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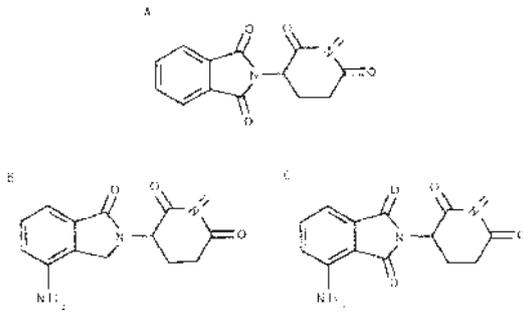
## From cell biology to therapy: lenalidomide in relapsed/refractory multiple myeloma

### Introduction

Multiple myeloma (MM) is a hematological malignancy of plasma cells that is characterized by clonal expansion, bone marrow infiltration, hypercalcemia, renal insufficiency, and the presence of immunoglobulin paraproteins in the serum and urine in the vast majority of patients (Blade *et al.* 1998). The disease arises from a B-cell of the normal germinal center as a result of a chromosomal translocation that places an oncogene under the control of immunoglobulin enhancers (Kuehl & Bergsagel 2002). In the US, MM is the second most common hematological malignancy after non-Hodgkin's lymphoma with approximately 20,000 new cases each year (Jemal *et al.* 2008). It has remained incurable, with a reported median survival of 3–4 years and a 5-year relative survival of approximately 33% (Greipp *et al.* 2005; ACS 2007). Prior approaches to treatment, including high dose therapy, have prolonged survival in MM, although remissions are inevitably followed by relapse (Blade *et al.* 1998). Previously, the aims of treatment were to control disease by safely achieving a

sequence of durable responses, without compromising quality of life (Smith *et al.* 2006). Novel therapies, including lenalidomide, thalidomide and bortezomib, have transformed the clinical management of MM and are increasingly recognized as potent therapies in overcoming resistant disease, with improvements in survival being seen, even in the relapsed and refractory setting (Kumar & Rajkumar 2006; Piazza *et al.* 2007).

Lenalidomide is an oral compound that has immunomodulatory, antiproliferative, anti-angiogenic, and erythropoietic properties (Figure 1; Anderson 2005). In preclinical studies, lenalidomide has demonstrated potent antimyeloma activity and a favorable adverse events profile (Davies *et al.* 2001; Gupta *et al.* 2001; Hideshima *et al.* 2002; Mitsiades *et al.* 2002; Hayashi *et al.* 2005; Kumar & Rajkumar 2006; Kastiris & Dimopoulos 2007). Lenalidomide was approved by the US Food and Drug Administration in June 2006 and by the European Medicines Agency in June 2007 for use in combination with dexamethasone in the treatment of MM in patients who have received at least one prior therapy.



**Figure 1.** Structure of thalidomide (A) and the immunomodulatory drugs lenalidomide (B) and CC-4047 (C). Lenalidomide and CC-4047 (also known as pomalidomide) were derived from thalidomide by adding an amino group (NH<sub>2</sub>) at the 4 position of the phthaloyl ring. Lenalidomide was generated by removal of the carbonyl group (C=O) from the 4-amino-substituted phthaloyl ring.

### Mechanism of action in multiple myeloma

The molecular mechanisms associated with disease progression in MM are critically dependent on the interaction between MM cells and the bone marrow microenvironment (Anderson 2005). Briefly, the adhesion of MM cells to bone marrow stromal cells triggers the release of cytokines that mediate separate pathways of MM cell growth and survival, including proliferation, anti-apoptosis, cell cycle progression, and migration. Lenalidomide has been shown to affect many of the interactions that are crucial to myeloma development by both direct and indirect mechanisms (Davies *et al.* 2001; Gupta *et al.* 2001; Hideshima *et al.* 2002; Mitsiades *et al.* 2002; Bartlett *et al.* 2004; Hayashi *et al.* 2005). Lenalidomide has been shown to directly potentiate apoptosis of MM cells via several pathways, including inhibition of expression of the cellular inhibitor of apoptosis protein-2, potentiation of the activities of other apoptosis inducers such as TNF-related apoptosis-inducing ligand (TRAIL), increased sensitivity to Fas induction, and enhanced caspase 8 activation (Davies *et al.* 2001; Gupta *et al.* 2001; Hideshima *et al.* 2002; Mitsiades *et al.* 2002; Bartlett *et al.* 2004; Hayashi *et al.* 2005;

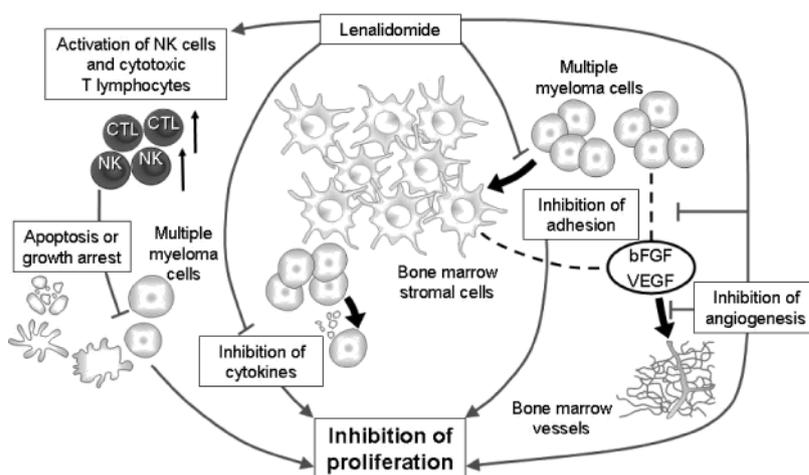
Knight 2005). Caspase 8, an integral component of Fas-mediated apoptosis, is sharply upregulated by lenalidomide (Mitsiades *et al.* 2002). Lenalidomide has been associated with direct antiproliferative activity against MM cells in the absence of immune cells or proapoptotic mechanisms by inducing G1 growth arrest (Hideshima *et al.* 2000; Knight 2005). Importantly, lenalidomide inhibits the proliferation of malignant B cells while protecting normal CD34<sup>+</sup> progenitor cells (Verhelle *et al.* 2007). The various mechanisms of action of lenalidomide are summarized in Figure 2.

### Clinical efficacy of lenalidomide-based therapy

Following comprehensive phase I and phase II trials that showed lenalidomide to have promising activity with a manageable toxicity profile when used as monotherapy and in combination with low-dose dexamethasone, large-scale international comparative studies were initiated (Richardson *et al.* 2002; Richardson *et al.* 2006a).

In 2 multicenter, double-blind, randomized, placebo-controlled phase 3 studies (MM-009/010) investigating the efficacy and safety of lenalidomide plus dexamethasone versus dexamethasone alone in patients with relapsed/refractory MM, patients were randomized and to either receive lenalidomide (25 mg/day on days 1-21 of each 28-day cycle) plus dexamethasone (40 mg on days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles and 40 mg on days 1 to 4 only from cycle 5 onwards) or matched placebo plus dexamethasone. Treatment was continued until disease progression. The primary endpoint of time-to-progression (TTP) was evaluated according to EBMT criteria (Blade *et al.* 1998).

Lenalidomide plus dexamethasone led to a significantly better response rates, and signifi-



**Figure 2.** Mechanism of action of lenalidomide and other immunomodulatory drugs in multiple myeloma. bFGF, basic fibroblast growth factor; CTL, cytotoxic T lymphocytes; NK, natural killer cells; VEGF, vascular endothelial growth factor.

cantly improved TTP and overall survival (OS) compared with dexamethasone alone (Dimopoulos *et al.* 2007; Weber *et al.* 2007a). The overall response rate (ORR) in the MM-009 study was 61.0% for patients treated with lenalidomide plus dexamethasone versus 19.9% for those treated with dexamethasone alone ( $p < 0.001$ ). In MM-010, the ORR was 60.2% with lenalidomide plus dexamethasone versus 24.0% with dexamethasone alone ( $p < 0.001$ ). The median TTP was significantly longer in patients receiving lenalidomide plus dexamethasone versus dexamethasone alone (MM-009: 11.1 vs. 4.7 months,  $p < 0.001$ ; MM-010: 11.3 vs. 4.7 months,  $p < 0.001$ ). At a median follow-up post-randomization of 17.1 months in the MM-009 study, median OS in patients receiving lenalidomide plus dexamethasone was 29.6 months vs. 20.2 months for dexamethasone alone ( $p < 0.001$ ) (Weber *et al.* 2007a). With median follow-up of 16.5 months in the MM-010 study, median OS in patients receiving lenalidomide plus dexamethasone had not been reached versus 20.6 months for dexamethasone alone ( $p = 0.03$ ) (Dimopoulos *et al.* 2007). In a pooled analysis that included data from all 704 patients enrolled in both trials, the ORRs were 60.6% and 21.9% for lenalidomide plus dexamethasone and dexamethasone alone, respectively ( $p < 0.001$ ) (Weber *et al.* 2007b). The median TTP in patients treated with lenalidomide plus dexamethasone versus dexamethasone alone was 11.2 versus 4.7 months ( $p < 0.001$ ) (Weber *et al.* 2007b). With an extended follow-up of 31.3 months, median OS was 35.0 months for those receiving lenalidomide plus dexamethasone and 31.0 months for those on dexamethasone alone ( $p < 0.05$ ) (Weber *et al.*, 2007b). It should be noted that this significant difference in OS was maintained despite 47% of patients receiving dexamethasone alone crossing over to lenalidomide-based therapy following unblinding of the study (Weber *et al.*, 2007b).

Subgroup analyses of the pooled data consistently showed significantly improved response rates, TTP, and OS with lenalidomide plus dexamethasone versus dexamethasone alone, regardless of number of prior therapies, prior stem-cell transplantation, or prior thalidomide use (Stadtmauer *et al.* 2006; Chanan-Khan *et al.* 2006; Wang *et al.* 2007). Patients with renal impairment, those with del(13) or t(4;14) and the elderly also showed this significant benefit (Weber *et al.* 2008b; Bahlis *et al.* 2007; Lonial *et al.* 2007).

Among patients who received lenalidomide plus dexamethasone, the median duration of

response was significantly higher for those who achieved a CR or nCR compared with those who achieved a PR (not yet reached versus 8.8 months,  $p<0.001$ ) (Harousseau *et al.* 2007). Finally, a post-hoc analysis of data from the MM-009/010 trials indicated that maintaining patients on lenalidomide by using dexamethasone dose reductions improved the efficacy of lenalidomide plus dexamethasone treatment compared with patients who continued to receive dexamethasone at the planned dose (San Miguel *et al.* 2007). Patients assigned to lenalidomide plus dexamethasone and who had a subsequent dexamethasone dose reduction experienced a significantly higher ORR and complete response (CR) rate (69.6% and 23.9%, respectively) compared with patients who continued to receive the standard dexamethasone regimen in combination with lenalidomide (50.8% and 13.0%, respectively;  $p<0.05$  for both).

The MM-016 study was a multicenter, single-arm, open-label expanded access program for lenalidomide in relapsed and refractory MM that reported on the efficacy of lenalidomide plus dexamethasone in patients according to their del13q, t(4;14) and del17p13 status. Patients received lenalidomide 25 mg daily on days 1-21 of a 28-day cycle plus dexamethasone 40 mg on days 1-4, 9-12 and 17-20 for 4 cycles then days 1-4 only beginning with cycle 5 (Bahlis *et al.* 2007). In the entire group, the median OS was not reached at a median follow-up of 16 months. Compared with the overall cohort, treatment with lenalidomide plus dexamethasone overcame poor prognosis conferred by del13q and t(4;14), with no increased risk of a reduction in OS (del13q: HR 0.56 [0.25-1.29],  $p=0.179$ ; t(4;14): HR 1.26 [0.46-3.42],  $p=0.641$ ). However, patients with del17p13 had a reduced OS despite a rapid initial response to therapy (HR 3.83 [1.34-10.93],  $p=0.012$ ).

In an ongoing Dutch compassionate use pro-

**Table 1.** Summary of response rates, TTP, and OS for lenalidomide-based therapies.

Trial	ORR (%)	TTP (months)	OS (months)
Len plus Dex (Weber <i>et al.</i> 2007)	61	11.1	29.6
Len plus Dex (Dimopoulos <i>et al.</i> 2007)	60	11.3	20.6
Len plus Dex (Weber <i>et al.</i> 2008)	60	11.2	35.0
Len plus Dex (Kneppers <i>et al.</i> 2008)	83	N/A	not reached
Len plus doxorubicin (Baz <i>et al.</i> 2006)	75	N/A	N/A
RCD (Kumar <i>et al.</i> 2007)	75	N/A	N/A
RAD (Knop <i>et al.</i> 2008)	85	2.2	N/A
RV (Richardson <i>et al.</i> 2006b)	58	N/A	N/A
RMPT (Palumbo <i>et al.</i> 2008)	91	N/A	N/A
RVD (Anderson <i>et al.</i> 2008)	73	N/A	N/A

Dex, dexamethasone; Len, lenalidomide; N/A, not available; ORR, overall response rate; OS, overall survival; RAD, lenalidomide plus adriamycin plus dexamethasone; RCD, lenalidomide plus cyclophosphamide plus dexamethasone; RMPT, lenalidomide plus melphalan plus prednisone plus thalidomide; RV, lenalidomide plus bortezomib; RVD, lenalidomide plus bortezomib plus dexamethasone; TTP, time to progression.

gram, patients with relapsed or refractory multiple myeloma were treated with lenalidomide 25 mg on days 1-21 every 28 days in combination with dexamethasone 40 mg/day on days 1-4 and 15-18 until disease progression, unacceptable toxicity, or for a maximum of 8 courses. Fifteen patients received lenalidomide 10 mg/day maintenance therapy without dexamethasone after 6-8 courses of therapy (Kneppers *et al.* 2008). The preliminary response data of the first 42 patients showed an ORR of 83% (CR 5%, VGPR 45%, PR 45%, MR 5%). The median OS has not been reached (median progression-free survival 10 months).

In addition to monotherapy and lenalidomide plus dexamethasone therapy, lenalidomide has been investigated in other combination therapies. In a phase 1/2 study, lenalidomide was investigated in combination with pegylated liposomal doxorubicin-based chemotherapy (Baz *et al.* 2006). Sixty-two patients received liposomal doxorubicin (40 mg/m<sup>2</sup>) and vincristine (2 mg) on day 1, dexamethasone (40 mg on days 1-4), and lenalidomide (5-15 mg on days 1-21) of each 28-day cycle. Among 52 evaluable patients, the ORR of the combination was 75%, including 29% of patients with

either a CR or near CR (nCR). Best response occurred after a median of 115 days and 4 cycles of therapy.

A retrospective analysis investigated the combination of lenalidomide with cyclophosphamide and dexamethasone (RCD). Of 21 patients who were administered lenalidomide 25 mg on days 1-21, cyclophosphamide 500 mg on days 1, 8, 15 and 21, and dexamethasone 40 mg on days 1-4, and 12-15 of every 28-day cycle for a maximum of 9 cycles, 15 of 20 (75%) evaluable patients had a response, including 1 CR, 3 VGPR, and 9 PR. The median time to response was 31 days. There was no difference in response rate between patients who required a dose reduction compared with those who tolerated the full treatment schedule (Kumar *et al.* 2007).

In a phase 1/2 study, lenalidomide was evaluated in combination with doxorubicin and dexamethasone (Knop *et al.* 2007; Knop *et al.* 2008). A total of 69 patients (median age 65 years) received six 28-day cycles of lenalidomide 10-25 mg daily on days 1-21, doxorubicin 4-9 mg/m<sup>2</sup> as a 24-hour infusion on days 1-4, and dexamethasone 40 mg on days 1-4 and 17-20, including 20 patients who received treatment at 5 different lenalidomide and doxorubicin dose levels during phase 1. In phase 2 of the study, all patients received the fifth dose level of lenalidomide 25 mg on days 1-21, doxorubicin 9 mg/m<sup>2</sup> on days 1-4, and dexamethasone 40 mg on days 1-4 and 17-20 (Knop *et al.* 2008). Granulocyte-colony stimulating factor support was given at 6 mg on day 6. ORR for patients receiving treatment at dose levels 1-4 in the phase 1 study was 60%, including 5 patients (25%) with nCR. ORR for the 41 patients receiving the highest dose level in phase 2 of the study was 85%, including 10 patients (24%) with CR and 24 patients (59%) with VGPR. The median TTP after a median follow-up of 5 months was 9.3 weeks. OS was 79% after a median follow-up of 5 months

(Knop *et al.* 2008).

Lenalidomide plus corticosteroids was investigated in a study of 69 patients who received lenalidomide plus corticosteroids (pulsed dexamethasone or prednisone) as part of an Expanded Access Program in Canada. The ORR was 58% in patients aged 65 years and older and 56% in patients younger than 65 years; the OS was 74% in patients aged 65 years and older compared with 76% in patients younger than 65 years (Reece *et al.* 2006a).

Informed by combination studies performed pre-clinically which showed potential synergy (Mitsiades *et al.* 2002), lenalidomide and bortezomib were studied in a phase 1 dose escalation trial of 36 patients, which yielded an objective response rate of 58%, including 6% of patients with CR or nCR (Richardson *et al.* 2006b). Lenalidomide was administered at a dose of 5, 10, 15 or 20 mg on days 1 to 14, and bortezomib was given at 1.0 or 1.3 mg/m<sup>2</sup> on days 1, 4, 8 and 11 of every 21-day cycle for a median of 6 cycles. The median duration of response was 6 months, with 11 patients remaining on therapy beyond 1 year. Dexamethasone was added in 14 patients with progressive disease, with an objective response subsequently achieved in 10 patients with excellent tolerability.

These promising results, together with the preclinical observation that lenalidomide can sensitize MM cells to bortezomib and dexamethasone, have led to a series of studies in other disease settings. In a recently completed phase 2 trial of 65 patients, 43 patients (median age 67 years) with relapsed or refractory MM have received up to 8 cycles of lenalidomide 15 mg on days 1-14 of a 21-day cycle, bortezomib 1.0 mg/m<sup>2</sup> on days 1, 4, 8, and 11 of a 21-day cycle, and dexamethasone 40 mg (cycles 1-4)/20 mg (cycles 5-8) twice weekly for 2 weeks of every 21-day cycle (Richardson *et al.* 2007a; Anderson *et al.* 2008). Based on safety data, dexamethasone dosing was subse-

quently reduced to 20 mg for cycles 1-4 and 10 mg for cycles 5-8. In 33 evaluable patients with a median of 2 prior therapies including dexamethasone (90%), thalidomide (78%) and bortezomib (68%), the ORR (minor response or better) of major response or better was 73%, including 36% with CR, unconfirmed CR or VGPR. The median duration of response was 39 weeks (Anderson *et al.* 2008).

Palumbo *et al.* investigated the addition of lenalidomide to melphalan/prednisone/thalidomide (RMPT) in the relapsed setting (Palumbo *et al.* 2008). In this phase 2 study, 43 patients were administered 6 cycles of lenalidomide (10 mg on days 1-21 every 28 days), melphalan (0.18 mg/kg on days 1-4), prednisone (2 mg/kg on days 1-4), and thalidomide (50-100 mg on days 1-28), followed by maintenance therapy of lenalidomide 10 mg/day. Therapy was administered as second-line in 61% of patients and third-line in 39%. After 2 cycles, 52% of patients achieved at least PR and after a median of 4 cycles, 91% achieved at least PR including 45% with VGPR.

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### Safety of lenalidomide-based therapy

In the MM-009 and MM-010 studies, grade 3 or 4 hematologic adverse events were more common in patients receiving lenalidomide plus dexamethasone versus dexamethasone only. The most common grade 3 or 4 adverse events were neutropenia, anemia, thrombocytopenia, and febrile neutropenia. Venous thromboembolic events were also more common with lenalidomide plus dexamethasone versus dexamethasone alone (14.7% versus 3.4% and 11.4% versus 4.6% for MM-009 and MM010, respectively) (Dimopoulos *et al.* 2007; Weber *et al.* 2007). The increased incidence of venous thromboembolism in patients receiving lenalidomide plus dexamethasone compared with dexamethasone alone does not

appear to affect survival. In an analysis of the 177 patients who received lenalidomide plus dexamethasone in MM-009, OS ( $p=0.4$ ) and TTP ( $p=0.7$ ) were not significantly different for the 31 patients who experienced deep-vein thrombosis compared with those that did not experience deep-vein thrombosis (Zangari *et al.* 2008).

Among 1,400 patients with relapsed/refractory MM who were administered lenalidomide 25 mg plus high-dose dexamethasone in 28-day cycles as part of an Expanded Access Program in North America, the most commonly reported grade 3 or 4 adverse events were neutropenia (7.9%), thrombocytopenia (6.0%), fatigue (3.6%), anemia (3.5%), pneumonia (3.1%), and hyperglycemia (2.0%) (Chen *et al.* 2006). Although the adverse events were the same as those reported in the two phase 3 studies, their frequencies were lower.

In the combination of bortezomib, dexamethasone, and lenalidomide described above, manageable toxicities were observed. These were consisting mainly of grade 1 or 2 myelosuppression (Anderson *et al.* 2008). Attributable non-hematologic toxicities were deep vein thrombosis in 2 of 41 patients, grade 3 atrial fibrillation in 2 patients, and grade 3 peripheral neuropathy in a single patient. Dose reductions were required for lenalidomide in 9 patients, for bortezomib in 5 patients and for dexamethasone in 14 patients.

The combination of lenalidomide with melphalan, prednisone and thalidomide described above was generally well tolerated in patients who received up to 6 cycles of therapy as second- or third-line treatment (Palumbo *et al.* 2008c). The most frequent adverse events were hematologic, with 48% of patients experiencing grade 3 neutropenia and 16% experiencing grade 4 neutropenia. Grade 3 and 4 thrombocytopenia occurred in 26% and 10% of patients, respectively. Growth factor support was required in 39% of patients and a single

patient required platelet transfusion. The most frequent non-hematologic toxicity was infection in 19% of patients. No thromboembolic events were described.

In the RAD trial described above, grade 3 or 4 infection occurred in 10% of patients and venous thromboembolism occurred in 5% (Knop *et al.* 2008). Eight patients prematurely discontinued due to catheter-related septicemia (n=2), thrombosis of basal artery (n=1), prolonged pneumonia (n=1), or withdrawal of consent (n=4). Adverse events were generally of moderate severity and manageable.

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## Conclusions and future directions

Lenalidomide has impressive clinical activity with manageable side effects in advanced MM, and is a key component of combination therapies for the treatment of patients with relapsed or refractory MM, both now and in the future. Novel combinations offer an especially exciting platform with a biologically-derived rationale for partnerships between small molecule inhibitors, monoclonal antibodies and vaccinations all being explored, as well as integration with treatment modalities such as transplant (Raje *et al.* 2004; Richardson *et al.* 2007b; Hideshima *et al.* 2007; Tai *et al.* 2008).

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