ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics 1 (3) 2013, 85-88

REVIEW ARTICLE

POMALIDOMIDE: A NOVEL PROMISING IMMUNOMODULATORY AGENT IN THE TREATMENT OF REFRACTORY AND RELAPSED MULTIPLE MYELOMA

***Ruchika Nandha[1], Kavita Sekhri[2], Harpal Singh[3]**

[*1,2]Assistant Professor, Department of Pharmacology, Dr Harvansh Singh Judge Institute of Dental Sciences, Panjab University, Chandigarh , India

[3] Consultant, Department of Critical Care, Max Superspeciality hospital, Phase 6, Mohali, India

ABSTRACT

Revival of thalidomide in the treatment of multiple myeloma (MM) has paved a path to search for compounds with increased antiangiogenic and anti-tumor effects, but decreased side-effects resulting in the development of thalidomide analogues .After lenalidomide, recently pomalidomide (3 amino thalidomide) has come up as a potential immunomodulatory drug (IMiD) which is found to be effective in relapsing and refractory MM. This novel agent has recently been approved by USFDA on 8th February, 2013. Pomalidomide differs from existing immunomodulatory agents in being extremely potent and safe in comparison. Lack of cross resistance with the existing agents offers advantage for its use in MM not responding to thalidomide, lenalidomide and bortezomib. Manageable myelosuppression is the only demonstrable effect observed. This review elucidates the available evidence on efficacy and safety of this drug in refractory and relapsing MM after analyzing various studies of this drug. Searches of pubmed, Cochrane database, Medscape, Google and clinicaltrial.org were made for terms like pomalidomide, multiple myeloma, immunomodulatory drugs.

KEY WORDS: Pomalidomide, multiple myeloma, thalidomide analogues, immunomodulatory drugs.

INTRODUCTION:

Multiple myeloma (MM), a mature plasma B cell neoplasm is a multi process disease which is characterized by monoclonal expansion of plasma cells in bone marrow with a peak age of onset of 65-70 years. [1,2]It is a second most common cancer (10%) after non Hodgkin lymphoma [3] and constitutes 1% of haematological malignancies. With first case detected in 1844, this disease has remained incurable in majority of cases.[4,5] Conventional management of MM includes corticosteroids and chemotherapeutic agents.Use of melphlan and predisolone is the most preferred therapy since more than two decades for managing MM. Despite the progress in delineating the activity of such regimens either at conventional doses or high doses, MM remains incurable disease with median survival duration 3-5 years. Disease has the tendency to relapse in many patients irrespective of the treatment given.[4,6] MM who progresses after multiple lines of therapy has limited treatment options.[7] Hence to improve the outcome and extend the survival ,demand for the addition of novel more efficacious drugs in drug armamentarium was witnessed . That led to major spark in the development of new drugs in this area resulting in introduction of immunomodulatory drugs revisiting thalidomide for treating MM in 1999.

Thalidomide has proved to be a major therapeutic advance in management of MM but found highly toxic because its use was associated with dose limiting adverse effects like neuropathy, constipation, somnolence and increased incidence of venoconstriction .[1,8] Hence search for better alternative led to synthesis of analogues by chemical modification of thalidomide. [9]Lenalidomide is second generation IMiD which has been found to be more efficacious, potent and safer as compared to thalidomide but increased risk of myelosuppression was observed. [4,5]

Pomalidomide [CC4047] is another second generation IMiD which has demonstrated still improved outcome than its predecessors with the tendency to improve relapsing and refractory MM along with better safety profile, hence causing major shift in therapeutic paradigm in treatment of MM. Promising response in MM refractory to thalidomide and lenalidomide explores lack of cross resistance of pomalidomide with other IMiDS. [1,5,9]This novel second generation IMiD has recently been approved on 8th feb,2013 by United States Food and Drug Administration [USFDA] for the treatment of relapsing and refractory MM .[10]

CHEMISTRY AND PHARMACOKINETICS:

Pomalidomide is chemically 3 amino thalidomide with molecular weight 273.24 gm/mol [11] Parent drug is well absorbed with time to reach maximum concentration (t_{max}) of 3 hours and half life ($t_{1/2}$) of 11.2 hours .Drug is extensively hydroxylated by CyP_{450} enzyme before being excreted and the metabolite is 26 fold less active than pomalidomide.[12]

MECHANISM OF ACTION:

*Corresponding author: Ruchika Nandha | Email: rnandha23@yahoo.co.in

Pomalidomide has similar mechanism of action as thalidomide in possessing pleiotropic anti-myeloma properties including immune-modulation, anti-angiogenic, anti-inflammatory and anti-proliferative effects[6,13].It possesses central dual actions including direct inhibition of angiogenesis and myeloma cell growth with additional upregulation of Interferon gamma, interleukin -2(IL-2),IL-10 and down regulation of tumour necrosis factor α (TNF α),IL-1β and IL-6 [14,15] Anti angiogenic effect is attributed to decrease in vascular endothelial growth factor(VEGF) and basic fibroblast growth factor (bFGF). [4,15,16] Direct antiproliferative and proapoptotic effects are exerted by inhibiting nuclear factor kappa B(NFKB) transcription activity and its anti-apoptotic target gene [6]Also this drug is found to directly activate caspase 8 which cause apoptosis and hence myeloma cell death.[4].It is found to Indirectly target MM cells by abolishing interactions of tumour cell with bone marrow stromal cells [4,6,15] Its immunostimulating action demonstrating T cell co stimulation has been confirmed by a phase 1 study .[14] In addition, it has been found to enhance transcription factor T-bet which reverts Th2 to Th1 in vitro.[17,18]

In comparison with thalidomide, it has been found to be100 times more potent in anti tumour activity, 100-1000 times more potent in stimulating T cells, [13] and 2-3 times more potent in antiangiogenic activity in vitro assays[17].Its anti-inflammatory action has been observed to be 10 times more than lenalidomide in vitro. [13]

CLINICAL STUDIES OF POMALIDOMIDE:

Various phase 1 and phase 2 trials have marked either 2mg or 4 mg/day oral dose of pomalidomide as maximum tolerated dose (MTD) but it is not clear whether higher dose has any advantage over the 2mg/day dose.

In a phase 1 study aimed to find out MTD, safety and efficacy of pomalidomide in refractory MM already receiving lenalidomide and bortezomib, pomalidomide 4mg/day with or without dexamethasone was found to have encouragable activity with manageable toxicity. Pomalidomide was given to 38 patients with dose escalation at 4 dose levels; pomalidomide was given from day 1 -21 in 28 day cycle. Patients who progressed /had not achieved minimal response (serum and urine M protein ≥25% and 50%) could receive dexamethasone 40mg/week. Study results demonstrated 4 mg/day dose of pomalidomide as maximum tolerated dose as grade 4 neutropenia was observed at 5 mg /day dose.40%patients had minimal response, 21%had partial response and 3% patients had complete response. Median duration to response (DOR) was 4.6 months. Median progression free survival (PFS) was calculated as 4.6 months and overall survival (OS) as 18.3 months.[19] Another phase 1 study (n=24) results demonstrated MTD of pomalidomide as 2mg/day with 67% patients having >25% reduction, 54% showing >50% reduction in paraprotein levels and 17% patients showing complete remission.[14]

Alternate day therapy with pomalidomide 5mg/day showed excellent efficacy with no thromboembolism events in a study.MTD of study drug was found to be 5 mg/day when given to 20 patients with relapsed MM as 1, 2, 5, 10 mg doses on alternate days. Follow up with MTD at 14 months resulted in >50% reduction in paraprotein in 50% patients .Median PFS and OS were 10.5 months and 33 months respectively.[20]

MTD of pomalidomide was found in a phase 1 study conducted on patients with advanced solid tumours. Pomalidomide was given as 4mg, 5mg, 7mg and 10 mg doses in two cohorts with 21 days treatment and 28 days treatment in 28 day cycle respectively. Study results demonstrated MTD to be 4 mg/day if drug is given uninterrupted for 28 days but 7 mg was the recommended dose if 7 day drug free period is there in 28 day cycle.[21]

Pomalidomide has also been found to be equally efficacious in immunoglobin light chain amyloidosis, a rare plasma cell tumour in a study on 33 patients where oral pomalidomide was given along with dexamethasone for 37 months. Mean DOR was 1.9 months where as hematological response rate was 48%. Median OS was 28 months and PFS was 14 months.1 year overall survival rate was 76% and PFS rate was 59% demonstrating promising efficacy .Neutropenia and fatigue were the only adverse effects observed in study .[22]

A phase 2, multicentre, randomized study on 84 patient's demonstrated promising efficacy of pomalidomide along with dexamethasone in patients with advanced refractory MM. Patients were randomized in 2 cohorts. One cohort(n=43) was given pomalidomide 4mg once daily orally for day 1 to 21 in 28 day cycle along with dexamethasone weekly whereas second cohort (n=41) was given pomalidomide 4mg once daily orally for 28 days of 28 day cycle along with dexamethasone weekly. Response rate was similar in both cohorts (35% in cohort 1 and 34% in cohort 2). Mean DOR and PFS were 7.3 months and 4.6 months respectively and found to be similar across both the cohorts. At 23 month follow up median OS was 14.9 months. Myelosuppression was the observed adverse effect but it was manageable.[7]

Another phase-2 randomized, multicentre, double-blind, active-control, parallel-group study was done on 84 patients with myelofibrosis-associated anemia where patients were equally randomized to 4 treatment groups with group1[n=22]:Pomalidomide (2 mg/day) + Placebo, group 2[n=19]: Prednisolone (30 mg/day) + Placebo, group

3[n=22]:Pomalidomide (2 mg/day) + Prednisolone (30 mg/day), and group4[n=21] : Pomalidomide (0.5 mg/day) + Prednisolone (30 mg/day). Pomalidomide therapy was given for up to twelve 28-day treatment cycle whereas prednisolone therapy was given in a tapering dose schedule during the first 3 of these 12 treatment cycles. Response rates in the four treatment arms were 23%, 16% , 36% , and 19% with infrequent grade 3 or more toxicities like neutropenia (9%; 16%; 5%; 5%), thrombocytopenia (14%; 16%; 9%; 5%), and thrombosis (9%; 5%; 0%; 0%) concluding efficacy and safety of Pomalidomide therapy at 0.5 or 2 mg/d with or without an abbreviated course of prednisone in patients with myelofibrosis associated anemia.[23]

Phase 2 trials results by 'lacy et al' on 60 patients refractory to either thalidomide, lenalidomide or bortezomib demonstrated pomalidomide 2mg/day for 28 days along with dexamethasone 40mg weekly to be well tolerated and extremely potent with a response rate of 63%(40% in lenalidomide refractory group,37% in thalidomide refractory group and 60% in bortezomib refractory group) suggesting non cross resistance between pomalidomide and other IMiDS. Median PFS was found to be 11.6 months .Observed toxicity was myelosuppression with anaemia in 5%, thrombocytopenia in 3% and neutropenia in 32% patients.[24]

Similar study was done on 34 Patients with multiple myeloma refractory to lenalidomide. Pomalidomide was given orally 2 mg daily, continuously in 28-day cycles along with dexamethasone (40 mg) given weekly. An overall response rate of 47% was seen with median time to response of 2 months and OS was 13.9 months. Toxicity was primarily hematologic, with grade 3 or 4 toxicity seen in 18 patients (53%) consisting of anemia (12%), thrombocytopenia (9%) and neutropenia (26%).[25]

Results of a recent study done on dual refractory (lenalidomide and bortezomib) MM patients indicate that pomalidomide plus low-dose dexamethasone combination is significantly active at both 2 mg (n=35)and 4 mg doses (n=35)with an overall response rate of 49% versus 43% ,mean OS of 78% versus 56% and mean PFS of 56% versus 34% respectively. The rate of grade 3 or 4 neutropenia was 51% in the 2-mg cohort and 66% in the 4-mg cohort This study expanded the efficacy data of pomalidomide and low dose dexamethasone in patients refractory to both lenalidomide and bortezomib with no significant advantage with higher dose .[26]

A Phase 3 multicentre randomized open label study was conducted in 455 patients with refractory MM who failed to be treated by lenalidomide and bortezomib. One group was given pomalidomide 4mg orally for 1-21 days along with low dose dexamethasone 40 mg oral weekly in 28 day cycle, whereas the other group was given dexamethasone high dose 40 mg on day1-4,9-12 and 17-20.Results demonstrated better median PFS in group1 than 2(3.6 months vs 1.8 months ;$p<0.001$).Mean OS was also significantly higher with group 1($p<0.001$).21% overall survival rate was shown in group 1 as compared to 3% in group 2 thus confirming superior efficacy of pomalidomide dexamethasone combination . Grade 3 and 4 hematological toxicities like neutropenia, anaemia, thrombocytopenia were found to be 42% vs 15%,27% vs 29% and 21% vs24% in both groups respectively.[27]

ADVERSE EFFECTS:

Adverse effects demonstrated with thalidomide are constipation, sedation and neuropathy which are found to be less common with pomalidomide. [17]Studies on pomalidomide demonstrated myelosuppression as common adverse effect resulting in anaemia, thrombocytopenia and neutropenia which are manageable toxicities . No thromboembolism events are demonstrated with use of this novel agent .Case report study of 2 patients demonstrated pomalidomide to have potential to cause pulmonary toxicity. [28]

In conclusion pomalidomide is a novel IMiD which is recently approved for use in relapsing and refractory multiple myeloma. Various phase 1 and 2 trials have generated sufficient data to demonstrate promising activity of pomalidomide along with less toxicity as compared to its predecessors with myelosuppression as the demonstrable adverse effect. This novel agent offers an extra advantage in treating even IMiD refractory cases due to lack of cross resisatnce with thalidomide and lenalidomide. To mark it superior to existing IMiDS and proteasome inhibitors exploratory comparative clinical trials are warranted in future.

REFERENCES:

1. Lacy MQ. New immunomodulatory drugs in myeloma. Curr Hematol Malig Rep 2011; 6(2):120-5.
2. Tohnya TM, D. Figg W. Immunomodulation of Multiple Myeloma. Cancer Biology & Therapy 2004; 3, 1060-1.
3. Collins CD .Problems monitoring response in multiple myeloma. Cancer Imaging2005; 5:S119–26.
4. Latif T, Chauhan N, Khan R, Moran A, Usmani SZ. Thalidomide and its analogues in the treatment of Multiple Myeloma. Experimental Hematology & Oncology 2012; 1:27.
5. Castelli R, Cannavò A, Conforti F, Grava G, Cortelezzi A. Immunomodulatory drugs in multiple myeloma: from molecular mechanisms of action to clinical practice. Immunopharmacol Immunotoxicol 2012; 34(5):740-53.

6. Jain P, Gupta S, Parikh PM. Newer therapeutic molecules for multiple myeloma. Indian J cancer 2008; 45:142-8.

7. Leleu X, Attal M, Arnulf B, Moreau P, Traulle C, Marit G, et al. Pomalidomide plus low dose dexamethasone is active and well tolerated in bortezomib and lenalidomide refractory multiple myeloma: IFM 2009-02. Blood. 2013 Jan 14. [Epub ahead of print]

8. Andhavarapu S, Roy V. Immunomodulatory drugs in multiple myeloma. Expert Rev Hematol 2013; 6(1):69-82.

9. Lacy MQ, Tefferi A. Pomalidomide therapy for multiple myeloma and myelofibrosis: an update. Leuk Lymphoma. 2011; 52(4):560-6.

10. Chustecka Z, Mulcahy N.FDA approves pomalidomide for multiple myeloma. Available at: www.medscape.com/viewarticle/779048

11. Pomalidomide : Compound Summary available at: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=134780

12. Hoffmann M, Kasserra C, Reyes J, Schafer P, Kosek J, Capone L,et al. Absorption, metabolism and excretion of Pomalidomide in humans following oral administration. Cancer Chemother Pharmacol 2013 ;71(2):489-501.

13. Quach H, Ritchie D, Stewart AK, Neeson P, Harrison S, Smyth MJ, et al. Mechanism of action of immunomodulatory drugs (IMiDS) in multiple myeloma. Leukemia 2009; 24 (1): 22–32.

14. Schey SA, Fields P, Bartlett JB, Clarke IA, Ashan G, Knight RD, et al. Phase I study of an immunomodulatory thalidomide analog,CC-4047, in relapsed or refractory multiple myeloma. J Clin Oncol2004; 22(16):3269-76.

15. Hideshima T, Chauhan D, Shima Y, Raje N, Davies FE, Tai YT, et al: Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. Blood 2000, 96:2943–50.

16. D'Amato RJ, Loughman MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci U S A1994; 91:4082-5.

17. Kotla V, Goel S, Nischal S, Heuck C, Vivek K, Das B ,et al.Mechanism of action of lenalidomide in hematological malignancies. J Hematol Oncol 2009, 2:36.

18. Roberta M, Valentina D, Chiara D, Alessandra L, Anna Marina L. Biological Activity of Lenalidomide and Its Underlying Therapeutic Effects in Multiple Myeloma. Advances in Hematology 2012: 1–11.

19. Richardson P, Siegel D, Baz R, Kelley SL, Munshi NC, Laubach J, et al: Phase I study of pomalidomide MTD, safety and efficacy in patients with refractory multiple myeloma who have received lenalidomide and bortezomib Blood 2012 Dec 14. [Epub ahead of print]

20. Streetly MJ, Gyertson K, Daniel Y, Zeldis JB, Kazmi M, Schey SA. Alternate day pomalidomide retains anti-myeloma effect with reduced adverse events and evidence of in vivo immunomodulation.Br J Haematol 2008; 141(1):41-51.

21. Cooney MM, Nock C, Bokar J, Krishnamurthi S, Gibbons J, Rodal MB, et al. Phase I trial of pomalidomide given for patients with advanced solid tumors .Cancer Chemother Pharmacol. 2012;70(5):755-61.

22. Dispenzieri A, Buadi F, Laumann K, LaPlant B, Hayman SR, Kumar SK, et al. Activity of pomalidomide in patients with immunoglobulin light-chain amyloidosis Blood 2012 ;119(23):5397-404.

23. Tefferi A, Verstovsek S, Barosi G, Passamonti F, Roboz GJ, Gisslinger H, et al. Pomalidomide is active in the treatment of anemia associated with myelofibrosis . J Clin Oncol 2009; 27(27):4563-9.

24. Lacy MQ, Hayman SR, Gertz MA, Dispenzieri A,Buadi F, Kumar S, et al. Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma. J Clin Oncol 2009;27(30):5008-14.

25. Lacy MQ, Hayman SR, Gertz MA, Short KD, Dispenzieri A, Kumar S, et al: Pomalidomide (CC4047) plus low dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM). Leukemia 2010, 24:1934–39.

26. Lacy MQ, Allred JB, Gertz MA, Hayman SR, Short KD, Buadi F, et al. Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of 2 dosing strategies in dual-refractory disease. Blood 2011 118: 2970-5.

27. Phase III Study (MM-003) of Pomalidomide Plus Low-Dose Dexamethasone Demonstrates Significant Progression-Free and Overall Survival Improvement for Patients with Relapsed or Refractory Multiple Myeloma. Abstract at 54th American Society of Hematology annual meeting. Dec 11, 2012. available at :http://ir.celgene.com/phoenix.zhtml?c=111960&p=RssLanding&cat=news&id=1766190

28. Geyer HL, Viggiano RW, Lacy MQ, Witzig TE, Leslie KO, Mikhael JR, et al. Acute lung toxicity related to pomalidomide Chest. 2011 Aug; 140(2):529-33.