial evaluating efficacy of pomalidomide plus low dose dexamethasone and its safety were found using the PubMed database.

Outcomes measures: Efficacy of pomalidomide plus low-dose dexamethasone was measured by overall response rates (ORR) to the treatment according to the International Myeloma Working Group Criteria/European Group for Blood and Marrow Transplantation criteria.[9,10] Safety profile of the treatment regiment was assessed through measuring ANC looking for neutropenia.

Results: The studies by Richardson, et al. and Miguel et al. found pomalidomide plus low-dose dexamethasone led to an increased number of patients responding to treatment compared to controls as well as decreased cases of neutropenia.[3,4] The study by Leleu et. al. found the 28 day cycle of pomalidomide plus weekly 40 mg of dexamethasone with pomalidomide on days 1-21 had a more favorable safety profile for patients compared to pomalidomide on days 1-28.[2]

Conclusions: Based on analysis of these 3 randomized controlled trials, pomalidomide plus low dose dexamethasone is a safe and effective treatment option for RRMM. The open-label design of these studies warrants further follow-up with patients who are continuing with these studies to further verify the results established in these reviews.

Key words: Myeloma, Pomalidomide, relapsed/refractory

Introduction:

Multiple myeloma (MM) is a blood cancer causing uncontrolled proliferation of plasma cells leading to bone destruction, kidney damage and anemia.[1] MM is the most common primary bone cancer and the second most common hematologic cancer accounting for 1% of all cancers. Unfortunately, MM treatments are limited and all patients with this disease will relapse or become refractory to treatment in a relatively short period of time.[2,3,4] The 5-year survival rate for myeloma patients is now up to 45%, however more improvement is needed.[5] New medications to treat this disease will offer hope to patients with multiple myeloma. This represents why understanding the efficacy of novel agents is crucial to practicing physician assistants who will come into contact with these patients.

Treating cancer is very expensive and multiple myeloma is not any different. It is difficult to estimate the exact amount treatment costs due to the amount of individualized therapies and varying stages. However, daily costs for treatments with drugs such as Lenalidomide are around $428 per day. Treatment costs for newer agents, such as Pomalidomide, can cost over $121,000 per year when patients become refractory to treatments or relapse.[5]

Patients with multiple myeloma will require many healthcare visits and PA's will play a vital role in their care. These patients will need continuous monitoring, not only by their oncologist, but by their primary care provider (PCP) as well, due to increased morbidity due to weakened immune systems from chemotherapy, steroids, etc. The amount of healthcare visits a myeloma patient will require is dependent on the individual and their stage of the cancer. Each patient will spend weeks to months in the hospital for treatments such as stem cell transplants and weakened immune defenses due to neutropenia. These patients are also more prone to

infection and viral illness requiring multiple visits to their PCP. Periods of remission still require frequent visits for laboratory testing to monitor serum monoclonal protein antibodies.[1]

Multiple myeloma has been extensively researched and more information about the disease becomes available every year. The pathogenesis of multiple myeloma offers key insight into how the disease functions and why it is so difficult to treat.[7] Etiology of disease is another essential factor in determining the most effective treatments. Unfortunately, the causes of multiple myeloma are unknown. It is believed to be a summation of environmental and genetic factors leading to multiple gene mutations causing heterogeneous tumors of proliferating plasma cells.[8] These factors make treatment difficult and even more difficult for refractory/relapse patients who have more limited options.

Current treatment options are dependent upon age of onset and stage and health of the patient at initial presentation. The gold standard in providing years of remission for most patients is a stem cell transplant, however the procedure has a high morbidity and mortality rate.[8] Chemotherapy remains the most common treatment for myeloma and represents the treatment of choice for most patients. Agents such as bortezomib and thalidomide derivatives with or without dexamethasone are the current standards of therapy. However, when patients relapse or become refractory to these treatments they are no longer effective.[8] For this reason, novel treatments for myeloma are needed. The increase in 5-year survival rates, from 26% to 45%, in the last 30 years prove that new treatments are effective.[5]

Pomalidomide is a newer derivative of thalidomide that may provide myeloma patients another option when they have refractory or relapsed disease. Various clinical trials with pomalidomide have proven the agent effective in reducing plasma cell counts in this particular population. In addition, when combined with dexamethasone, pomalidomide increases the

amount of people who will respond to the treatment.[2,3,4] Although myeloma cannot be cured, ongoing advances in treatments are leading to longer remission periods and more treatment options that extend the life of those affected by this challenging disease.

This paper evaluates three randomized controlled trials comparing the efficacy of the novel agent pomalidomide alone or in combination with dexamethasone in patients with relapsed or refractory MM and its efficacy in reducing plasma cell proliferation rate.

Objective:

The objective of this selective EBM review is to determine whether or not pomalidomide plus low dose Dexamethasone is an effective and safe treatment for patients with relapsed or refractory multiple myeloma regardless of age, sex or gender.

Methods:

The studies chosen for this review involved using pomalidomide plus low dose dexamethasone in patients with relapse or refractory multiple myeloma (RRMM) with failed attempts at standard therapies. Table 1 provides more information on the demographics of these studies. All patients were treated with a pomalidomide PO (4mg) plus dexamethasone PO (40mg) combination over a 28 day cycle. Comparison groups included longer continuous time on pomalidomide, receiving pomalidomide alone and also receiving only dexamethasone. The outcomes measured in all of these studies were overall response rates (ORR), in accordance the to the international myeloma working group criteria,[9,10] as well as safety profile of the drug combination by measuring absolute neutrophil count. The types of studies included were two randomized, open-label, phase 2 clinical trials by Richardson, et al. and Leleu et al. as well as one open-label phase 3 clinical trial evaluating pomalidomide plus low dose dexamethasone

written by Miguel et al. Overall response rates were calculated using intention to treat populations as well the efficacy evaluable population.

The key words used to find these articles included myeloma, relapsed/refractory and pomalidomide. Each article was published in English in peer-reviewed journals and researched by the author. All articles were found using the PubMed database. Cochrane Systematic Reviews was also used to verify no past reviews of this topic. The articles were selected based on relevance and inclusion of patient oriented outcomes (POEM) as an evaluation criterion. Inclusion criteria for systematic reviews included randomized, controlled, clinical trials and patients previous treatments attempted. Exclusion criteria included any phase 1 studies or publication date prior to 2012 as well as non-patient oriented outcomes. Reported statistics that were used include p-values and 95% confidence intervals. Numbers needed to treat (NNT) and numbers needed to harm (NNH) were calculated by the author.

Table 1: Demographics of each study

Study	Type	#Pt	Age (yrs) with range	Inclusion Criteria	Exclusion Criteria	W/D	Intervention and Safety Profile
Richardson, et. al, 2013	Multicenter, open-label, randomized Phase 2 study	113	64 (34-88)	≥ 18 yo, RRMM, measurable M-paraprotein level, ≥2 previous failed therapies	ANC < 1000/μL, platelet count < 75,000/μL, serum creatinine ≥ 3.0 mg/dL, serum liver transaminase levels > 3.0 or serum bilirubin > 2.0 mg/dL	108	-Pomalidomide 4 mg/day PO on days 1-21 of each 28-day cycle with dexamethasone 40 mg/week PO - Neutropenia
Leleu, et. al., 2012	Multicenter, open-label, randomized Phase 2 study	43	60 (45-81)	RRMM after ≥ prior regime of treatment and failure, measurable disease, platelet count ≥ 75 X 10^9/L,	Not meeting inclusion criteria	35	- 28 day cycle of Pomalidomide PO 4 mg/day on days 1-21 + Dexamethasone 40mg PO QWK - Neutropenia

				neutrophils ≥ 1 X 10^9/L and creatinine clearance ≥ 50 mL/min.			
San Miguel, et. al., 2013	Randomized, open-label, phase 3 trial	302	64 (35-84)	RRMM and have failed two previous treatments with Bortezomib and lenalidomide.	Resistance to Bortezomib, Pomalidomide treatment previously or hypersensitivity to dex. or Pomalidomide.	242	- 28 day cycle of pomalidomide PO (4 mg/day on days 1 – 21) + low dose dexamethasone PO (40 mg/day on days 1, 8, 15 and 22) - Neutropenia

Outcomes:

Overall response rates to the treatment combination in these studies were determined according to the International Myeloma Working Group criteria.[9,10] Patients who had greater than or equal to partial responses were considered in the calculation of overall response rates in each article. Adverse reactions were addressed via patients presenting with neutropenia objectively measured by absolute neutrophil count (ANC). Decreased ANC can predispose patients to an increased risk of infections including, but not limited to, pneumonia and sepsis.

Results:

The analysis of these three open-label clinical trials allowed for an evidence based medicine review of the effectiveness of pomalidomide plus low dose dexamethasone in the treatment of relapsed and refractory multiple myeloma. The search criteria used in this review enabled evaluation of the most recent studies to provide an answer to the question addressed in this study. This review included two randomized, open-label, phase 2 clinical trials and one open-label phase 3 clinical trial all published in 2013 and 2014. Richardson, et al. and Leleue, et al. both compared pomalidomide 4 mg per day PO on days 1-21 of each 28-day cycle with

dexamethasone 40 mg per week PO versus pomalidomide 4 mg per day PO on days 1-21 of each 28-day cycle without dexamethasone or 28 days continuous pomalidomide, respectively, in multicenter, open-label, randomized phase 2 studies.[2,4] Miguel, et al. compared a 28 day cycle of pomalidomide PO (4 mg per day on days 1 – 21) plus low dose dexamethasone PO (40 mg per day on days 1, 8, 15 and 22) verse 28 day cycles of high dose dexamethasone PO 40 mg per day on days 1-4, 9-12 and 17-20 in a randomized, open-label, phase 3 clinical trial.[3]

Inclusion criteria included patients who have tried and failed other myeloma treatments, older than 18 years old and measureable serum M-protein levels. Each study had it's own exclusion criteria. Richardson, et al. had the largest amount of exclusion criteria enabling this article to highlight the safety profile of pomalidomide plus low dose dexamethasone and not due to co-morbidity of the disease. They specifically excluded patients coming into the study with an already reduced ANC level. Miguel, et al. excluded patients who have previously tried pomalidomide as well as those trying other novel agents such as brotezomib.

Richardson, et al. had 221 patients with an average time on treatment of 14.2 months. They saw an ORR 33% of patients on pomalidomide plus low dose dexamethasone compared to 18% in the pomalidomide alone group (95% CI = 1.21 – 2.49, p = 0.013). Special patient populations were also analyzed. Patients 65 years old or older showed a greater overall response rate of 35% when compared to patients younger than 65 years old at 31%. No p-values or confidence intervals reported. Five patients were divided into an extramedullary disease category with only 1 obtaining an ORR on pomalidomide plus low dose dexamethasone. Other populations include Lenalidomide-refractory disease, Lenalidomide and Bortezomib- refractory disease, lenalidomide as last prior therapy and prior carfilzomib. Results for these populations can be seen in table 2.[4]

Table 2: Overall Response Rates according to patient population (Richardson et al.)

Population Subgroup	Pom + LoDEX	Pom Alone	P-value
Lenalidomide refractory	30%	21%	0.224
Lenalidomide and Bortezomib refractory	31%	21%	0.243
Lenalidomide as last therapy	25%	15%	Not Reported
Prior carfilzomib	37%	10%	0.030

The study by Leleu, et al. included 84 patients with an average treatment time of 22.8 months. An ORR of 35% was seen in the group receiving pomalidomide for 21 to 28 days verse a 34% overall response rate in the group receiving pomalidomide for 28 days ($p = 0.817$). Several subgroups were also analyzed. Patients 65 years old or older had an overall response rate of 27% across both arms of this study. Patients with poor cytogenetic abnormalities and those refractory to previous therapies were also evaluated as seen in table 3. These patients were not divided into treatment arms but observed as a whole. No p-values or confidence intervals were reported for these special populations.[2]

Table 3: Overall response rates in patients with cytogenetic abnormality and various resistance to therapy (leleu et al.)

Population Subgroup	ORR
Lenalidomide refractory	36%
Lenalidomide as last treatment	23%
Bortezomib refractory	29%
Refractory to bortezomib and lenalidomide	31%
More than 6 therapies	21%
Del 17p and/or t(4;14)	27%

The study by Miguel, et al. included 455 patients with an average time on treatment of 10 months. There was a significant difference ($p<0.0001$) between the population receiving

pomalidomide plus low dose dexamethasone (ORR of 31%) compared to the high-dose dexamethasone alone group (ORR of 10%). Various subgroups were also analyzed in this study including those resistant to lenalidomide, brotezomib and the combination. Others included lenalidomide or brotezomib as last treatment. ORR for these subgroups can be found in table 4. No p-values or confidence intervals were provided for these subgroups.[3]

Table 4: Overall response rates according to patient population (Miguel et al.)

Subgroup	Pom + DEX	DEX alone
Lenalidomide refractory	30%	9%
Bortezomib intolerance	31%	13%
Lenalidomide + Bortezomib refractory	28%	12%
Lenalidomide as last treatment	33%	6%
Bortezomib as last therapy	34%	12%

Table 5 summarizes the ORR, duration of treatment and numbers needed to treat of pomalidomide plus low dose dexamethasone in the three studies used in this review. Richardson, et al. needed to treat 7 people in order to achieve one more with ORR to therapy compared to their control.[4] Leleu, et al. found they needed to treat 100 patients in order for one more response.[2] Miguel, et al. found they needed to treat 5 patients in order to achieve one more with a response.[3]

Table 5: Summary of ORR vs. comparison with treatment duration, NNT and P-value

Study	Treatment	ORR	Average Duration of Treatment	NNT	Sig. (p-value)
Richardson, et al.	Pom (day 1-21)+ LoDEX (40 mg weekly)	33% vs. 18%	14.2 months	7	0.013
Leleu, et al.	Pom (day 1-21) + LoDEX (40 mg weekly)	35% vs. 34%	22.8 months	100	0.817
Miguel, et al.	Pom (day 1-21) + LoDEX (40 mg weekly)	31% vs. 10%	10 months	5	<0.0001

The most common adverse reaction in all studies was neutropenia.[2,3,4] Richardson, et al. saw 41% of patients develop neutropenia while on pomalidomide plus dexamethasone versus 48% of patient in pomalidomide alone group. There were not any p-values or confidence intervals provided. For every fourteen patients treated, one fewer case of neutropenia was noted with experiment verse control. There were 3% of patients on pomalidomide plus dexamethasone that developed severe neutropenia requiring termination of treatment.[4] Leleu, et al. found neutropenia present in 65% of patients on the 21 day arm of pomalidomide plus dexamethasone compared to 58.5% of patients on the 28 day arm.[2] For every fifteen patients treated, one more case of neutropenia developed. No patients had to stop due to toxicity of the drug. Miguel, et al. found neutropenia in 51% of patients on pomalidomide plus dexamethasone compared to 21% of patients on high-dose dexamethasone.[3] For every four patients treated, one more patient developed neutropenia compared to control. 2% of patients had to discontinue therapy due to fever with neutropenia. Table 6 summarizes these results as well as number needed to harm.

Table 6: Neutropenia in Pom + LoDEX groups

Study	Treatments	NNH	Pts withdrawal due to ADR
Richardson, et al.	Pom + LoDex vs. Pom alone	-14	3% vs. 5%
Leleu, et al.	Pom + LoDex (21 day vs. 28 day)	15	0% vs. 5%
Miguel, et al.	Pom + LoDex vs. High dose DEX	4	2% vs. 0%

Discussion:

This systematic review investigated the effectiveness and safety of pomalidomide plus low dose dexamethasone in relapsed/refractory multiple myeloma. All three studies have demonstrated that this drug combination is an effective and safe in the management of RRMM. The synergistic effects of this drug combination have anti-proliferative actions on plasma cells.[4] The use of immunomodulatory drugs, such as pomalidomide, warrants expectations of adverse

reactions. These drugs inhibit angiogenesis and decrease cytokine production leading to cell arrest and apoptosis within any tissue of the body.[11] However, the evidence proves sufficient to state pomalidomide is safe and well tolerated.[2,3,4] Patients who present with neutropenia should be monitored constantly and treated aggressively with any signs of infection.[12] As demonstrated in this review, few patients needed to discontinue treatment due to sever neutropenia with 3% of patients being the highest.[4] It must be noted that patients should stop pomalidomide with severe neutropenic fever and have dose reduced when the fever subsides.[8]

Most patients will be able to take pomalidomide but few contraindications exist. Some contraindications exist including pregnancy, an allergy to the medicine or those who already have neutropenia. The exclusion criteria in these studies were limited and highlight the importance of finding new treatments. More patients were able to qualify for this study and receive the treatments their lives were dependent upon. The exclusion criteria are also limited to make sure those selected for the study were representative of patients with RRMM who have significant history of failed treatments.

It is important to understand the maximum tolerated dose of pomalidomide plus dexamethasone to maintain efficacy while decreasing adverse reactions. Phase 1 studies of these articles have demonstrated the maximum tolerated dose to be 4 mg per day.[2] These studies have shown 4 mg/day of pomalidomide on day 1-21 with weekly 40 mg of dexamethasone to be the most beneficial therapy when compared to 28 straight days of pomalidomide.[2]

Although pomalidomide is expensive, its availability is not an issue in the United States. Insurances would like proper authorization and demonstration of medical necessity prior to initiation. However, the patient population who will need these drugs will continue to grow and the cost of the drug will hopefully become lower.

A couple important challenges in this study are the number of patients who would need moved from a comparison group to pomalidomide plus low dose dexamethasone group as well as the number of patients who had to withdraw due to disease progression. This creates overall response rates that may not be as accurate, however patients who required a change in groups were accounted by using efficacy evaluable populations and intention to treat analysis. The amount that withdrew at time of analysis will be more critical to open-label design of these studies. As time continues the population in the study will become too small for an effective analysis. RRMM is a rapid and progressive disease demonstrating the difficulty in performing long-term studies with these novel agents.

Conclusion:

This review has demonstrated pomalidomide plus low dose dexamethasone is an effective and safe treatment for patient with relapsed/refractory multiple myeloma. These open-label studies remain ongoing and more publications are expected in the future.

Pomalidomide alone was not as effective as the combination with dexamethasone. This warrants further investigation into the mechanism of action of these drugs to enhance efficacy. Continuing studies on pomalidomide can observe various combinations of pomalidomide and other novel agents searching for similar synergistic effects as when combined with dexamethasone. In addition, studies that analyze patients with specific previous treatments will help determine the best treatments for these specific patients when they relapse. These studies can further be divided into specific age groups to further customize treatments.

Research provides RRMM patients with new hope and extended life. As time continues we can only hope that more novel agents will come out to treat this disease and ultimately lead to a cure.

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