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## NEW DRUGS

# Lenalidomide: A new therapy for multiple myeloma

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**Summary** The last decade has seen rapid evolution in the management of multiple myeloma. Cytogenetic, molecular, and proteomic techniques have led to a better understanding of the pathophysiology and prognostic markers of this heterogeneous malignancy. New immunomodulatory drugs, such as lenalidomide, which interrupt myeloma growth and survival pathways have entered into clinical usage. Combined with dexamethasone, oral lenalidomide has proved to be highly effective in patients whose disease has become resistant to conventional therapy. Currently, several clinical trials are ongoing in order to define the optimal use of this new agent and its combinations across the spectrum of patients with myeloma. Whether the ultimate outcome of future research will be a single-treatment solution for all patients, or whether

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treatments will become better-tailored to the individual (based on prognostic markers and pre-existing co-morbidities) has yet to be determined.

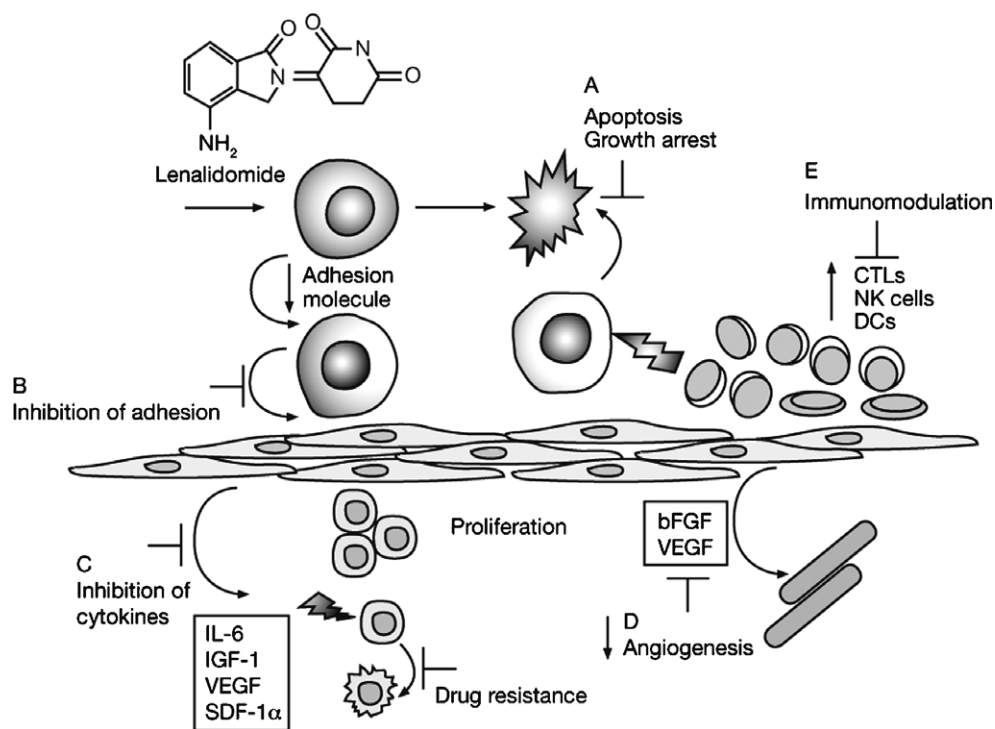
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## Introduction

Multiple myeloma (MM) is a haematological malignancy characterised by proliferating plasma cells in the bone marrow, with subsequent over-production of a monoclonal protein in most patients.<sup>1,2</sup> MM accounts for 1.5–2% of all cancer deaths and approximately 20% of deaths from haematological malignancies.<sup>3</sup> Although MM is initially sensitive to conventional chemotherapy, it remains incurable with almost all patients eventually relapsing. The median overall survival achieved with conventional approaches is approximately 33 months.<sup>4,5</sup> High-dose melphalan and autologous stem-cell transplantation (ASCT) increase the rate of complete remission, and extend event-free survival and overall survival in selected patients. However, relapse rates are high and, until recently, there were few salvage therapies. With the advent of biologically-based treatment strategies such as bortezomib, thalidomide, and lenalidomide, treatments are now available which specifically target myeloma

cell interactions within the bone marrow microenvironment. These interactions are key to the growth and survival of malignant cells, and have proved to be powerful tools in overcoming drug resistance and prolonging the duration of response in patients with MM.<sup>6,7</sup>

Lenalidomide (Revlimid<sup>®</sup>; Celgene, NJ, USA) is an oral immunomodulatory derivative of thalidomide with potent activity, but a different toxicity profile to the parent compound. It possesses pleiotropic (immunomodulatory, anti-angiogenic, and antineoplastic) activities, as well as anti-inflammatory effects.<sup>7,8</sup> Lenalidomide induces apoptosis, decreases the binding of MM cells to bone marrow stromal cells, and inhibits the production of cytokines (e.g. interleukin-6, vascular endothelial growth factor, tumour necrosis factor alpha) in the bone marrow milieu, which mediate angiogenesis and the growth and survival of resistant MM cells (Fig. 1).<sup>9</sup> It also enhances dexamethasone cytotoxicity, stimulates host anti-MM natural killer cell immunity, and inhibits osteoclast differentiation.<sup>10,11</sup>



**Figure 1** Antitumour activity of lenalidomide against multiple myeloma (MM) cells in the bone marrow microenvironment. A: Direct cytotoxicity of MM cells by causing G1 growth arrest or apoptosis. B: Inhibiting adhesion of MM cells to bone marrow stromal cells. C: Inhibiting the expression or bioactivity of interleukin (IL)-6, and other cytokines (e.g. vascular endothelial growth factor [VEGF], insulin-like growth factor [IGF-1], stromal cell-derived factor 1 [SDF-1 $\alpha$ ]) necessary for cytokine-mediated growth, survival (proliferation, cell cycle progression), drug resistance (anti-apoptosis), and migration of MM cells within the bone marrow milieu. D: Inhibiting the production of VEGF and basic fibroblast growth factor (bFGF) necessary for angiogenesis. E: Providing co-stimulatory action on primary human T-cells, which enhance antitumour activity, mediated by T helper-1 cells, cytokines IL-2 and interferon- $\gamma$ , and increases the number and function of natural killer (NK) cells, cytotoxic T-cells (CTLs) and dendritic cells (DCs). Figure reproduced from Expert Rev Anticancer Ther 2006;6(9):1239–1247 with permission of Future Drugs Ltd.<sup>9</sup>

Recently, lenalidomide has been found to have a direct anti-proliferative effect on MM cell lines (via p21WAF-1 up-regulation), while protecting normal B-cells from apoptosis, suggesting a potential role in bone marrow regeneration.<sup>12</sup>

This paper reviews the recent clinical findings with lenalidomide, an agent which has demonstrated remarkable activity against resistant MM cells.<sup>6,7</sup> Lenalidomide has been approved by the Food and Drug Administration (FDA) in the USA, and the European Medicines Agency for use in combination with dexamethasone in patients with MM who have received at least one prior therapy.

### Relapsed/refractory MM

#### Lenalidomide as a single agent

Two phase I dose-escalation trials of oral lenalidomide in advanced MM defined 25 mg/day as the maximum tolerated dose.<sup>10,13</sup> These studies revealed the favourable pharmacokinetic profile and the acceptable toxicity profile of lenalidomide in patients with relapsed/refractory disease. In a subsequent phase II study, 25% of patients with relapsed/refractory MM responded to lenalidomide (complete response [CR], partial response [PR], or minor response). In patients who failed to respond to lenalidomide monotherapy, after the addition of oral dexamethasone 29% responded. In this study, the efficacy of lenalidomide was observed in heavily pre-treated patients, including those who had received prior treatment with thalidomide.<sup>14</sup>

#### Lenalidomide plus dexamethasone

Recently, two phase III randomized clinical trials (MM-009 and MM-010) have demonstrated the superiority of lenalidomide plus dexamethasone, compared with dexamethasone alone in previously treated patients with relapsed/refractory MM (Table 1).<sup>15,16</sup>

In the first of these two trials (MM-009), researchers in the USA and Canada enrolled 354 patients.<sup>15</sup> Two-thirds of the patients had previously had a stem cell transplant, and nearly half had previously been treated with thalidomide. Patients received either oral lenalidomide (25 mg/day on Days 1–21, of every 28-day cycle) plus dexamethasone (40 mg/day on Days 1–4, 9–12, and 17–20, of every cycle), or placebo plus dexamethasone (same dose and regimen as in the lenalidomide group) (Table 1). At the start of cycle 5, the dose of dexamethasone was reduced to 40 mg/day on Days 1–4 only, of every cycle. The study found that the time-to-progression (TTP) of disease was delayed in patients who had received lenalidomide plus dexamethasone, compared with those treated with dexamethasone alone (median 11.1 months vs 4.7 months, respectively;  $p < 0.001$ ). Also improved in patients treated with lenalidomide plus dexamethasone, compared with those treated with dexamethasone alone, were overall response rate (61.0% vs 19.9%, respectively;  $p < 0.001$ ) and median overall survival (29.6 months vs 20.2 months, respectively;  $p < 0.001$ ).<sup>15</sup>

In a second study (MM-010), paralleling the findings from the North American trial, researchers from Europe, Israel, and Australia enrolled 351 patients.<sup>16</sup> In this study, the

**Table 1** Summary of clinical trials with lenalidomide combination treatment in the management of relapsed/refractory multiple myeloma

Therapy	n	Median age, years (range)	≥PR, %	CR, %	Median PFS, months	Median OS, months	Peripheral neuropathy grade 3–4, %	VTE grade 3–4, %	Neutropenia grade 3–4, %	Thrombocytopenia grade 3–4, %	Infection grade 3–4, %
Len + Dex <sup>15</sup>	177	64 (36–86)	61	14	30	30	2	15	41	15	22
Len + Dex <sup>16</sup>	176	63 (33–84)	60	16	NR	NR	5	11	30	11	10
Len + DVd <sup>41</sup>	62	62	75	15	12	NR	0	9	32	13	13
RAD <sup>42</sup>	61	64 (44–77)	82	8				2	Neutropenia/thrombocytopenia: 13		8
RCD <sup>43</sup>	21	59 (34–76)	65	5					Grade 4: 38 <sup>a</sup>		
Len + Bort <sup>44</sup>	38	60 (37–79)	39	3							

Bort = bortezomib; CR = complete response; Dex = dexamethasone; DVd = pegylated liposomal doxorubicin, vincristine and dexamethasone; Len = lenalidomide; NR = not reached; OS = overall survival; PFS = progression-free survival; PR = partial response; RAD = lenalidomide plus adriamycin and dexamethasone; RCD = lenalidomide plus cyclophosphamide and dexamethasone; VTE = venous thromboembolism.

<sup>a</sup> Neutrophil count was managed with granulocyte-colony stimulating factor in 12 patients; dose reductions/interruptions of cyclophosphamide were needed in 10 patients, and of lenalidomide in 5 patients.

researchers found a similar response with lenalidomide plus high-dose dexamethasone compared with dexamethasone alone: the median TTP was 11.3 months vs 4.7 months, respectively ( $p < 0.001$ ), the overall response rate was 60.2% vs 24.0% ( $p < 0.001$ ), and the median overall survival was not reached in the lenalidomide plus dexamethasone arm vs 20.6 months in the dexamethasone alone arm ( $p = 0.03$ ).<sup>16</sup>

Subgroup analyses of patients from these two phase III studies found that when lenalidomide plus dexamethasone was administered at the first relapse, the treatment response rate was higher (65% vs 58%) and the TTP longer (18 months vs 10 months), than when treatment was used later as salvage therapy.<sup>17</sup> Thus, earlier treatment with lenalidomide may further improve the length of response duration. Another subgroup analysis has shown that regardless of prior thalidomide exposure, the TTP and overall response were consistently higher with lenalidomide plus dexamethasone treatment, compared with dexamethasone alone (prior thalidomide: 36 weeks and 54% vs 20 weeks and 14%, no prior thalidomide: 60 weeks and 65% vs 20 weeks and 28%).<sup>18</sup> Even among those patients who were resistant to prior treatment with thalidomide, lenalidomide plus dexamethasone led to a high overall response rate (50%) and a longer TTP (31 weeks).<sup>18</sup> A multivariate analysis found that previous exposure to thalidomide, the duration of MM disease, and the number of prior therapies were all predictors of a shorter TTP.<sup>19</sup>

At the start of treatment, several patient characteristics can predict poor survival including: thrombocytopenia (platelet count  $< 150 \times 10^9/L$ ); serum albumin  $\geq 3$  mg/dL; serum calcium  $\geq 11$  mg/dL; and serum creatinine  $\geq 2$  mg/dL.<sup>4</sup> Lenalidomide was shown to be predominantly eliminated via urinary excretion, and effects of lenalidomide are therefore dependent on renal function.<sup>20</sup> In patients with severe renal dysfunction (creatinine clearance  $< 30$  mL/min), TTP and overall survival after lenalidomide plus dexamethasone treatment tended to be shorter, compared with patients with a better creatinine clearance ( $> 30$  mL/min); these results were still significantly higher than for patients treated with dexamethasone alone.<sup>21</sup> In patients with impaired renal function dose adjustments are required. Recently, recommendations for initial starting doses in these patients have been provided.<sup>20</sup>

Recently recognised chromosomal changes, such as deletion of chromosome 13 (del 13), deletion of chromosome 17, and translocation of 4;14 (t[4;14]), have been found to be prognostic for a more unfavourable clinical course, and these findings are likely to find application in future risk-adaptive treatment strategies.<sup>22</sup> A recent study from the University of Calgary, Canada, has found that patients with and without chromosomal changes (del 13 or t[4;14]) responded equally well to lenalidomide plus dexamethasone treatment, with little difference between the patient groups in either the response rate (CR + PR) or event-free survival.<sup>23</sup>

Notably, neither advancing age ( $> 65$  years) nor the inclusion of patients ineligible for ASCT had a significant impact on the treatment response with lenalidomide plus dexamethasone.<sup>24–27</sup> Subgroup analysis from the phase III studies found that the same clinical benefit was achieved in both elderly ( $> 65$  years) and younger ( $\leq 65$  years) patients

in terms of the overall response (58.9% vs 60.9%, respectively). However, TTP and overall survival were slightly shorter in the young (11.0 months and 29.8 months, respectively) compared with the elderly (14.0 months and overall survival not reached, respectively);<sup>24</sup> similar results were also obtained in patients aged  $\geq 75$  years.<sup>26</sup> These findings are reflected in data from the Canadian Expanded Access Programme, which found that among the elderly and the young, there was little difference in PR (58% vs 56%, respectively;  $p = 0.15$ ), progression-free survival (PFS; 43% vs 43%, respectively), or overall survival (74% vs 76%, respectively) following a median of 4 cycles (range 1–8) of treatment with lenalidomide plus dexamethasone, with or without prednisone.<sup>27</sup>

Evidence from the phase III studies found that both previously-transplanted and non-transplanted patients achieved comparable rates of overall response (63% vs 55%, respectively) and CR (13% vs 16%, respectively) with lenalidomide plus dexamethasone treatment. However, there was a trend towards a slightly longer TTP in those without prior ASCT (median 10.3 months vs 14.3 months;  $p = 0.13$ ).<sup>25</sup>

## Adverse events

While the phase III studies found that combining lenalidomide with high-dose dexamethasone was associated with more side effects than dexamethasone alone (19.8% vs 10.2%, respectively, of patients dropped out of the study because of side effects), this has to be considered in the context of the improved overall response rate. Only 38.4% of patients in the lenalidomide plus dexamethasone group withdrew from the study because of disease progression, compared with 71.6% of those taking dexamethasone alone.<sup>15</sup>

Lenalidomide is not associated with the same frequency or severity of side effects commonly seen with thalidomide, such as neuropathy, constipation, or somnolence. Myelosuppression (grade 3–4 neutropenia and thrombocytopenia), which was the dose-limiting side effect from phase I studies of lenalidomide, is the most frequent adverse event and can be effectively managed by dose reductions and interruptions. The incidence of grade 3–4 neutropenia (41.2% in the MM-009 study and 29.5% in the MM-010 study) was three-times higher than that of thrombocytopenia (14.7% in MM-009 and 11.4% in MM-010).<sup>15,16</sup>

Notably, Richardson et al. observed that the proportion of patients who experienced grade 3–4 myelosuppression was significantly higher in patients who had received prior treatment with ASCT.<sup>14</sup> This finding was confirmed by the phase III studies which found that the incidence of grade 3–4 neutropenia with lenalidomide plus dexamethasone was significantly higher in patients who had received prior ASCT (38.1% vs 27.3%;  $p < 0.05$ ).<sup>25</sup> The risk of grade 3–4 myelosuppression, and thrombocytopenia in particular, following treatment with lenalidomide is also significantly increased in patients with impaired renal function<sup>21,28,29</sup> emphasizing the need for appropriate dose reduction. Evidence from the Canadian Expanded Access Programme shows that treatment with lenalidomide plus dexamethasone (with or without prednisone) was equally well-toler-

ated in both elderly (>65 years) and young ( $\leq 65$  years) patients with 46% and 49%, respectively, remaining on therapy after a median of 4 cycles (range 1–8) of treatment.<sup>27</sup> Regardless of age, among the elderly and young a similar incidence of grade 3–4 neutropenia (46% vs 44%, respectively), grade 3–4 thrombocytopenia (38% vs 24%), febrile neutropenia (12% vs 9%), infection (25% vs 16%), and grade 3–4 fatigue (13% vs 11%) was recorded, with no significant differences between the groups.<sup>27</sup>

Since myelosuppression is common with lenalidomide treatment a group of experts have provided some clinical guidance for the management of cytopenias. In general, patients' blood count should be monitored on a biweekly basis during lenalidomide treatment, but weekly monitoring is recommended in patients with cytopenias at baseline.<sup>30</sup> In case cytopenias occur, granulocyte-colony stimulating factor (G-CSF) or erythropoietin stimulating agents might be needed, and in more severe cases dose reductions or interruptions might be required.<sup>30</sup> In addition, the group recommends the consideration of routine antibiotic prophylaxis for all patients upon initiation of lenalidomide treatment.<sup>31</sup>

While there is a benefit of the combination of lenalidomide and dexamethasone for the treatment of MM compared with lenalidomide as monotherapy,<sup>14</sup> studies also show that the addition of dexamethasone increases the risk of deep-vein thrombosis. In the North American study (MM-009), grade 3–4 thromboembolic events occurred in 14.7% of patients treated with lenalidomide plus dexamethasone, and 3.4% of patients in the dexamethasone alone group.<sup>15</sup> In the other study (MM-010), grade 3–4 thromboembolic events occurred in 11.4% of patients treated with lenalidomide plus dexamethasone and 4.5% of patients in the dexamethasone alone group.<sup>16</sup> Additional studies have shown that the risk of a thrombotic event further increased in patients treated with lenalidomide, who had a history of prior thalidomide treatment, or concomitant erythropoietin use.<sup>18,32</sup>

Also, both lenalidomide and thalidomide are associated with an increased risk of venous thromboembolism, particularly when used with high-dose dexamethasone. Across a number of studies in MM patients treated with lenalidomide plus dexamethasone, venous thromboembolism rates vary widely (3–75%).<sup>14,32–35</sup> As a result, safety concerns persist for lenalidomide in MM despite FDA approval.<sup>36</sup> It should be remembered, however, that patients with MM are at relatively high baseline-risk of developing thromboembolic events, especially deep-vein thrombosis. Upfront combinations, including thalidomide plus low-dose dexamethasone and/or alkylating agents, are associated with intermediate risk, whereas the same regimens for relapsed/refractory MM seem to be associated with lower risk.<sup>37</sup> The risk of thromboembolic events may be particularly high when specific risk factors increase the thrombogenic potential of the immunomodulatory agents. These risk factors are: combinational regimen including doxorubicin or high-dose dexamethasone; newly diagnosed disease; immobilization; infection; and history of thromboembolism.<sup>32,37,38</sup> National Comprehensive Cancer Network Guidelines recommend prophylactic anticoagulation in patients treated with lenalidomide plus dexamethasone.<sup>5</sup> Several different thromboprophylaxis strategies have been effective in lowering the risk of developing clots: daily aspirin (81–325 mg/day);

full-intensity warfarin (International Normalized Ratio 2–3); and prophylactic subcutaneous enoxaparin (40 mg/day). However, none of these prevention strategies has been prospectively compared, so the choice often reflects physician and/or patient preference.<sup>34,37,36,39</sup> A panel of experts recommend a 4- to 6-month course of prophylaxis in patients with risk factors, with low-dose aspirin (81–100 mg) or prophylactic doses of low-molecular-weight heparin.<sup>40</sup>

### Other lenalidomide combinations

The clinical safety and efficacy of lenalidomide in combination with other agents for the management of patients with relapsed/refractory MM has been evaluated in a number of clinical trials (Table 1). In a phase I/II clinical trial at the Cleveland Clinic Cancer Center, the combination of lenalidomide (10 mg/day, on Days 1–21) plus DVd, which comprised intravenous pegylated liposomal doxorubicin (40 mg/m<sup>2</sup>), intravenous vincristine (2 mg on Day 1), and oral dexamethasone (40 mg/day on Days 1–4) every 28-day cycle was evaluated. Overall, 41 of 62 patients included in the trial had failed a previous thalidomide-containing regimen. The lenalidomide plus DVd regimen was found to be well tolerated with a PR or better, recorded in 75% of patients (29% achieving a CR or near-CR) and a median PFS of 12 months.<sup>41</sup> Myelosuppression was acceptable, with a 7% incidence of febrile neutropenia. Thromboembolic events were recorded in 9% of patients and grade 3 peripheral neuropathy in 5%.

Data of a phase I/II study evaluating the efficacy and safety of lenalidomide (15 mg for 21 days) used in combination with adriamycin (9 mg/m<sup>2</sup> for Days 1–4 as a continuous infusion) and dexamethasone (40 mg/day on Days 1–4 and 17–20) have also been presented. After two unexpected events of non-febrile neutropenia, the protocol was amended to include G-CSF support (6 mg of pegfilgrastim on Day 6), resulting in an uneventful course in all patients treated subsequently at the two highest dose levels of lenalidomide.<sup>42</sup> Of the 22 patients evaluable for a response, a response (at least PR) was achieved in 18 patients (82%). These data provide evidence for the efficacy and acceptable toxicity profile of lenalidomide plus adriamycin and dexamethasone in the treatment of relapsed MM.<sup>18</sup>

In a second study, heavily pre-treated patients (median of previous lines of therapy 4 [range 1–8]) were treated with oral daily doses of lenalidomide (25 mg for 21 days of a 28-day cycle) in combination with dexamethasone (40 mg/day on Days 1–4 and 12–15) and cyclophosphamide (500 mg/day on Days 1, 8, 15, and 28) of for a maximum of 6 cycles. The study found that this combination was effective, and had a manageable toxicity profile. Of the 20 patients assessed, 15 patients achieved a response, including 1 CR and 3 very good partial responses (VGPR).<sup>43</sup> Only 2 patients discontinued treatment due to a failure to respond, and another patient discontinued due to liver toxicity. Neutrophil counts were maintained and managed by administration of G-CSF in 12 patients, a dose reduction or interruption of cyclophosphamide in 10 patients, and a dose reduction or interruption of lenalidomide in 5 patients. A further study is now ongoing to investigate this treatment regimen with cyclophosphamide on Days 1 and 8 only.

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