Current treatment strategies with lenalidomide in multiple myeloma and future perspectives.

Current treatment strategies with Lenalidomide in Multiple Myeloma and future perspectives

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Summary

Lenalidomide is an immunomodulatory drug derived from thalidomide, developed to maximize its anti-inflammatory and anti-neoplastic properties while reducing toxicity. Lenalidomide administered orally at 25 mg/d for 21 days of 28-day cycles plus dexamethasone is indicated for the treatment of relapsed/refractory multiple myeloma patients, who received at least one prior therapy. In the pivotal MM-009 and MM-010 phase III registration trials, lenalidomide-dexamethasone compared with placebo-dexamethasone, significantly improved response rate (60% vs 20%), time-to-progression and survival. The most common adverse events included hematologic toxicity and venous thromboembolism. The drug is currently being investigated for the treatment of newly diagnosed myeloma and in association with chemotherapy drugs (cyclophosphamide and melphalan) or novel agents (bortezomib, carfilzomib and elotuzumab) to develop highly active combination regimens.

Keywords immunomodulatory drug, lenalidomide, multiple myeloma, relapsed, refractory, newly diagnosed patients

1. Introduction

Multiple myeloma (MM) is a malignant disease characterized by uncontrolled plasma tumor cell proliferation, driven by intrinsic chromosomal abnormalities and extrinsic stromal cell support, that accumulate in bone marrow, leading to bone destruction and marrow failure [1,2]. Typical clinical symptoms at presentation includes anemia (commonly presenting as fatigue), skeletal lesions (presenting as bone pain), renal impairment, and hypercalcemia.

In Western countries, the annual age-adjusted incidence is 5.6 cases per 100,000 people. The median patient age at diagnosis is approximately 70 years; only 37% of newly-diagnosed patients are aged <65 years, 26% are aged 65-74 years, and 37% are aged ≥75 years. The annual prevalence of MM in patients aged 65-74 years is approximately 31 cases per 100,000 people, and it increases to 46 cases per 100,000 people in patients aged ≥75 years [3]. The prevalence of myeloma is likely to increase due to the prolonged survival and the growing life expectancy of the general population [4,5].

Treatment of MM has rapidly evolved over the last decade due to the introduction of novel therapeutic agents, including thalidomide, the immunomodulatory (IMiD®) drug lenalidomide, and the proteasome inhibitor bortezomib. Lenalidomide was first developed and evaluated in relapsed and refractory patients, but more recently, it has also been studied for newly diagnosed MM. This review focuses on the efficacy and safety of lenalidomide in the treatment of MM.

2. Overview of the market

In younger MM patients, an increased survival of approximately 2-3 years has been shown after the introduction of novel agents, in combination with high-dose therapy and autologous stem cell transplantation (ASCT) [6]. Patients over 65 years of age and younger patients with significant co-morbidities are usually considered ineligible for transplantation. For these patients, the combination melphalan-prednisone (MP) has been the reference treatment for more than 40 years. [7,8] In 2008 the European Medicines Agency (EMA) granted approval for thalidomide in the treatment of newly diagnosed MM and for bortezomib as initial treatment for patients with MM, in combination with MP. [9,10,11]. Furthermore, thalidomide and bortezomib in combination with dexamethasone or with several chemotherapy agents such as melphalan and cyclophosphamide are commonly used in the treatment of relapsed/refractory MM [12].

Lenalidomide is the leading drug among compounds, known as IMiDs®, originally developed to overcome the toxic effects and to improve the poor tolerability associated with thalidomide. The adverse events somnolence, constipation and peripheral neuropathy, commonly associated with thalidomide, were not observed with lenalidomide. Lenalidomide is the most recent novel agent approved in the United States and Europe for the treatment of relapsed/refractory MM patients who received at least one prior therapy. The focus has recently turned to the role of new agents, including lenalidomide, in the treatment of newly diagnosed MM, as potential maintenance therapy or combined with newer drugs under development.

3. Introduction to the compound

Lenalidomide (CC-5013 trade name REVLIMID) is a novel second-generation IMiD® , manufactured by Celgene Corp [13].

3.1 Chemistry

Thalidomide analogs, including lenalidomide and pomalidomide, were first developed in 1990s to increase potency and to have decreased toxicity profile of their parent drug [14].

Lenalidomide (3-(4'aminoisoindoline-1'-one)-1-piperidine-2,6-dione) is a synthetic glutamic acid derivative obtained by removal of an oxy group from the phtalyl ring and by the addiction of an amino group to the backbone of thalidomide (Figure 1). Lenalidomide has peculiar mechanisms of action: its immunomodulatory, antiangiogenic and anti-neoplastic effects directly lead to tumor cell death, and its immunomodulatory effect may keep the tumor in remission.

3.2 Pharmacokinetic characteristics

In phase I studies, lenalidomide displays linear pharmacokinetics. The plasma exposure of this drug is proportional to doses and without accumulation for multiple doses. Lenalidomide is rapidly orally absorbed with maximum plasma concentrations (C_{max}) occurring between 0.5 and 6.0 hours post-dose in patients with myeloma or myelodysplastic syndrome. Lenalidomide is metabolized through hydrolytic cleavage of glutarimide amide bonds, with an in vitro half-life of approximately 8 hours. The terminal elimination half life ($t_{1/2}$) was approximately 3 hours in clinically dose range of 5-50 mg. The predominant clearance mechanism of lenalidomide is the urine excretion that accounts for about 82% of the dose within 24 hours [15].

3.3 Pharmacodynamics & preclinical studies

The therapeutic activity of lenalidomide is due to its anti-infllammatory, immunomodulatory, anti-proliferative and anti-angiogenic properties [16]. IMiDS®, including lenalidomide, inhibit the secretion of TNF-alpha, interleukin (IL)-1β, IL-6 and IL-12, while production of IL-10 is increased by lypopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells. Moreover, lenalidomide induces T-cell proliferation, IL-2 and interferon (IFN)-gamma production and augments the cytotoxic activity of natural killer cells. The activity profile of this IMiD® is similar to that of its parent drug thalidomide, but *in vitro*, it is 50 to 2000 times more potent in inhibition activity [17,18]

4. Clinical efficacy

4.1 Potential clinical uses of lenalidomide in cancer

Lenalidomide is currently indicated in combination with dexamethasone for previously treated MM and for deletion 5q myelodysplastic syndrome. It is currently being investigated in newly diagnosed MM, as maintenance therapy in MM, in chronic lymphocytic leukemia and in non-Hodgkin's

lymphoma.

5. Lenalidomide in multiple myeloma

5.1 Phase I and II trials

5.1.1 Relapsed/refractory myeloma

The first clinical evaluation of lenalidomide in MM started in 2000 with two phase I studies. Richardson et al. reported a phase I dose escalation study of lenalidomide in monotherapy (5-10-25-50 mg/day) in 27 patients with relapsed/refractory MM after a median of 3 prior regimens. The maximum tolerated dose (MTD) was 25 mg/day for 21 days/month. The median duration of therapy was 6 months and no significant somnolence, constipation or neuropathy were seen. The most common adverse events included fatigue, skin rash, neutropenia, thrombocytopenia, and leg cramps. Best responses including at least 50% reduction in paraprotein occurred in 29% of patients, and 71% of patients demonstrated a benefit from treatment with a 25% M-protein reduction. [19]

Zangari et al. showed that lenalidomide monotherapy was effective and well tolerated in heavily pre-treated patients with relapsed/refractory MM after a median of 10 cycles of chemotherapy. At least 50% reduction of the M-protein with a concomitant marrow response was reported in 20% of patients [20].

A subsequent phase II study evaluated 2 dose regimens of lenalidomide for relapsed/refractory MM patients, 30 mg once-daily and 15 mg twice-daily. An increased grade 3-4 myelosuppression was reported in patients receiving 15 mg twice-daily (41% versus 13%, p=0.03). Overall response rate (ORR), including complete response (CR), partial response (PR), or minor response, was 25% and the median overall survival (OS) in the once-daily and twice-daily groups was 28 and 27 months, respectively. Dexamethasone was added in 68 patients, and 29% of patients responded. The study provides the basis for future studies as monotherapy and with dexamethasone [21] (Table 1)

5.1.2 Newly diagnosed myeloma

In a phase II trial conducted in 34 patients with newly diagnosed MM, the combination of lenalidomide and dexamethasone produced an overall response rate (ORR) of 91%, including six patients (18%) with a CR and 13 (38%) with very good partial response (VGPR). The long term results showed a 2-year progression-free survival (PFS) of 59% and a 3-year OS rate for all patients of 88%. Most frequent grade 3 or higher non-hematologic toxicity included fatigue (15%), muscle weakness (6%), pneumonitis (6%) and rash (6%). [22,23] (Table 1)

5.2 Phase III trials

5.2.1 Relapsed/refractory myeloma

In preclinical studies dexamethasone proved to enhance the anti-myeloma activity of lenalidomide. [24,25]. Based on these laboratory findings and the preliminary results of phase I and II trials, two double-blind randomised phase III studies compared lenalidomide plus dexamethasone with placebo

plus dexamethasone in relapsed/refractory patients after a median of 2 prior therapies (MM-009 and MM-010). Lenalidomide was given orally at a dose of 25 mg/day on days 1–21 of each 28-day cycle until disease progression. In both treatment groups, dexamethasone was given orally at a dose of 40 mg/day on days 1–4, 9–12, and 17–20 for the first four cycles and then on days 1–4 only of each cycle. The results of the two studies were similar and both studies demonstrated the superiority of lenalidomide-dexamethasone in terms of ORR (60% and 61%), CR (20% and 24%), time to progression (TTP) and OS. [26,27] In a pooled analysis of MM-009 and MM-010 trials including 704 patients, treatment with lenalidomide-dexamethasone significantly improved ORR (60.6% versus 21.9%, $p<0.001$), CR (15% versus 2%, $p<0.001$), TTP (13.4 versus 4.6 months, $p<0.001$) and duration of response (15.8 versus 7 months, $p<0.001$), compared with dexamethasone-placebo. A significant benefit in OS (median 38 versus 31.6 months, $p=0.045$) was retained after a median follow-up of 48 months, despite the crossover of almost half of the placebo-dexamethasone treated patients to the lenalidomide arm after disease progression or study unblinding.[28] The most frequent grade 3 or 4 adverse events in the lenalidomide group were neutropenia (41.2% and 29.5%) and venous thromboembolism (VTE, 14.7% and 11.4%) in both MM-009 and MM-010 trials. (Table 2) Lenalidomide was most effective when given at first relapse [29] and a clinical benefit was observed regardless of previous thalidomide therapy and prior ASCT [30,31]. Thus, lenalidomide appears to be an option as retreatment in patients with relapsed/refractory MM who were previously treated with thalidomide. The quality of response to lenalidomide-dexamethasone improved over time, with 38% of patients achieving a CR with continuous treatment. The achievement of CR or VGPR was linked to improved OS, irrespective of when CR or VGPR was achieved. [32] Continuing treatment with lenalidomide until disease progression appears to improve OS. Response rates were comparable in patients with mild (creatinine clearance ≥ 60 ml/min; 64%), moderate (30–60 ml/min; 56%) or severe renal impairment (<30 ml/min; 50%). Patients with severe renal impairment were more likely to experience thrombocytopenia, to require lenalidomide dose reductions (as well as patients with moderate renal dysfunction), and to have shorter OS [33].

5.2.2 Newly diagnosed myeloma

A phase III trial conducted by the Eastern Cooperative Oncology Group (ECOG; E4A03) compared lenalidomide (25 mg) plus standard high-dose (40 mg on days 1–4, 9–12 and 17–20) or low-dose dexamethasone (40 mg on days 1, 8, 15 and 22) as induction therapy in 445 untreated MM patients. Although the response rate was higher in patients assigned to high-dose dexamethasone treatment, a significant survival advantage (2-year OS: 87% versus 75%) and a significant reduction in the rate of serious adverse events were seen with lenalidomide plus low-dose dexamethasone. A 4-month landmark analysis was performed to determine the effect of transplantation; the 3-year OS was 55% in patients who discontinued therapy at 4 months, 92% in patients who received ASCT and 79% in patients who continued treatment until progression or until tolerated. The incidence of any grade 3-4 non-haematological adverse event was 35% in the low-dose dexamethasone and 52% in the high-

dose dexamethasone regimen, particularly evident in patients older than 70 years (59% versus 78%). The three most common grade ≥ 3 adverse events were thrombosis (26% versus 12%), infections (16% versus 9%) and fatigue (15% versus 9%). Discontinuation rate due to adverse events was 19% in the low-dose dexamethasone and 27% in the high-dose dexamethasone regimen, with higher figures in older patients. [34]

A second phase III trial, conducted by the Southwest Oncology Group (SWOG, S0232), compared the effects of lenalidomide combined with high dose dexamethasone with placebo-dexamethasone in newly diagnosed MM patients. One-year PFS and ORR were superior with lenalidomide-dexamethasone (78% versus 52%, p=0.002; 78% versus 48%, p< 0.001), whereas 1-year OS was similar (94% vs 88%; p=0.25). [35]

Lenalidomide has raised concerns regarding its potential impact on the ability to collect stem cells for ASCT, after exposure to the drug. Some reports indicated that lenalidomide may reduce stem cell numbers, without harming the stem cells themselves, and that the duration of lenalidomide therapy may influence mobilization. [36,37] The use of cyclophosphamide plus granulocyte colony-stimulating factor (G-CSF) to mobilize peripheral blood stem cells may overcome this concern [38], particularly for patients treated with longer duration of lenalidomide. [39] An expert panel recommended early stem cell mobilization, after 3-4 cycles of lenalidomide-based therapy if ASCT is considered a potential future treatment option. [40]

A phase III, randomized, placebo-controlled trial (MM-015) compared melphalan-prednisone-lenalidomide followed by lenalidomide maintenance (MPR-R) with fixed-duration melphalan-prednisone-lenalidomide (MPR) and melphalan-prednisone MP in 459 transplant-ineligible MM. Patients received nine 28-day cycles of melphalan 0.18 mg/kg (days 1-4), prednisone 2 mg/kg (days 1-4), and lenalidomide 10 mg (days1-21) (MPR-R and MPR) or melphalan and prednisone with placebo (MP), followed by lenalidomide maintenance in MPR-R (10 mg, days 1-21) or placebo. After a median follow-up of 30 months, MPR-R reduced the risk of progression by 70% and significantly prolonged median PFS (31 months) compared with MP (13 months; HR 0.40; p<0.001). Response rates were higher (77% versus 50%; p<0.001) and of better quality (33% versus 12% ≥ VGPR) for MPR-R versus MP. A trend for extended OS with MPR-R versus MP (3-yr OS rates 70% versus 66%; p =0.81) was observed. Similarly, MPR-R significantly extended median PFS compared with MPR (31 versus 15 months; HR 0.48; p<0.001). MPR-R was most beneficial among patients aged 65-75 years of age, while its benefits were less evident in older patients. The most common grade 4 hematologic toxicities were neutropenia (MPR-R 35%, MPR 32%, MP 8%) and thrombocytopenia (11%, 12%, and 4%). [41] (Table 2)

The activity and the acceptable safety profile of lenalidomide have prompted its evaluation in high-risk smoldering myeloma to prevent or delay progression to symptomatic MM. A phase III study compared the efficacy of lenalidomide (25 mg/day for 21 days) plus dexamethasone (20 mg on days 1-4, 12-15) for 9 cycles, followed by lenalidomide maintenance, with therapeutic abstention. After a median follow-up of 22 months, the median TTP was not reached in the lenalidomide group

compared with 25 months in the abstention arm, with an acceptable tolerability. OS was significantly longer in the lenalidomide group (98% versus 82% at 3 years). [42]

5.3 Lenalidomide-based combinations in multiple myeloma

In vitro studies suggested that lenalidomide activity may be synergistic with a number of conventional chemotherapeutic agents.

Lenalidomide plus adriamicyn and dexamethasone was investigated in a phase I-II trial including 69 intensively pre-treated MM patients. The MTD was not reached at the highest dose level (lenalidomide, 25 mg on days 1-21; adriamicyn 9 mg/m^2 intravenously on days 1-4; and dexamethasone 40 mg on days 1-4 and 17-20). The combination resulted in high response rate (ORR 77% at the MTD), with mainly hematologic toxicity (grade 3-4 neutropenia and thrombocytopenia 48% and 38%, respectively) and infections (10.5%) as adverse events. [43]

Other combinations included lenalidomide (10 mg for 21 days) combined with continuous low-dose oral cyclophosphamide (100 mg) and prednisone in 11 heavily pre-treated lenalidomide/dexamethasone-refractory MM patients. This regimen results in a remarkable activity (at least PR rate of 50%) and good tolerability. [44]

A retrospective analysis evaluated 21 multiple relapsed/refractory patients, who received lenalidomide (25 mg on days 1–21), cyclophosphamide (500 mg days 1, 8, 15 and 21), and dexamethasone (40 mg days 1–4, and 12–15). Side effects consisted primarily of neutropenia (38%), which was tolerable and manageable. Deep vein thrombosis occurred in 14% of patients with a heavy myeloma load. The observed overall response rate (at least PR) of 65% appears superior to lenalidomide alone or in combination with dexamethasone (60-61%). [45]

Lenalidomide-bortezomib-dexamethasone showed encouraging activity in 38 relapsed/refractory MM subjects [46]. The MTD of this regimen consisted of bortezomib 1.0 mg/m^2 on days 1, 4, 8, and 11 and lenalidomide 15 mg on days 1 to 14 of a 21-day cycle, with ORR rate of 60% (including minimal response) and an encouraging median OS of 37 months. In a phase II trial this combination achieved at least PR in 68% [47].

A subsequent phase II study evaluate dexamethasone (40 mg), bortezomib (1.0 mg/m^2) and pegylated liposomal doxorubicin (4.0 mg/m^2 administered on days 1, 4, 8, and 11) with lenalidomide (10 mg daily on days 1-14). A total of 40 heavily pre-treated patients were enrolled and 49% of patients achieved at least PR. Adverse events included fatigue (40%), thrombocytopenia (35%), neutropenia (35%), anemia (30%), peripheral neuropathy (25%) and pneumonia (15%). [48]

A recent phase I/II trial investigated the combination of bendamustine, lenalidomide and dexamethasone in 29 symptomatic relapsed MM patients. The MTD was bendamustine 75 mg/m^2 (days 1 and 2), lenalidomide 10 mg (days 1-21), and dexamethasone 40 mg (weekly) of a 28 day cycle. The PR rate was 52%, with 24% VGPR. Median PFS was 6.1 months with one-year PFS of 20%. Grade 3-4 adverse events included neutropenia, thrombocytopenia, anemia, hyperglycemia, and fatigue [49].

To further improve the efficacy of lenalidomide-based therapy, various other combinations with newer drugs are being explored [50].

Promising results were obtained with the combination of lenalidomide plus carfilzomib and low-dose dexamethasone in the phase I-II trial including 53 patients. Responses were rapid and improved over time reaching 100% VGPR and early time-to-event data were very encouraging. Hematologic toxicities were reversible and included grade 3-4 anemia (18%), neutropenia (12%), and thrombocytopenia (10%). Grade 3-4 non-hematologic adverse events included hyperglycemia (24%), VTE while on ASA prophylaxis (10%), infection (6%) [51]. These results provided the rationale for the currently ongoing phase III randomized trial (ASPIRE).

Preliminary experiences of lenalidomide combined with the potent CS1 antibody elotuzumab showed that the activity of the antibody is enhanced and more myeloma cells are killed both in cell lines and in primary patient myeloma cells [52]. In a phase I study currently ongoing, patients started with the full dose of lenalidomide (25 mg) and low-dose dexamethasone (40 mg weekly) with escalating doses of elotuzumab [53]. In the phase I portion of the trial, patients received elotuzumab up to 20 mg/kg without experiencing dose-limiting toxicity. The ORR for the phase I study was 82%, with 95% of lenalidomide-naive patients achieving PR or better. No significant reduction in ORR was noted among patients who had either > 3 prior lines versus those who had < 3 prior lines, suggesting that the novel approach of a monoclonal antibody was able to overcome resistance in heavily pre-treated patients, as well as in those in earlier clinical course.

Several groups explored new combinations of lenalidomide with small molecule inhibitors, such as histone-deacetylase inhibitors (HDACis), tyrosine kinase inhibitors, the VEGF inhibitor bevacizumab [54] and the signal transduction inhibitor perifosine [55]. In combination with lenalidomide, both the HDACis vorinostat [56] and panobinostat [57] showed promising results, with ORR of 60% and VGPR or better rate of 35%.

Several combination regimens have been evaluated in newly diagnosed myeloma. In 72 patients treated with lenalidomide, dexamethasone and clarithromycin (BiRd) in a phase II trial, CR was achieved in 39% of patients, VGPR in 74% of patients [58]. A subsequent case-match analysis comparing updated data of patients who received BiRd versus patients who received lenalidomide/low-dose dexamethasone showed a significantly higher response rate (CR 45.8% versus 13.9%, $p<0.001$; VGPR rate or better 73.6% versus 33.3%, $p<0.001$), TTP (median 48.3 versus 27.5 months, $p=0.071$), PFS (median 48.3 versus 27.5 months, $p=0.044$) and trend toward better OS in patients treated with BiRd. Main grade 3–4 toxicities of BiRd were hematologic, (in particular thrombocytopenia 23.6% versus 8.3%, $p=0.012$), infections (16.7% versus 9.7%, $p=0.218$) and dermatological (12.5% versus 4.2%, $p=0.129$). [59] (Table1) A randomized phase II trial (EVOLUTION) evaluated four different lenalidomide- and bortezomib-based combinations in 140 previously untreated MM patients: bortezomib-dexamethasone-cyclophosphamide (VDC), bortezomib-dexamethasone-cyclophosphamide modified (VDC-mod) bortezomib-dexamethasone-lenalidomide (VDR), bortezomib-dexamethasone-cyclophosphamide-lenalidomide (VDCR). All

regimens were highly active with VGPR or better of 58%, 51%, 41% and 53% in VDCR, VDR, VCD and VCD-mod arms, respectively and a corresponding 1-year PFS of 86%, 83%, 93% and 100%, respectively. Common side effects included hematological toxicities, peripheral neuropathy, fatigue, and gastro-intestinal disturbances. [60]

5.4 Lenalidomide as maintenance therapy

Lenalidomide is an attractive drug for maintenance therapy with the advantage of oral administration and good tolerability.

A pilot phase II study showed the feasibility and efficacy of lenalidomide consolidation and maintenance therapy in 102 elderly patients (65-75 years) after reduced dose ASCT (tandem 100 mg/m^2 melphalan) and laid the basis for further evaluations. [61]

Consequently, lenalidomide maintenance was studied in two phase III randomized, controlled trials comparing low doses of lenalidomide (10-15 mg/d) with placebo after ASCT. In the IFM 2005-02 study, 614 patients age ≤ 65 years were randomized to receive post transplant lenalidomide consolidation (25 mg for 21 days per month for 2 months) followed by lenalidomide maintenance (10–15 mg daily until relapse) or placebo [62]. The CALGB-100104 trial investigated maintenance treatment with lenalidomide 10 mg/day, escalated to 15 mg/day after 3 months and continued until disease progression, in 418 patients age ≤ 70 years after ASCT. [63]. Lenalidomide maintenance was associated with a better TTP (CALGB) and PFS (IFM). In the CALGB trial after a median follow-up of 34 months from ASCT, median TTP was 46 months in the lenalidomide maintenance, and 27 months in the placebo group (P<0.001); furthermore a significant survival benefit was reported. In the IFM trial, after a median follow up of 45 months from randomization, PFS probability after 4 years from randomization was significantly longer in patients randomized to lenalidomide maintenance therapy (43% vs. 22%, HR 0.5, p<0.001), but OS was similar. In both studies, maintenance therapy was well tolerated and the most frequent grade 3-4 adverse events were neutropenia (45-51%) and infections (1-13%). The incidence of second primary malignancies was similar in the two studies, and was 7.8-8.5% in the lenalidomide arm versus 1-3% in the placebo arm. Second primary malignancies include acute myeloid leukemia and myelodysplastic syndromes (1.6-2.6% in and 0-1.3% in the lenalidomide versus placebo groups, respectively). The incidence of second cancers was slightly higher in the IFM trial, where a proportion of patients was exposed to induction therapy incorporating drugs of known leukemogenic potential.

In elderly patients, the role of lenalidomide maintenance was tested in the MM015 three-arm trial, MP versus MPR versus MPR-R. After a median follow-up of 30 months, PFS was significantly longer with lenalidomide maintenance (31 vs. 14 vs. 13 months for MPR-R, MPR, and MP, respectively; MPR-R vs. MP, HR 0.40, p<0.001). The PFS benefit associated with MPR-R was noted in patients 65-75 years of age, but not in those older than 75 years of age (p=0.001). A landmark analysis after induction therapy showed a 66% reduction in the rate of progression with MPR-R (HR for the comparison with MPR, 0.34; p<0.001) that was age-independent.The 3-year OS rate was 70% with

MPR-R, 62% with MPR, and 66% with MP. The 3-year rate of second primary malignancies was 7% in both the MPR-R and MPR groups, compared to the MP group (3%). [41]

A recent study assessed the role of VDR consolidation and lenalidomide maintenance after VDR induction and ASCT in 31 NDMM patients [64]. This approach produced high quality responses with 38% of stringent CR and a good toxicity profile. The International Myeloma Working Group has recently reviewed the relevant data on maintenance treatment. [65] Since data are still preliminary and controversial, further studies and longer follow-up are needed to evaluate TTP, PFS, OS, the risk of second cancers and related risk factors, and to better assess the risk/benefit ratio of maintenance therapy.

6. Other clinical indications

Lenalidomide in combination with dexamethasone is approved by the US Food and Drug Administration and the European Medicines Agency for the second-line treatment of patients with MM. Currently, several clinical trials are evaluating its activity in combination with other conventional or novel therapies, in newly diagnosed MM patients.

Lenalidomide has also become the first-line FDA-approved treatment for patients with transfusion-dependent anemia due to low- or intermediate-1–risk MDS with 5q deletion (del5q), with or without additional cytogenetic abnormalities. The drug is also currently being investigated in higher-risk MDS and even acute myeloid leukemia with del5q, but it has also demonstrated some efficacy in MDS and AML without del5q. [66]

Recent studies have shown promising activity of lenalidomide in patients with relapsed/refractory chronic lymphocytic leukemia and as single agent in treatment-naive patients. The combination of lenalidomide with immunotherapy (rituximab and ofatumumab) has also shown clinical responses, but mature data and further studies are needed. [67] Initial activity in indolent and aggressive non-Hodgkin lymphoma was observed in 2 phase II trials as monotherapy. [68,69]

7. Safety and tolerability

Clinically relevant adverse events associated with lenalidomide treatment are hematologic (neutropenia and thrombocytopenia), and VTE (particularly in combination with dexamethasone). The majority of lenalidomide-related adverse events occur early during treatment, without cumulative adding toxicity. Table 3 resumes the frequencies of the main grade 3-4 side effects reported in phase III trials.

7.1 Hematologic toxicity

Myelosuppression, particularly neutropenia and thrombocytopenia, is quite common in patients treated with lenalidomide-based combination, but is generally predictable and manageable.

Neutropenia occurs early in the course of treatment. Lonial et al. found that in patients treated with lenalidomide-dexamethasone the most severe event occurred within 6 months in 52% of patients

and within 12 months in 76% of patients. However, the rate of febrile neutropenia was generally low (3%), and few patients discontinued treatment (3%) or required lenalidomide dose reductions (14%) due to neutropenia. The risk of thrombocytopenia decreased as treatment continued. [70].

General guidelines on the management of neutropenia during lenalidomide treatment suggest to stop lenalidomide therapy for severe neutropenia (absolute neutrophil count [ANC] <500 /ml), and to add G-CSF (see table 4 for dose reductions). At the next cycle, if ANC is >1000/ml, treatment may resume using lenalidomide at the same dose; if the ANC is <1000/ml, the lenalidomide dose should be reduced, unless the patient has a high tumor burden or aggressive disease. In this case, physician may consider maintaining the previous dose of lenalidomide and add G-CSF support. In some cases, the use of G-CSF in order to avoid treatment delays or dose reductions, or prophylactic use of G-CSF can help to prevent further neutropenia, treatment delays, dose reductions and infections. [71]

For low platelet counts, the general guidelines in the prescribing information for lenalidomide suggest to stop lenalidomide therapy for platelets (PLTs) <30000/ml. At the next cycle, patients may resume lenalidomide at 15 mg/day dose. In case of recurrent thrombocytopenia (with PLTs <30.000/ml), lenalidomide dose should be reduced. [72,73].

7.2 Non-hematologic adverse events

7.2.1 Venous thromboembolism (VTE)

Several factors increase the risk of VTE in myeloma patients. The risk is higher in newly diagnosed and in elderly patients, and increases when high-dose dexamethasone or chemotherapy (doxorubicin in particular) are used. [74,34] The use of lower doses of dexamethasone may reduce the risk of VTE. In the ECOG trial, enrolling newly diagnosed MM patients, incidence of VTE was 26% in the high-dose dexamethasone group, but only 12% in the low-dose dexamethasone arm [34]. The incidence of VTE in relapsed patients treated with lenalidomide/dexamethasone in MM-009/010 was 11-16% [26,27] without thromboprophylaxis. With prophylaxis with low-dose aspirin (ASA) or low-molecular-weight heparin (LMWH), VTE was reported in 2–5% of patients. [75,76]. Physicians should carefully evaluate patient risk of VTE, keeping into account all the risk factors (patient-related, disease-related and treatment-related). For patients with a standard risk of VTE, low-dose aspirin (81–100 mg) during lenalidomide therapy should provide sufficient thromboprophylaxis. A prospective, open-label, randomized sub-study of a phase III trial compared the efficacy and safety of thromboprophylaxis with low-dose ASA and LMWH in newly diagnosed MM patients, treated with lenalidomide and low-dose dexamethasone induction and MPR consolidation: the incidence of VTE was 2.27% in the ASA group and 1.20% in the LMWH group [77]. Pulmonary embolism was observed in 1.70% of patients in the ASA group and none in the LMWH group. For patients with a higher risk of VTE, prophylactic doses of LMWH should be considered. [74] (table 4) In patients with renal failure, the dose of LMWH should be adjusted accordingly. In relapsed patients treated with lenalidomide and dexamethasone, a panel of experts suggest to continue LMWH treatment for at least the first four cycles, corresponding to the period in

which high-dose dexamethasone is administered and the risk of VTE is highest. Patients should then be switched to ASA prophylaxis for the rest of their treatment. [71] It is important to consider that late VTE events have been recorded, especially after thromboprophylaxis is discontinued. Patients who develop VTE should stop lenalidomide treatment and receive LMWH at therapeutic doses. When patients are stable on anticoagulation therapy, treatment with lenalidomide could be restarted in patients who benefit from this therapy.

7.2.2 Dermatologic toxicity

The use of lenalidomide is often associated with dermatologic toxicity, most frequently rash, dry skin and mouth and atrophic lesions. These side effects are usually mild to moderate and they can be easily managed. Rash has been reported in 21% of patients receiving lenalidomide-dexamethasone [26,27]. Rash is more likely to occur during the first cycles of therapy, although late reactions have been noted. Toxic epidermic necrolysis and Stevens-Johnson syndrome are more serious, but fortunately quite uncommon. [72,73] If the rash is not severe, the patient may be given lenalidomide with caution. A panel of experts recently recommended that limited, localized rash should be treated with antihistamines and topical steroids as needed and treatment with lenalidomide may continue. [71] When mild toxicities occur, temporary discontinuation is generally the best method to solve the rash. If necessary, treatment should begin with antihistamines, if rash persists, low-dose prednisone (10-20 mg/day for up to 14 days) should be added. In case of severe toxicity, the treatment should be interrupted until complete resolution and then restarted with 50% lenalidomide dose reductions. If a diffuse, desquamating, exfoliative or bullous rash develops, lenalidomide treatment should be discontinued permanently. [78] (table 4)

Physicians should be very cautious while co-administering lenalidomide with agents with known dermatologic toxicity, such as sulfonamides, allopurinol, cotrimoxazole. In these cases a careful monitoring is needed.

7.2.3 Infections

MM itself can cause impairment in immune function, and consequently increase in risk of infections. The risk is higher in case of active and aggressive disease but decreases when the patient responds to therapy. Treatment type has also a determinant role, in particular the use of high-dose dexamethasone and myelotoxic drugs that can determine neutropenia may increase the risk of infections. Infections were reported in up to 31% of patients treated with lenalidomide (table 3). For patients receiving high-dose dexamethasone, elderly patients, patients with co-morbidities that increase the risk of infections (i.e. chronic obstructive pulmonary disease, diabetes, renal function impairment), and for patients with an increased infection rate, routine oral antibiotic prophylaxis could be considered at least for the first 3 months of therapy. Trimethoprim-sulphamethoxazole should be used at least during the first 2-3 months of chemotherapy or during steroid administration [78].

In some cases, lenalidomide may cause fever, that typically resolves with treatment with low-dose

steroids. Also in these cases, however, a standard diagnostic work-up for infection is recommended. [71]

7.2.4 Fatigue

Fatigue is a common problem in elderly MM patients. There are several possible causes of fatigue: anemia, hypothyroidism, depression, dexamethasone-related myopathy. They should be carefully taken into account and promptly resolved. Lenalidomide may cause fatigue, and in case of severe fatigue, a reduction in the dose of lenalidomide may be considered. [71]

7.2.5 Teratogenic potential

There are no reported data on foetal exposure to lenalidomide in humans, but lenalidomide is considered a potential teratogen, as it is chemically related to thalidomide, that is one of the most teratogenic drugs. Therefore lenalidomide is available under the conditions described in a specific risk management program, which requires prescriber, pharmacy and patient involvement, to prevent foetal exposure. The goals of the risk management program are to register and educate physicians who prescribe lenalidomide on the risk of teratogenic effects, and monitor pregnancy prevention activities in male and female patients.[15,79]

7.2.6 Second primary malignancies

A retrospective pooled analysis of 11 clinical trials assessed data from 3846 patients who received a lenalidomide-based therapy. The overall incidence rate events per 100 patient-years of second primary malignancies was 3.62 [80]. Another analysis pooled data from 703 relapsed/refractory MM patients enrolled in pivotal phase III trials. The overall incidence rate was 3.98 (95% confidence interval [CI], 2.51-6.31) with lenalidomide/dexamethasone and 1.38 (95% CI, 0.44-4.27) with placebo/dexamethasone. Despite the good benefit/risk profile of lenalidomide/dexamethasone, the risk of second primary malignancy remains a concern and must be considered.[81]

7.2.7 Lenalidomide in renal failure

Factors involved in the pathogenesis of renal failure in MM include the capacity of the light-chain component of the immunoglobulin to cause proximal tubular damage, dehydration, hypercalcemia, hyperuricemia, infections, and use of nephrotoxic drugs. Lenalidomide is excreted by the kidney and therefore lower doses may provide sufficient drug exposure in patients with renal failure. [82,83]. Common causes of renal failure in MM patients should be considered, and promptly resolved. In patients receiving lenalidomide-containing therapies, a constant monitoring of the hematologic function is necessary, particularly in the early cycles. Lenalidomide dose reductions are mandatory depending on the creatinine clearance values. When creatinine clearance ranges between 30 and 50 mL/min, the recommended dose of lenalidomide is 10 mg per day; with a value lower than 30 mL/min, the recommended dose of lenalidomide is 15 mg every other day for patients not requiring

dialysis; if creatinine clearance is below 30 mL/min and the patient requires dialysis, lenalidomide dose is 5 mg per day after dialysis on dialysis days. [72,73] (Table 4)

8. Conclusion

Lenalidomide is one of the most successful new therapeutic agents of recent years. The above mentioned studies confirm the remarkable antitumor activity of lenalidomide in MM and recent studies have demonstrated success in other hematologic malignancies as well. The most common reported adverse events are myelotoxicity and thromboembolism, mostly manageable with common dose reductions, supportive therapy and accurate prophylaxis. Lenalidomide has a significantly decreased incidence of the common side effects associated with its parent drug thalidomide, such as peripheral neuropathy, constipation and sedation. The advantage of an acceptable toxicity profile enables the drug to be given for longer periods, without cumulative adverse events. Lenalidomide can be administered regardless of previous treatments and age, with an initial dose adjustment for renal function and cytopenias. When combined with low-dose dexamethasone. lenalidomide shows better tolerance, without affecting efficacy. The manageable safety profile allows treatment to continue until disease progression at the best tolerated dose.

9. Future Perspective

Ongoing studies are currently exploring newer uses of lenalidomide in MM and in other hematologic malignancies. Lenalidomide maintenance is one of the most promising therapeutic directions in MM, with the potential to alter the natural course of the disease by prolonging the time to relapse and, as preventive therapy, by delaying the progression from smoldering to active disease. The risk of second primary malignancies continues to be investigated, particularly in newly diagnosed MM.

Executive Summary

Mechanism of action

- Direct antitumor effects on myeloma cells, including growth arrest and apoptosis.
- Indirect effects, including altered adhesion to bone marrow stromal cells, inhibition of bone marrow production of cytokines. inhibition of angiogenesis and stimulation of T- and natural killer-cells.
- Lenalidomide is rapidly orally absorbed with maximum plasma concentrations (C_{max}) occurring between 0.5 and 6.0 hours post-dose. Lenalidomide is metabolized through hydrolytic cleavage of glutarimide amide bonds, with an in vitro half-life of approximately 8 hours. The terminal elimination half life ($t_{1/2}$) was approximately 3 hours in clinically dose range of 5-50 mg. The predominant clearance mechanism of lenalidomide is the urine excretion that accounts for about 82% of the dose within 24 hours

Pharmacokinetics properties

- Absorption: lenalidomide is rapidly absorbed in healthy volunteers and in patients with

relapsed/refractory MM following oral administration with maximum plasma concentrations occurring between 0.5 and 6.0 hours post-dose. Co-administration with food does not alter the extent of absorption but does reduce the maximal plasma concentration by 50%. The pharmacokinetic disposition of lenalidomide is linear with area under the curve (AUC) and C_{max} values increasing proportionally with dose.

- Excretion: in healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours in healthy subjects and 3 to 5 hours in patients with multiple myeloma or myelodysplastic syndrome.

Clinical efficacy

- When given as monotherapy lenalidomide is moderately active in relapsed/refractory MM patients.
- Superior efficacy was noted in association with dexamethasone; therefore this combination was approved for MM patients who have received at least one prior therapy.

Safety and tolerability

- The most common adverse events reported in lenalidomide-based trials are neutropenia, thrombocytopenia, anemia, thromboembolic events and infections. Other events include fatigue, muscle weakness, cramps and skin rash.
- Importantly, the risk of adverse events, particularly myeloppression and venous thromboembolism, appears to be highest during the initial cycles of lenalidomide-dexamethasone and decreases progressively thereafter.
- Clinicians should be particularly careful during the initial cycles of therapy to prevent and promptly manage the potential side effects. Dose adjustments rather than discontinuation of the drug, can often be used to manage adverse events, ensuring that patients are able to receive the benefits of continuous therapy.

Drug Interactions

Results from human in vitro metabolism studies and non-clinical studies show that lenalidomide is neither metabolized by nor inhibits or induces the cytochrome P450 pathway suggesting that the drug is not likely to cause or be subject to P450-based metabolic drug interactions. Periodic monitoring of digoxin plasma levels, in accordance with clinical judgment, in patients receiving this medication, is recommended during administration of lenalidomide. Previous data reported an increased incidence of VTE in patients with cancer treated with erythropoiesis-stimulating agents.

Dosage and administration

- The recommended starting dose of REVLIMID® (lenalidomide) is 25 mg/day with water orally administered as a single 25 mg capsule on days 1-21 of repeated 28-day cycles.

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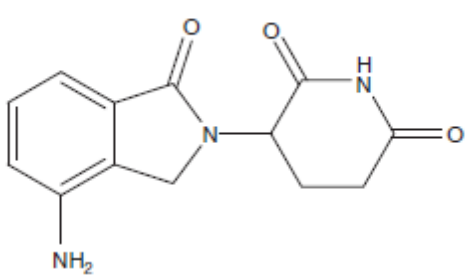
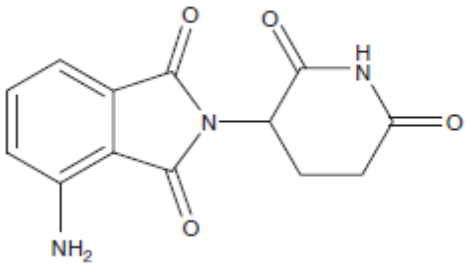
Figure 1 Chemical structure of lenalidomide and thalidomide



Lenalidomide



Thalidomide

Table 1: Lenalidomide phase I/II trials							
Trial	**Patients**	**Schedule**	**CR**	**≥VGPR**	**≥PR**	**PFS/TTP/EFS**	**OS**
Relapsed and relapsed/refractory patients							
Lenalidomide alone [21]	*70*	*R: 30 mg once-daily or 15 mg twice-daily day 1-21*	*4%*	*NA*	*17%*	*50% at 5 months*	*50% at 28 months*
Lenalidomide, doxorubicin, dexamethasone [43]	*69*	*R: 25 mg on days 1-21 Doxo: 9 mg iv on days 1-4 D: 40 mg on days 1-4 and 17-20*	*21%*	*53%*	*77%*	*50% at 40 weeks*	*NA*
Lenalidomide, bortezomib, dexamethasone [46]	*38*	*R: 15 mg on days 1 to 14 V: 1 m /m^2 on days 1,4,8 and 11 of 21-day cycles. D:20 mg or 40 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 added for progressive disease after two cycles.*	*NA*	*NA*	*39%*	*NA*	*50% at 37 months*
Lenalidomide, dexamethasone, doxorubicin, bortezomib [48]	*40*	*R: 10 mg on days 1-14. Doxo: 4 mg/m^2 on days 1,4,8 and 11 V: 1 mg/m^2 on days 1,4,8 and 11 D: 40 mg on days 1,4,8 and 11*	*21%*	*31%*	*49%*	*50% at 9 months*	*NA*
Lenalidomide, bendamustine, dexamethasone [49]	*29*	*R: 10 mg on days 1-21. Benda: 75 mg/m^2 on days 1, 2. D: 40 mg weekly.*	*NA*	*24%*	*52%*	*50% at 6 months*	*62% at 24 months*
Newly diagnosed patients							
Lenalidomide, dexamethasone [22]	*34*	*R: 25 mg on days 1- 21. D: 40 mg on days 1- 4, 9-12, 17- 20*	*18%*	*38%*	*91%*	*59% at 24 months*	*88% at 36 months*
Lenalidomide, clarithromycin, dexamethasone [58]	*72*	*R: 25 mg on days 1-21 Cl: 500 mg twice daily D: 40 mg weekly*	*39%*	*73%*	*NA*	*NA*	*NA*
Lenalidomide, bortezomib, and dexamethasone [60]	*42*	*V: 1,3 mg/m2 on days 1,4,8,11 R 25 mg on days 1-14. D: 40 mg on days 1,8,15.*	*24%*	*51%*	*85%*	*83% at 12 months*	*100% at 12 months*
Lenalidomide, bortezomib, cyclophosphamide and dexamethasone [60]	*48*	*V 1,3 mg/m^2 on days 1,4,8,11 R: 15 mg on days 1-14 C: 500 mg/m2 on days 1,8. D 40 mg on days 1,8,15*	*25%*	*58%*	*88%*	*86% at 12 months*	*92% at 12 months*

R, Lenalidomide; D, Dexamethasone; C, Cyclophosphamide; B, Bortezomib; P, Prednisone; Doxo, Doxorubicina; Benda, Bendamustine;Cl, Clarithromycin.

Table 2: Lenalidomide phase III trials in MM							
Trial	**Patients**	**Schedule**	**CR**	**≥VGPR**	**≥PR**	**Median PFS/TTP**	**Median OS**
Newly diagnosed patients							
ECOG [34]*							
RD	223	R: 25 mg/day for 21 days, D: 40 mg/day on days 1-4, 9-12, 17-20	5%	50%	81%	22.3 months	Not reached
Rd	222	R: 25 mg/day for 21 days, d: 40 mg/day on days 1, 8, 15, 22	4%	40%	70%	26.1 months	Not reached
SWOG [35]§							
RD	97	R: 25 mg/day for 28 days D: 40 mg/day on days 1-4, 9-12, 17-20	NA	63%	78%	52% at 3 years	Not reached
Placebo-D	95	Placebo D: 40 mg/day on days 1-4, 9-12, 17-20	NA	16%	48%	32% at 3 years	Not reached
CALGB 100104 [63]							
R maint.	231	R: 10-15 mg on days 1-21 until progression	NA	NA	NA	46 months	88% at 3 years
IFM 2005-02 [62]							
R maint.		R: 10-15 mg on days 1-21 until progression	29%	84%	99%	41 months	73% at 4 years
MM015 [41]							
MPR-R	116	M: 0.18 mg/kg on days 1-4 P: 2 mg/kg on days 1-4 R: 10 mg/day on days 1-21 (as induction and maintenance)	10%	33%	77%	31 months	70% at 3 years
MPR	116	M: 0.18 mg/kg on days 1-4 P: 2 mg/kg on days 1-4 R: 10 mg/day on days 1-21	3	33%	68%	14 months	63% at 3 years
MP	116	M: 0.18 mg/kg on days 1-4 P: 2 mg/kg on days 1-4	3%	12%	50%	13 months	66% at 3 years
Relapsed and relapsed/refractory patients							

MM09 [26]							
RD	177	R: 25 mg/day on days 1-21 D: 40 mg/day on days 1-4, 9-12, 17-20; after cycle 4, on days 1-4	14%	10%	37%	11.1 months	29.6 months
Placebo-D	176	Placebo Dex: 40 mg/day on days 1-4, 9-12, 17-20; after cycle 4, on days 1-4	<1%	1%	18%	4.7 months	20.2 months
MM010 [27]							
RD	176	R: 25 mg/day on days 1-21 D: 40 mg/day on days 1-4, 9-12, 17-20; after cycle 4, on days 1-4	16%	9%	36%	11.3 months	Not reached
Placebo-D	175	Placebo D: 40 mg/day on days 1-4, 9-12, 17-20; after cycle 4, on days 1-4	3%	2%	19%	4.7 months	20.6 months

RD, lenalidomide high-dose dexamethasone; Rd, lenalidomide low-dose dexamethasone; MPR-R, melphalan-prednisone-lenalidomide followed by lenalidomide maintenance; MPR, melphalan-prednisone-lenalidomide; MP, melphalan-prednisone; CR, complete response; VGPR, very good partial response; PR, partial response; PFS, progression free survival; TTP, time to progression; OS, overall survival; NA, not available.

* After the first four cycle, patients could discontinue therapy to pursue stem-cell transplantation (or other treatment options) or continue therapy on study until disease progression. All patients were recommended to receive bisphosphonates monthly. Thromboprophylaxis was added for all patients

§ Maintenance consisted of lenalidomide or placebo (25 mg/day for 21 days) and dexamethasone (40 mg/day on days 1-4 and 15-18)

Table 3 : Grade 3-4 adverse events reported in the main randomized phase III trials					
Trial	**Thrombocytopenia**	**Neutropenia**	**Infections**	**Fatigue**	**VTE**
Newly diagnosed patients					
ECOG [34]					
RD	6%	12%	16%	15%	26%
Rd	5%	20%	9%	9%	12%
SWOG [35]					
RD	NA	21%	NA	NA	24%
Placebo-D	NA	5%	NA	NA	5%
CALGB 100104 [63]					
R maint.	14%	45%	NA	NA	NA
IFM 2005-02 [62]					
R maint.	14%	51	8%	NA	3%
MM015 [41]					
MPR-R	33%*	39%*	NA	NA	NA
MPR	12%*	29%*	NA	NA	NA
MP	4%*	7%*	NA	NA	NA
Relapsed and relapsed/refractory patients					
MM09 [26]					
RD	15%	41%	21%	6%	15%
Placebo-D	7%	5%	12%	6%	3%
MM010 [27]					
RD	11%	30%	10%	7%	11%
Placebo-D	6%	2%	6%	3%	5%

RD, lenalidomide high-dose dexamethasone; Rd, lenalidomide low-dose dexamethasone; MPR-R, melphalan-prednisone-lenalidomide followed by lenalidomide maintenance; MPR, melphalan-prednisone-lenalidomide; MP, melphalan-prednisone; VTE, venous thromboembolism; NA, not available.

*indicate only grade 4

Table 4: Management of adverse events in multiple myeloma patients treated with lenalidomide and lenalidomide dose reductions

Adverse Event	Description	Action	Dose adjustment
Neutropenia	First fall to < 500/µl	Interrupt lenalidomide treatment and add G-CSF	
	Return to ≥ 500/µl when neutropenia is the only observed toxicity	Resume lenalidomide at starting dose once daily	25 mg
	Return to ≥ 500/µl when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at dose level -1 once daily	15 mg
	For each subsequent drop below < 500/µl	Interrupt lenalidomide	
	Return to ≥ 500/µl	Resume lenalidomide at next lower dose level	10 mg or 5 mg
Thrombocytopenia	First fall to < 30000/µl	Interrupt lenalidomide	
	Return to > 30000/µl	Resume at dose level -1	15 mg
	For each subsequent drop below 30000/µl	Interrupt lenalidomide	
	Return to > 30000/µl	Resume lenalidomide at next lower dose level	10 mg or 5 mg
Infection		Trimetoprin-cotrimoxazole for *Pneumocystis carinii* prophylaxis during high-dose dexamethasone.	
Cutaneous toxicity		Steroids and antihistamines.	
		Drug temporary interruption in case of severe toxicity; at the next cycle resume lenalidomide at next lower dose level	15 mg, 10 mg, 5 mg
		Permanent interruption in case of diffuse, desquamating, exfoliative or bullous rash.	
Thrombosis		Prophylaxis with aspirin if no or one individual/myeloma thrombotic risk factor is present. LMWH or full dose warfarin if two or more individual/myeloma risk factors are present.	

		Drug temporary interruption and full anticoagulation, then resume treatment, in case of occurrence of thrombosis.	
Renal toxicity	Mild renal impairment: creatinine clearance ≥50 mL/min		25 mg
	Moderate renal impairment (creatinine clearance 30-50 ml/min)		10 mg
	Severe renal impairment (creatinine clearance <30 ml/min, not requiring dialysis)		15 mg every other day
	End-stage renal disease (creatinine clearance <30 ml/min, requiring dialysis)		5 mg once daily (following dialysis on dialysis days)

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