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REVIEW ARTICLE

Lenalidomide in the treatment of multiple myeloma: a review

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SUMMARY

Lenalidomide is an immunomodulatory drug derived from thalidomide. It was developed to maximize the anti-inflammatory and anti-neoplasic properties of thalidomide and to reduce its toxicity. The molecular mechanism of action of lenalidomide is unclear, but its therapeutic activity is mainly due to its well defined anti-inflammatory, immunomodulatory, anti-proliferative and anti-angiogenic properties. In relapsed or refractory multiple myeloma (MM), lenalidomide, combined with standard dose dexamethasone, is superior to dexamethasone alone in terms of time to progression, response rate and overall survival. The most commonly reported adverse events include haematological toxicity with manageable neutropenia and thrombopenia. Lenalidomide does not trigger the limiting toxicities of thalidomide: somnolence, neuropathy and constipation. Lenalidomide, in combination with dexamethasone, is indicated for the treatment of MM patients who have received at least one prior therapy and is administered orally at the dose of 25 mg q.d. for 21 days of 28-day cycles. The drug is being investigated for the treatment of newly diagnosed MM. In this review, we summarize the pharmacokinetic, pharmacodynamic and clinical trial data on lenalidomide.

Keywords: **immunomodulatory drugs, lenalidomide, myeloma**

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INTRODUCTION

Multiple myeloma (MM), also called *Kahler's disease*, is a rare progressive neoplastic disorder of unknown aetiology (1, 2) characterized by accumulation of a plasma cell clone in the bone marrow. The diagnosis is mainly based on plasma cells infiltration in the bone marrow (more than 10% of nuclear cells), osteolytic lesions and the presence of monoclonal (M) immunoglobulin (or fragment) in serum or urine (3). MM represents about 10% of haematological malignancies and 1% of all cancers. The diagnosis of MM is made in about 21 000 patients/year in Europe with approximately 16 000 annual deaths from the disease (4). MM is primarily a disease of the elderly, with a median age at diagnosis of 68 years. Prior to the introduction of alkylating agents, the median survival for patients with MM was 12–17 months from time of diagnosis (5). The combination of melphalan plus prednisone (MP) has remained the gold standard therapy for decades, although complete remission (CR) was rare (<5%) and median survival did not exceed 3 years (6). In the 1990s, high-dose therapy (HDT) with autologous stem cell transplantation was shown to prolong survival (about 12 months with an acceptable mortality rate of 1–2%), when compared with conventional therapy (7). Despite intensive therapy, MM remains an incurable disease. In the last 10 years, thalidomide and bortezomib have been shown to be effective in the treatment of relapsed or refractory MM (8–10) and promising in newly diagnosed MM (11–13). More recently, lenalidomide has been developed and evaluated, not only for relapsed or refractory MM but also for newly diagnosed MM (14–17). Lenalidomide (CC-5013 trade name REVLIMID®) is the leading drug among the immunomodulatory

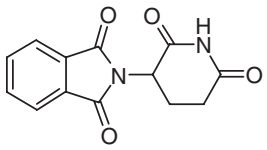

Fig. 1. Chemical structure of thalidomide.

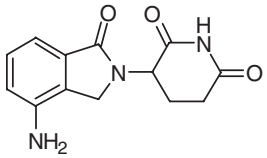

Fig. 2. Chemical structure of lenalidomide.

compounds derived from thalidomide aimed at maximizing its anti-inflammatory and anti-neoplasic properties and improve its tolerability. This new drug is a synthetic glutamic acid derivative obtained from thalidomide by the removal of an oxy group from the phthalyl ring and by the addition of an amino group (Figs 1 and 2). This review focuses on the efficacy and tolerability of lenalidomide in the treatment of MM.

PHARMACODYNAMIC PROPERTIES

Lenalidomide is a small molecule analogue of thalidomide that was originally identified based on its ability to potently inhibit tumour necrosis factor (TNF)-α production. It is now known that the therapeutic activity of lenalidomide is likely due to multiple mechanisms of action: *anti-inflammatory*, *immunomodulatory*, *anti-proliferative* and *anti-angiogenic* (Fig. 3).

Lenalidomide exerts direct anti-proliferative and pro-apoptotic effects on MM cells grown *in vitro*.

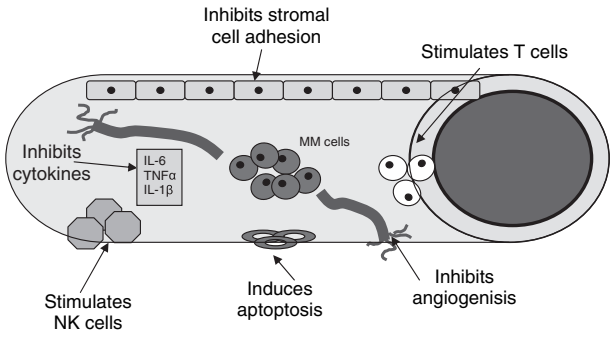

Fig. 3. Mechanisms of action of lenalidomide in multiple myeloma (from Celgene Corporation, France).

As an immunomodulatory drug, lenalidomide inhibits the secretion of pro-inflammatory cytokines including TNF-α, interleukin (IL)-1β, IL-6 and IL-12 from lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells (PBMC) (18, 19). It also increases production of the anti-inflammatory cytokine IL-10 by LPS-stimulated PBMC and consequently inhibits the expression, but not the enzymatic activity, of cyclooxygenase-2 (20). Lenalidomide induces T-cell proliferation and IL-2 and interferon (IFN)-γ production (19, 21) and it augments cytotoxic activity of natural killer cells (22).

Lenalidomide has anti-angiogenic properties as it suppresses vascular endothelial growth factor and basic fibroblast growth factor production by the endothelium and bone marrow stroma, with consequent inhibition of angiogenesis (23).

The activity profile of lenalidomide is similar to that of thalidomide but, *in vitro*, lenalidomide is 50 to 2000 times more potent in inhibiting cytokines production by LPS-stimulated PBMC, such as TNF-α, IL-1β or IL-6 (24).

PHARMACOKINETIC PROFILE

Single-dose lenalidomide pharmacokinetics was assessed in a phase I, single-blind, placebo-controlled, ascending study in 19 healthy volunteers (25). Lenalidomide was rapidly absorbed following oral administration with maximum plasma concentrations (T_{max}) occurring between 0·6 and 1·5 h post-dose. Maximal plasma concentration (C_{max}) and area under the curve (AUC) increased in a dose-proportional manner over the single dose range of 5–400 mg. Co-administration with food did not alter the extent of absorption (AUC) but did reduce C_{max} by 36%. The pharmacokinetic disposition of lenalidomide is linear. *In vitro* (14C)-lenalidomide binding to plasma proteins is approximately 30%. The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and is therefore partially or entirely active. Half-life of elimination is approximately 3 h. In patients with MM, maximum plasma concentrations occurred between 0·5 and 4·0 h post-dose both on days 1 and 28. AUC and C_{max}

values increase proportionally with dose following single and multiple doses. Exposure (AUC) in MM patients is 57% higher than in healthy male volunteers.

In a phase I trial in patients with MM (26), the mean terminal elimination half-lives were 3·1–4·2 h on both day 1 and day 28. There was little or no accumulation of CC-5013. Intersubject variability was generally low to moderate for AUC and C_{max}, with values ranging from 10·6% to 51·8% and 3% to 33% on day 1 and day 28, respectively.

Multiple myeloma patients with mild renal impairment had an AUC 56% greater than those with normal renal function. Pharmacokinetic differences due to race, gender, age or hepatic impairment have not been studied.

THERAPEUTIC TRIALS

Main studies for the approval in relapsed or refractory MM

Phase I and phase II trials. The clinical programme of lenalidomide in MM started in April 2000 with the initiation of two phase I studies in heavily pretreated patients with relapsed or refractory MM. Both trials were designed to identify the maximum tolerated dose (MTD) and to evaluate the safety of lenalidomide monotherapy in this population. Cytopenias were the dose-limiting toxicity in both studies and the MTD of lenalidomide was determined to be 25 mg/day for 21 days/month. No significant somnolence, constipation or neuropathy was observed with continued lenalidomide therapy. However, reversible cytopenias were observed during the second cycle of treatment in subjects who received 25 mg/day. In the first study of the 24 evaluable patients treated according to this schedule, 29% had an M paraprotein reduction superior to 50%; in 71% of patients, the M component decreased to at least 25% (26). In the second study, 20% of the subjects achieved a reduction of M paraprotein superior to 50% at doses of 25–50 mg/day (27).

The results of two phase II trials are also available (28, 29).

The first one was a multicentre, single-arm, open-label study conducted to evaluate the efficacy and safety of single-agent lenalidomide, administered at a dose of 30 mg q.d. for 21 days every 28 days (28-day cycle) in patients (n = 222) with relapsed or refractory MM (28). Twenty-five per cent of patients achieved partial reference or complete response (PR + CR) and 71% achieved stable disease or better and the median time to progression (TTP) was approximately 6 months.

The second study was an open-label, randomized trial to evaluate two dose-regimens of lenalidomide for patients (n = 102) with relapsed or refractory MM (29). Patients were randomized to receive either 30 mg q.d. or 15 mg b.i.d., for 21 days of every 28-day cycle. With progressive or stable disease after two cycles, patients received, additionally, 40 mg dexamethasone for 4 days every 14 days. Patients receiving 15 mg twice daily showed an increased rate of grade 3/4 myelosuppression (41% vs. 13%, P = 0·03). The overall response (OR) rate was 25% and the median overall survival (OS) in the 30 mg once-daily and twice-daily groups was 28 and 27 months, respectively. Dexamethasone was added in 68 patients and 29% responded.

The preliminary results of this study were the basis for the once-daily regimen of lenalidomide, combined with dexamethasone, used in the subsequent phase III trials.

Phase III trials. The approval of lenalidomide for the treatment of relapsed or refractory MM was mainly based on the results of pivotal studies (MM-009 and MM-010) initiated in 2003. The FDA agreed that the best comparator was standard dose dexamethasone. The studies were multicentre, multinational, randomized, double-blind, placebo-controlled trials to evaluate and compare the efficacy of lenalidomide plus high-dose dexamethasone (Rev-Dex) vs. dexamethasone alone (Dex).

MM-009 trial was undertaken in North America and MM-010 in Europe, Israel and Australia. A total of 354 and 351 patients were recruited respectively.

Lenalidomide was given at the dose of 25 mg q.d. for 21 days of every 28-day cycle and dexamethasone at the dose of 40 mg from days 1 to 4, 9 to 12 and 17 to 20 every 28-day cycle for four cycles then from days 1 to 4 for subsequent cycles. Investigational treatment had to be stopped at the time of disease progression or in case of unacceptable adverse events.

The primary endpoint was TTP according to Blade *et al.*'s criteria (30) and secondary endpoint included OS, OR rate and safety. A preplanned interim analysis of TTP, response rate and safety was performed by an Independent Data Monitoring Committee (IDMC).

The results presented below relate to analyses of data encompassing the whole double-blind period (2003 to summer 2005).

In the MM-009 North American Phase III trial (31, 32), the median TTP with Rev-Dex was superior to the one in the Dex arm (48·1 weeks vs. 20·1 weeks, $P < 0·01$). The hazard ratio for TTP was 2·82 (95% CI, 2·14–3·7, $P < 0·001$). The OR rate was 61% in the Rev-Dex arm and 19·9% in Dex arm including 14·1% and 0·6% of CR, respectively. OS time was longer for patients treated in the Rev-Dex arm (29·6 vs. 20·2 months) with a hazard ratio of 1·52 (95% CI, 1·04–2·24, $P = 0·03$).

The MM-010 trial reported very similar results with TTP of 48·7 weeks in the Rev-Dex arm vs. 20·1 weeks in the Dex arm (33, 34). The hazard ratio for TTP was 2·85 (95% CI, 2·16–3·76, $P < 0·001$). OR rate was greater with Rev-Dex regimen (60·2% vs. 24% including 15·9% and 3·4% of CR respectively). The OS was also superior for patients in the Rev-Dex arm (not estimable as of May 2006 in this arm vs. 20·6 months in the Dex arm, $P < 0·01$) with a hazard ratio of 2·10.

The interim analysis of TTP and response rate was performed at the start of 2005. Since the results already surpassed the preplanned significance threshold, the IDMC decided in early 2005 to lift the blind and recommended that all patients in the Dex arm should be offered the choice of treatment with lenalidomide–dexamethasone combination.

The impact of prior therapy with thalidomide on sensitivity of MM to subsequent lenalidomide was evaluated in a prospective subgroup analysis of MM-009 and MM-010 (35). In patients who had received prior thalidomide, the major response rate (CR + PR) was significantly higher in the group assigned to receive Rev-Dex than in those who received Dex alone (53·2% vs. 15·2%, $P < 0·001$). In this subgroup, the CR rate was also significantly higher for the Rev-Dex vs. Dex alone group (8·1% vs. 1·4%, $P < 0·05$).

Influence of previous treatments was also assessed (36). Median TTP for patients with one prior regimen was 16·5 months in Rev-Dex patients vs. 4·6 months in Dex alone patients (HR, 2·86). For patients with two or more prior regimens, median TTP was also significantly higher in Rev-Dex group (10·2 months vs. 4·7 months; HR, 2·66).

There was also a significant difference between the patients with one prior regimen vs. two or more regimens within the Rev-Dex group ($P < 0·05$).

Ongoing clinical development in MM

Newly diagnosed MM. Patients eligible for HDT: A first non-comparative phase II trial assessed the efficacy of lenalidomide plus dexamethasone for newly diagnosed MM (14). Results showed a 91% OR rate including 38% of CR/near complete response (nCR). The 2-year progression-free survival rates for patients proceeding to HDT and patients remaining on Rev-Dex were 83% and 59%, respectively; the OS rates were 92% and 90% at 2 years and 92% and 85% at 3 years, respectively. The 3-year OS rate for the whole cohort was 88% (15). On this encouraging basis, phase III trials are being conducted in order to evaluate lenalidomide plus dexamethasone as frontline therapy.

The Eastern Cooperative Oncology Group conducted a randomized study comparing lenalidomide plus standard-dose dexamethasone (L-highD: 12 days of dexamethasone per month) with lenalidomide plus low-dose dexamethasone (L-lowD: 4 days of dexamethasone per month) (16). The interim analysis reported a 1 year survival rate of 96·5% in the R-lowD arm vs. 86% in the R-highD arm (17). Major grade 3 or higher toxicities were significantly higher in the R-highD arm: thromboembolism (22·1% vs. 6·1%), infection/pneumonia (15·7% vs. 7·5%) and hyperglycaemia (9·7% vs. 6·6%).

Patients not eligible for HDT: With the same therapeutic approach taken with bortezomib and thalidomide (11–13), lenalidomide is being evaluated in combination with the MP standard (R-MP) for the treatment of newly diagnosed MM in patients not eligible for HDT (elderly patients). Recently, a phase I/II trial conducted in 54 patients estimated that the MTD was 0·18 mg/kg melphalan and 10 mg lenalidomide (37). With these doses, 81% of patients achieved at least a partial response, 47·6% achieved a very good partial response and 23·8% achieved a CR. A phase III trial comparing R-MP to MP (MM-015) is ongoing (38).

Maintenance therapy. The use of maintenance therapy is mainly discussed in younger patients in order to improve the quality of response or to maintain it. Lenalidomide is being evaluated in two phase III placebo-controlled trials conducted by two cooperative groups (the *Intergroupe Francophone du Myélome* and the *Cancer and Leukemia Group B*), to assess its efficacy at prolonging the duration of the response after autologous stem cell transplantation in patients under the age of 65 (39, 40). In elderly patients, the MM-015 study comparing R-MP to MP will also investigate the role of lenalidomide maintenance (38).

Other lenalidomide-based combinations for relapsed or refractory MM. Other lenalidomide-based regimens are under investigation for the treatment of relapsed or refractory MM such as lenalidomide plus doxorubicin and dexamethasone (RAD) or lenalidomide plus pegylated liposomal doxorubicin–vincristin–dexamethasone (R-Dvd) (41). In a phase I/II trial evaluating RAD regimen, 26 patients out of 31 (84%) achieved a partial response including one confirmed CR with an acceptable toxicity profile (42). Another phase I/II trial reported an OR response rate of 75%, with 29% of CR/nCR in patients treated with R-Dvd regimen (43).

SAFETY AND TOLERABILITY

Neutropenia were reported more frequently in the Rev-Dex arm than in the Dex arm (39·4% vs. 6·3%) including grade 3 (30% vs. 2·9%) and grade 4 (5·4% vs. 0·6%) severities (44). Grade 4 febrile neutropenia episodes were observed infrequently (0·6% in the Rev-Dex group compared with 0·0% in the placebo/dexamethasone group). In case of neutropenia, the physician should consider the use of growth factors in patient management. Thrombocytopenia and anaemia were also more frequent in the Rev-Dex arm as compared with the placebo/Dex arm (18·4% vs. 5·7% and 17·0% vs. 6·3%, respectively).

The non-haematological adverse reactions which occurred significantly more frequently in the Rev-Dex arm group compared with the Dex arm were fatigue (27·2% vs. 18%), asthenia (17·6% vs. 10·9%), constipation (23·5% vs. 8·9%), muscle cramp (20·1% vs. 10·6%), diarrhoea (14·2% vs. 7·1%) and rash (10·2% vs. 3·4%).

Lenalidomide has almost no sedative effects and neuropathic effect is minimal.

Other adverse events, such as nausea, vertigo, dyspnoea, occurred less frequently.

As with thalidomide, thrombotic or thromboembolic events, including deep venous thrombosis, pulmonary embolism, were reported more frequently in the Rev-Dex arm (11·3%) than in the Dex arm (3·8%) (45). Furthermore, a combined review of studies MM-009 and MM-010 showed that the incidence of deep venous thrombosis was significantly higher among the Rev-Dex patients who received erythropoietic agents concomitantly (19·2% vs. 6·8%, $P = 0·001$). Therefore, antithrombotic prophylaxis using low-molecular-weight heparin, aspirin or warfarin, should be given to all patients receiving lenalidomide plus dexamethasone and low-molecular-weight heparin should be recommended for patients with additional thrombotic risk-factors.

In MM-009 and MM-010 phase trials, atrial fibrillation occurred more frequently in the Rev-Dex arm (4·0% vs. 0%).

TERATOGENIC POTENTIAL

There is no reported data on foetal exposure to lenalidomide in humans.

Embryo-foetal development studies in rats revealed no teratogenic effects at the highest dose of 500 mg/kg (approximately 600 times the human dose of 10 mg based on body surface area). A pre and post-natal development study in rats revealed few adverse effects on the offspring of female rats treated with lenalidomide at doses up to 500 mg/kg. The male offspring exhibited slightly delayed sexual maturation and the female offspring had slightly lower body weight gain during gestation when bred to male offspring (25).

As lenalidomide is chemically related to thalidomide, and thalidomide is one of the most teratogenic drugs, there is a strict contra-indication to the use of lenalidomide during pregnancy. Therefore, lenalidomide is available in Europe under the conditions described in a specific risk management programme for female patients with childbearing potential. Prior to the start of treatment, a medically supervised pregnancy test should be performed during the consultation, when lenalidomide is prescribed or in the 3 days prior to the

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