RESEARCH ARTICLE

Pooled Analysis of Pomalidomide for Treating Patients with Multiple Myeloma

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Abstract

Background: Patients with refractory or relapsed multiple myeloma are considered to have a very poor prognosis, and new regimens are needed to improve this setting. Pomalidomide is a new immunomodulatory drug with high *in vitro* potency. Immunomodulatory drugs are hypothesized to act through multiple mechanisms. Here we performed a systemic analysis to evaluate pomalidomide-based chemotherapy (pomalidomide in combination with low-dose dexamethasone) as salvage treatment for patients with refractory and relapsed multiple myeloma. Methods: Clinical studies evaluating the efffectiveness of pomalidomide based regimens on response and safety for patients with refractory and relapsed multiple myeloma were identified using a predefined search strategy. Pooled response rate (RR) of treatment were calculated. Results: For pomalidomide based regimens, 4 clinical studies which including 291 patients with refractory and relapsed multiple myeloma were considered eligible for inclusion. Systemic analysis suggested that, in all patients, pooled RR was 41.2% (120/291). Major adverse effects were hematologic toxicity, including grade 1 or 2 anemia, leucopenia and thrombocytopenia with pomalidomide based treatment. No treatment related death occurred. Conclusion: This pooled analysis suggests that pomalidomide in combination with low-dose dexamethasone is active with good tolerability in treating patients with refractory or relapsed multiple myeloma.

Keywords: Pomalidomide - multiple myeloma - treatment - prognosis

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Introduction

Multiple myeloma (MM) is the most common primary tumor of bone marrow, and it is an incurable tumor that occurs in 4.8 to eight per 1,000,000 in the US. MM is characterized by the proliferation of malignant plasma cells in bone marrow and the production of monoclonal immunoglobulin (Rollig et al., 2009). The majority of MM patients will relapse or become refractory to therapy after achieving complete remission (CR) (Genadieva-Stavric et al., 2014; Lin et al., 2014; Weng et al., 2014; Zhang et al., 2014; Zheng et al., 2014). Over the past decade, treatment for MM has been greatly improved due to autologous stem cell transplantation and new drugs (thalidomide, lenalidomide, and bortezomib). These management increased rate of CR and subsequently extended survival in patients with MM (Genadieva-Stavric et al., 2014). MM patients usually achieved CR more quickly by using the new drugs, which was associated with longer survival. However, most patients eventually relapse after CR, indicating that residual tumor cells exist. Resistance to conventional therapy caused by residual diseases displays multifactorial characteristics, which are difficult to overcome by targeting one single mechanism (Dalton et al., 2002). Alternatively, identification of novel cellular targets or signaling pathways regulating myeloma cell growth would improve clinical outcome and survival in MM patients refractory to chemotherapy.

Pomalidomide is a distinct IMiDs (R) immunomodulatory compound with multiple cellular effects that inhibit the growth of myeloma cells (Quach et al., 2010). Pomalidomide has direct effects by inhibiting the growth and survival on myeloma cells, and it also inhibits stromal support from the bone marrow microenvironment that can promote myeloma cell growth (Fonseca et al., 2009; Pratt et al., 2002; Stewart et al., 2007; Corral et al., 1999; Jourdan et al., 1999; Hideshima et al., 2001). In addition, pomalidomide was reported has potent immunomodulatory effects that enhance the immune response to myeloma cells by stimulating natural killer cells and by inhibiting regulatory T cells (Davies et al., 2001; Hayashi et al., 2005; Galustian et al., 2009). Previous research suggests that the effects of pomalidomide could be supposed to partially due to cereblon, a component of the E3 ubiquitin ligase complex (Lopez-Girona et al., 2012; Stewart et al., 2013). Preclinical data indicate that pomalidomide is active in drug-resistant myeloma cell lines, including lenalidomide-resistant cells, and produces synergistic effects when combined with dexamethasone (Hideshima et al., 2000;

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Ocio et al., 2011; Rychak et al., 2011; Lopez-Girona et al., 2012; Rychak et al., 2013).

On this background, we hypothesize that pomalidomide based treatment could be established as an optimal schedule for treating patients with MM.

Materials and Methods

Search strategy

We searched PUBMED, by using the following search term: (pomalidomide) and (multiple myeloma). All clinical studies evaluating the impact of pomalidomide on multiple myeloma. Published in English prior to January 1st of 2015 were identified. If samples of two studies overlap, only the latest one was included. Additional articles were obtained from references within the articles identified by the electronic search. We did not consider meeting abstracts or unpublished reports.

Inclusion and exclusion criteria

We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include published studies: (1) clinical studies, combined with dexamethasone or prednison; (2) The study was performed in accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Eligibility criteria included histologically or cytologically verified multiple myeloma (assessed by the International Myeloma Working Group Criteria.) 2, age 18 years. Studies were excluded if one of the following existed: (1) duplicate data; (2) no sufficient data were reported.

Data collection and analysis

Selection of trials and data extraction: The titles and abstracts of publications identified according to the above search strategy were assessed independently for inclusion by two authors, the full text was selected for further assessment if the abstract suggests relevance. Disagreement was resolved by discussion. Data was extracted by independent authors. The following recorded data were extracted: author, publication data, and country of the first or corresponding author, the number of patients.

Results

There were 4 papers relevant to the search words by the January 1st, 2015. Via steps of screening the title and reading the abstract, 4 studies were identified (Lacy et al., 2009; Lacy et al., 2010; Leleu et al., 2013; Richardson et al., 2014) when pomalidomide was used as a base in the treatment. These studies had been carried out in The USA, and Europe. The following outcomes were presented in all studies and extracted for combined analysis: response rate, including the rate of complete or partial response (CR or PR) and toxicities.

Characteristics of pomalidomide based treatment, studies included in this study are presented as short-term outcomes: the response rate of Richardson et al. (2014) was 33%, of Lacy et al. (2010) was 47%, of Lacy et al. (2009) was 63.3%, of Leleu et al. (2013) was 35%. Totally, 120 patients were enrolled and 291 patients achieved CR or PR, the pooled response rate thus was 120/291 (41.2%). Observation on major adverse effects included anemia, thrombocytopenia, and neutropenia. All adverse effects were manageable, and no treatment related death occurred with pomalidomide based treatment.

Discussion

Treatment for patients with MM depends on characteristics of patients, e.g., eligibility for autologous stem cell transplantation, age and co-morbidities. The role of induction therapy is to induce remission, but characteristics of patient impact significantly on the result of treatment. The purpose of induction therapy is to reduce tumor burden, including cancer stem cell, to explore the realization of possible aims that is quality of life, survival prolongation and eventually the possibility of cure (Engelhardt et al., 2014; Palumbo et al., 2014). Bortezomib- and lenalidomide-based regimens are the most commonly used agents in the treatment of relapsed or refractory MM in combination with corticosteroids and sometimes an alkylating agent or with an anthracycline (Ludwig et al., 2011). Pomalidomide is a structural analog of lenalidomide and thalidomide, which belong to the class of immunomodulating agents. The precise molecular mechanism of action and the targets through which pomalidomide and similar agents exert their antitumor effect are unclear. A marketing authorization was granted in the European Union for pomalidomide in combination with dexamethasone for the treatment of adult patients with relapsed and refractory MM who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

In a previous study published in 2014, Richardson et al. conducted a multicenter, open-label, randomized phase 2 study to assess the efficacy and safety of pomalidomide with low-dose dexamethasone in patients with relapsed/refractory MM (Richardson et al., 2014). They treated 113 patients with pomalidomide with low-dose dexamethasone. With a median follow-up of 14.2 months, median PFS was 4.2, overall response rates were 33%, and median overall survival was 16.5 months (Richardson et al., 2014). Grade 3-4 neutropenia occurred in 41% of patients; no grade 3-4 peripheral neuropathy was reported. Thus, they concluded that pomalidomide with low-dose dexamethasone was effective and generally well tolerated and provides an important new treatment option for patients with relapsed/refractory MM who have received multiple prior therapies (Richardson et al., 2014).

In another study, Lacy et al. treated 34 patients with MM progressing on current therapies (Lacy et al., 2010). To better define its efficacy in this group, Lacy et al. treated a cohort of lenalidomide refractory patients. Pomalidomide was given orally (2 mg) daily, continuously in 28-day cycles along with dexamethasone (40 mg) given weekly. Responses were assessed by the International Myeloma Working Group Criteria (Lacy et al., 2010). In their results, very good partial response was observed in 3 (9%), partial response in 8 (23%) patients, thus

the overall response rate of 47%. The median overall survival was 13.9 months (Lacy et al., 2010). Toxicity was primarily hematologic, with grade 3 or 4 toxicity that was observed in 18 patients (53%), including anemia (12%), thrombocytopenia (9%) and neutropenia (26%). Therefore, they concluded that the combination of pomalidomide and dexamethasone is highly active and well tolerated in patients with refractory MM (Lacy et al., 2010).

In a French research, Leleu used a combination of pomalidomide and dexamethasone to treat 84 patients with MM whose disease progressed after multiple lines of therapy (Leleu et al., 2013). In their study, pomalidomide (4 mg) was given orally on days 1 to 21 (arm 21/28) or continuously (arm 28/28) over a 28-day cycle, plus dexamethasone given weekly. These 84 patients (43, arm 21/28 and 41, arm 28/28) were randomized. In their results, overall response rate was 35% (arm 21/28) and 34% (arm 28/28), independent of the number of prior lines and level of refractoriness. Toxicity consisted primarily of myelosuppression, which was manageable. From these results, they suggested that pomalidomide 4 mg per day on days 1 to 21 of 28 with dexamethasone could be active and should be investigated in future trials. (Leleu et al., 2013).

With a purpose to evaluate the effectiveness and safety of pomalidomide in combination with low-dose dexamethasone, Lacy et al. treatied 60 patients with relapsed or refractory MM using this regimen (Lacy et al., 2009). Pomalidomide was administered orally at a dose of 2 mg daily on days 1 through 28 of a 28-day cycle. Dexamethasone 40 mg daily was administered orally on days 1, 8, 15, and 22 of each cycle. In their results, 38 patients (63%) achieved confirmed response including complete response in three patients (5%), very good partial response in 17 patients (28%), and partial response in 18 patients (30%). Responses were observed in 40% of lenalidomide-refractory patients, 37% of thalidomide-refractory patients, and 60% of bortezomib-refractory patients. Responses were seen in 74% of patients with high-risk cytogenetic or molecular markers (Lacy et al., 2009). Toxicity consisted mainly of myelosuppression. Grade 3 or 4 hematologic toxicity consisted of anemia (5%), thrombocytopenia (3%), and neutropenia (32%). One patient (1.6%) had a thromboembolic event. The median progression-free survival time was 11.6 months and was not significantly different in patients with high-risk disease compared with patients with standard-risk disease (Lacy et al., 2009). Thus, they concluded that the combination of pomalidomide and low-dose dexamethasone is extremely active in the treatment of relapsed MM (Lacy et al., 2009).

Our current study evaluated the efficacy and safety of pomalidomide in combination with low-dose dexamethasone as salvage treatment for patients with refractory and relapsed MM. Our results suggested that in treating 291 patients with refractory and relapsed MM, the pooled RR was 41.2% (120/291) in pomalidomide based regimens. Major adverse effects were hematologic toxicities, including grade 1 or 2 anemia, leucopenia and thrombocytopenia in pomalidomide based treatment. No treatment related death occurred in pomalidomide based treatment. Thus we concluded that pomalidomide in combination with low-dose dexamethasone is active with good tolerability in treating patients with refractory or relapsed MM.

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References

Cai X, Shen YL, Zhu Q, et al (2000). Arsenic trioxide-induced apoptosis and differentiation are associated respectively with mitochondrial transmembrane potential collapse and retinoic acid signaling pathways in acute promyelocytic leukemia. *Leukemia*, **14**, 262-70.

Chen YC, Lin-Shiau SY, Lin JK (1998). Involvement of reactive oxygen species and caspase 3 activation in arsenite-induced apoptosis. *J Cell Physiol*, **177**, 324-33.

Corral LG, Haslett PA, Muller GW, et al (1999). Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha. *J Immunol*, **163**, 380-6.

Dalton WS (2002). Targeting the mitochondria : an exciting new approach to myeloma therapy. Commentary re: Bahlis NJ, et al. Feasibility and correlates of arsenic trioxide combined with ascorbic acid-mediated depletion of intracellular glutathione for the treatment of relapsed/refractory multiple myeloma. *Clin Cancer Res*, **8**, 3658-68.

Davies FE, Raje N, Hideshima T, et al (2001). Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. *Blood*, **98**, 210-6.

Engelhardt M, Trepos E, Kleber M, et al (2014). European myeloma network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. *Haematologica*, **92**, 232-42.

Fonseca R, Bergsagel PL, Drach J, et al (2009). International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. *Leukemia*, **23**, 2210-21.

Galustian C, Meyer B, Labarthe MC, et al (2009). The anti-cancer agents lenalidomide and pomalidomide inhibit the proliferation and function of T regulatory cells. *Cancer Immunol Immunother*, **58**, 1033-45.

Genadieva-Stavric S, Cavallo F, Palumbo A (2014). New approaches to management of multiple myeloma. *Curr Treat Options Oncol*, **15**, 157-70.

Jia P, Chen G, Huang X, et al (2001). Arsenic trioxide induces multiple myeloma cell apoptosis via disruption of mitochondrial transmembrane potentials and activation of caspase-3. *Chin Med J (Engl)*, **114**, 19-24.

Hayashi T, Hideshima T, Akiyama M, et al (2005). Molecular mechanisms whereby immunomodulatory drugs activate natural killer cells: clinical application. *Br J Haematol*, **128**, 192-203.

Hideshima T, Chauhan D, Schlossman R, et al (2001). The role of tumor necrosis factor alpha in the pathophysiology of human multiple myeloma: therapeutic applications. *Oncogene*, **20**, 4519-27.

Hideshima T, Chauhan D, Shima Y, et al (2000). Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. *Blood*, **96**, 2943-50.

Jourdan M, Tarte K, Legouffe E, et al (1999). Tumor necrosis factor is a survival and proliferation factor for human myeloma cells. *Eur Cytokine Netw*, **10**, 65-70.

Lacy MQ, Hayman SR, Gertz MA, et al (2010). Pomalidomide (CC4047) plus low dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM). *Leukemia*, **24**, 1934-9.

Lacy MQ, Hayman SR, Gertz MA, et al (2009). Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma. *J Clin Oncol*, **27**, 5008-14.

Leleu X, Attal M, Arnulf B, et al (2013). Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: Intergroupe Francophone du Myélome 2009-02. *Blood*, **121**, 1968-75.

Lin MG, Liu LP, Li CY, et al (2014). Scutellaria extract decreases the proportion of side population cells in a myeloma cell line by down-regulating the expression of ABCG2 protein. *Asian Pac J Cancer Prev*, **14**, 7179-86.

Lopez-Girona A, Mendy D, Ito T, et al (2012). Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. *Leukemia*, **26**, 2326-35.

Ludwig H, Beksac M, Blade J, et al (2011). Multiple myeloma treatment strategies with novel agents in 2011: a European perspective. *The Oncologist*, **16**, 388-403.

Ocio EM, Fernández-Lázaro D, San-Segundo L, et al (2011). Reversibility of the resistance to lenalidomide and pomalidomide and absence of cross-resistance in a murine model of MM Blood (ASH Annu Meet Abstr) (abstract 134).

Palumbo A, Rajkumar V, San Miguel F, et al (2014). International Myeloma Working Group Consensus Statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. *J Clin Oncol*, **32**, 587-600.

Pratt G (2002). Molecular aspects of multiple myeloma. *Mol Pathol*, **55**, 273-83.

Quach H, Ritchie D, Stewart AK, et al (2010). Mechanism of action of immunomodulatory drugs (IMiDS) in multiple myeloma. *Leukemia*, **24**, 22-32.

Richardson PG, Siegel DS, Vij R, et al (2014). Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. *Blood*, **123**, 1826-32.

Rollig C, Illmer T (2009). The efficacy of arsenic trioxide for the treatment of relapsed and refractory multiple myeloma: a systematic review. *Cancer Treat Rev*, **35**, 425-30.

Rychak E, Mendy D, Miller K, et al (2011). Overcoming resistance; the use of pomalidomide (POM) and dexamethasone (DEX) in re-sensitizing lenalidomide (LEN)-resistant multiple myeloma (MM) cells Haematologica (EHA Annu Meet Abstr) (abstract P-328).

Rychak E, Mendy D, Shi T, et al (2013). Pomalidomide and dexamethasone are synergistic in preclinical models of lenalidomide-refractory multiple myeloma (MM) Clin Lymphoma Myeloma Leuk (IMW Annu Meet Abstr) (Suppl 1)): abstract P-294.

Siegel R, Naishadham D, Jemal A (2012). Cancer statistics. *CA Cancer J Clin*, **62**, 10-29.

Stewart AK, Bergsagel PL, Greipp PR, et al (2007). A practical guide to defining high-risk myeloma for clinical trials, patient counseling and choice of therapy. *Leukemia*, **21**, 529-34.

Weng WW, Dong MJ, Zhang J, et al (2014). A systematic review of MRI, scintigraphy, FDG-PET and PET/CT for diagnosis of multiple myeloma related bone disease--which is best? *Asian Pac J Cancer Prev*, **15**, 9879-84.

Zhang XZ, Su AL, Hu MQ, et al (2014). Elevated serum ferritin levels in patients with hematologic malignancies. *Asian Pac J Cancer Prev*, **15**, 6099-101.

Zheng H, Yang F (2014). Gemcitabine in treating patients with refractory or relapsed multiple myeloma. *Asian Pac J Cancer Prev*, **15**, 9291-3.