Pomalidomide

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Abstract

Pomalidomide (originally CC-4047 or 3-amino-thalidomide) is a derivative of thalidomide that is antiangiogenic and also acts as an immunomodulator. Pomalidomide, as the newest immunomodulatory agent (IMiD), has shown substantial in vitro antiproliferative and proapoptotic effects. In vivo studies have suggested limited cross-resistance between lenalidomide and pomalidomide, and the response of pomalidomide in relapsed and refractory (RR) multiple myeloma (MM) patients, including those who are refractory to both lenalidomide and bortezomib, has induced notable enthusiasm. Several studies have evaluated continuous (2 mg/day) or alternate (5 mg/2 day) dose schedules of pomalidomide, as well as 2 versus 4 mg schedules, and pomalidomide alone versus in combination with dexamethasone or other antimyeloma agents. Since pomalidomide plus low-dose dexamethasone has shown better responses, progression-free and overall survival than high-dose dexamethasone or pomalidomide alone, subsequent trials investigating pomalidomide combination therapy have been initiated. Among these trials combinations with alkylating agents (cyclophosphamide, bendamustin), anthracyclins (pegylated liposomal doxorubicin), proteasome inhibitors (bortezomib, carfilzomib), and various others can be found. Pomalidomide has also been assessed in AL amyloidosis, MPNs (myelofibrosis [MF]), Waldenstrom's macroglobulinemia, solid tumors (sarcoma, lung cancer), or HIV and—for AL amyloidosis and

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MF—has already proven remarkable activity. Due to its potency, pomalidomide was approved by the US Food and Drug Administration (FDA) for RRMM in 2/2013 and has also been approved by the European Medicines Agency (EMA).

Contents

1 Structure and Mechanism of Action

The structurally related parent compound of pomalidomide, thalidomide, was originally discovered to inhibit angiogenesis in 1994 (Fig. 1). Further structure activity studies led to the first report in 2001 (D'Amato et al. 2001) that pomalidomide was able to directly inhibit both the tumor cell and vascular compartments of multiple myeloma (MM). This dual activity of pomalidomide suggested it to be more potent than thalidomide in vitro and in vivo. In subsequent studies, pomalidomide was shown to directly inhibit angiogenesis and myeloma cell growth. This dual effect is central to its activity in myeloma, whereas other pathways, such as tumor necrosis factor (TNF)-α inhibition, are of less relevance (Fig. 2): it has been shown that potent TNF-α inhibitors, including rolipram and pentoxifylline, do not inhibit myeloma cell growth nor angiogenesis (D'Amato et al. 2001). Up-regulation of IFN-γ, IL-2, and IL-10 and down-regulation of IL-6 have been reported for pomalidomide. These changes may contribute to pomalidomide's antiangiogenic and antimyeloma activities (Corral et al. 1999; Hideshima et al. 2000; Escoubet-Lozach et al. 2009; Verhelle et al. 2007) (Fig. 1). Albeit the precise molecular mechanism of action and targets through which immunomodulatory agents (IMiDs) exert their antitumor effects remains to be fully elucidated, threshold levels of cereblon (CRBN) expression are presumably important for therapy responses. Current data suggest that CRBN, a primary teratogenic target of thalidomide, is an essential requirement for IMiD activity and a possible biomarker for the clinical assessment of antimyeloma activity (Zhu et al. 2011).

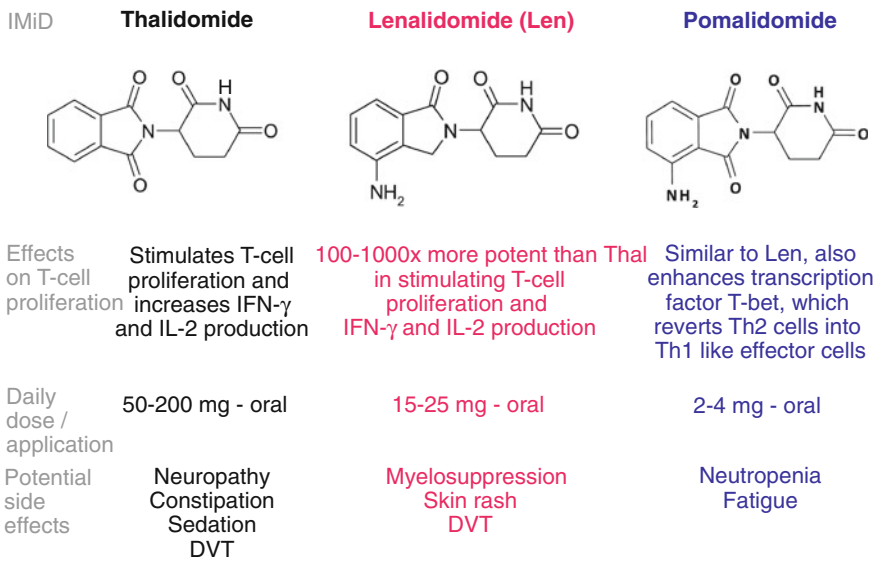

Fig. 1 Thalidomide, lenalidomide, and pomalidomide structure, immune effects, daily recommended doses, and common side effects. Albeit these 3 IMiDs are structurally similar, they are functionally different, both qualitatively and quantitatively

2 Preclinical Data

IMiDs may have antineoplastic effects by blocking signaling through nuclear factor-κB and may induce apoptosis via caspase-8/death receptor pathway. IMiDs have potent immunomodulatory properties including down-regulation of TNF, interleukin-1ß, augmentation of antimyeloma natural killer (NK) cell activity, and stimulation of cytotoxic T cells (Corral et al. 1999; D'Amato et al. 2001; Escoubet-Lozach et al. 2009; Hideshima et al. 2000; Verhelle et al. 2007; Udi et al. 2013; Waldschmidt et al. 2012) (Fig. 2). In vitro, IMiDs antagonize angiogenesis and expression of TNF-α and IL-6, while they facilitate production of IL-2 and IFN-γ and enhance T-cell and NK-cell proliferation and activity. Nevertheless, the precise mechanism of their action is not entirely revealed, but seems to include down-regulation of cytokine signaling (Görgün et al. 2010). Moreover, Görkün et al. demonstrated that the tumor suppressor molecule SOCS1 plays an important role in the tumor cell-immune cell-bone marrow (BM) microenvironment interaction in MM. Importantly, lenalidomide and pomalidomide induced epigenetic modifications of SOCS1 gene in MM cells, as well as modulated cytokine signaling via SOCS1-mediated cytokine signaling in effector cells. Therefore, characterization of the molecular mechanisms of IMiDs on immune cells in the BM environment needs to be further defined and suggest that novel immune-based targeted therapies, such as the combination of IMiDs with epigenetic modulating drugs (such as histone

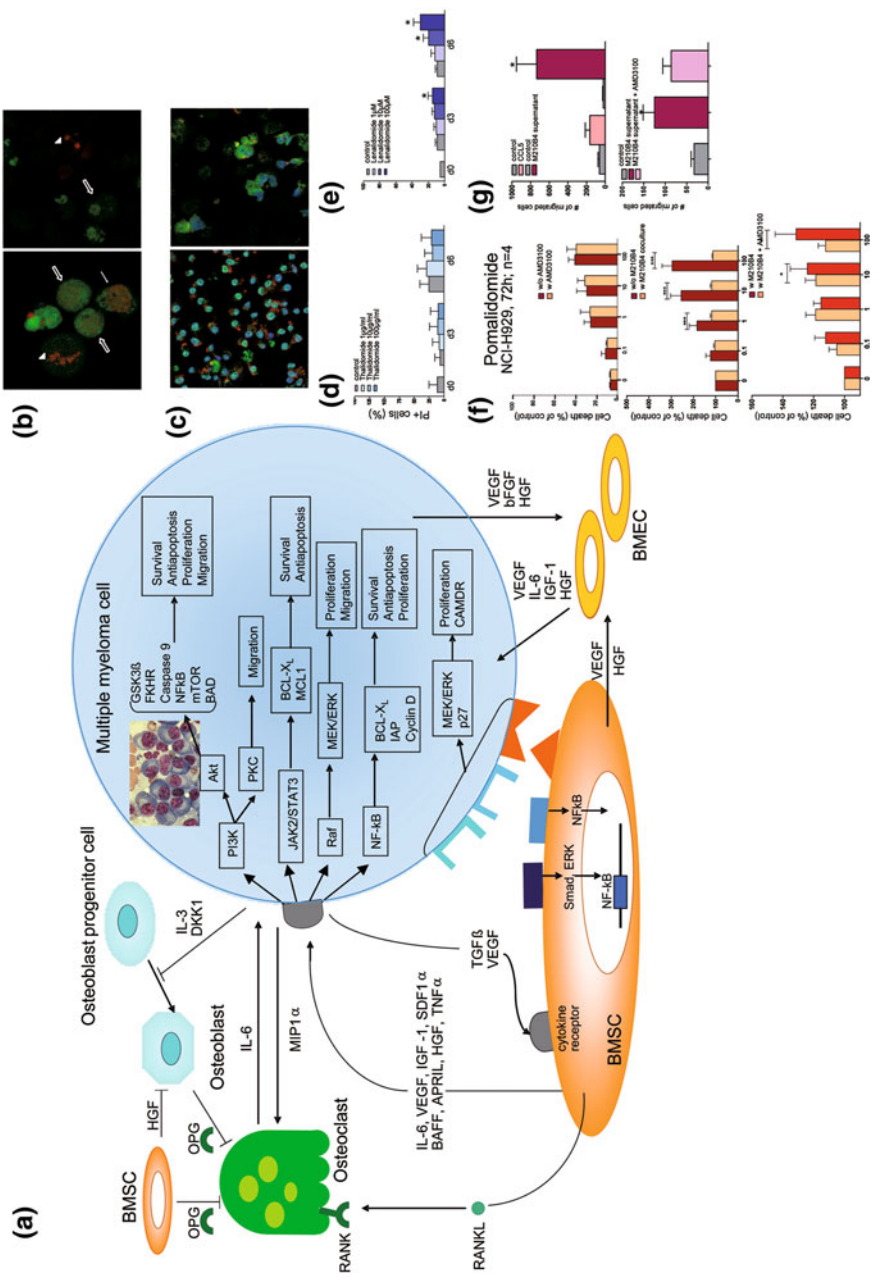
(a)
Osteoblast progenitor cell
IL-3
DKK1
Osteoblast
IL-6
MIP1α
HGF
OPG
OPG
BMSC
Osteoclast
RANK
RANKL
IL-6, VEGF, IGF-1, SDF1α
BAFF, APRIL, HGF, TNFα
TGFß
VEGF
cytokine receptor
BMSC
Smad
ERK
NFkB
NF-kB
VEGF
HGF
BMEC
VEGF
bFGF
HGF
VEGF
IL-6
IGF-1
HGF
Multiple myeloma cell
PI3K
Akt
GSK3ß
FKHR
Caspase 9
NFkB
mTOR
BAD
Survival
Antiapoptosis
Proliferation
Migration
PKC
Migration
JAK2/STAT3
BCL-XL
MCL1
Survival
Antiapoptosis
Raf
MEK/ERK
Proliferation
Migration
NF-kB
BCL-XL
IAP
Cyclin D
Survival
Antiapoptosis
Proliferation
MEK/ERK
p27
Proliferation
CAMDR
(b)
(c)
(d)
(e)
(f)
Pomalidomide
NCI-H929, 72h; n=4
(g)

Fig. 2 **a** Myeloma growth within the bone marrow (BM) microenvironment is affected by osteoclasts, osteoblasts, BM stroma cells (BMSC), and endothelial cells (BMEC), which secrete cytokines and chemokines as depicted and are multiple targets of IMiDs. **b** Apoptotic changes induced by exposure of MM cells to antimyeloma agents can be visualized via confocal images, these cells coexpressing fluorescently labeled cytochrome c-GFP (*green*) and histone 2B-mCherry (*red*) and showing early and late apoptosis after antimyeloma agent treatment such as IMiDs. The release of cytochrome c is evident, as the freckled pattern (*filled white arrow*) of cytochrome c-GFP becomes diffuse (*framed white arrows*). Chromatin condensation and fragmentation (*white arrow heads*), as a typical marker for late apoptosis, are also observed. **c** Antimyeloma agents, such as IMiDs, may down-regulate CD138-expression and induce actin depolymerization and cell shape changes in vitro. Confocal images after immunocytochemistry staining with CD138-FITC, Phalloidin-594-Alexa (actin filaments), and Dapi (DNA) show CD138-down-regulation, changes in cell size, and reduction in F-actin in MM cells. **d** In vitro effect of thalidomide on cell death is less substantial after 3 and 6 days of culture despite logarithmic increases of thalidomide concentrations, whereas the effect of lenalidomide shows significant cytotoxicity. **e** Significantly increased PI-positive cells are observed on d3 with 100 μM lenalidomide and on d6 with 10 and 100 μM, as compared to the control; $*p < 0.05$. **f** Pomalidomide also induces concentration-dependent cell death increases. This is not increased with additional treatment of the CXCR4 inhibitor AMD3100, in the absence of stroma cells. With coculture of BMSCs (M210B4), MM cells' sensitivity to antimyeloma agents, such as pomalidomide, is significantly reduced; however, with addition of AMD3100 to stroma-cultured MM cells, this increases pomalidomide's toxicity and thus can restore the sensitivity to antimyeloma agent treatment. **g** Chemotaxis of MM cells can be significantly increased with M210B4 supernatant as compared to control media or CCL5 ($*p < 0.05$). In the presence of the CXCR4 inhibitor AMD3100, chemotaxis to M210B4 supernatant does decrease, however insignificantly, supporting the involvement of chemokines other than CXCL12 and chemotaxis of M210B4 not entirely being blocked by the CXCR4 inhibitor

deacetylase inhibitors and/or demethylating agents) may provide potent immunomodulatory therapies in MM. Given the new promising clinical activity of pomalidomide even in lenalidomide-refractory MM, current efforts therefore attempt to delineate direct and epigenetic mechanisms to account for important differences (Görgün et al. 2010). Several preclinical and clinical studies have also demonstrated that threshold levels of CRBN expression are important to induce response to IMiDs (Zhu et al. 2011; Schuster et al. 2012): Zhu et al. demonstrated that CRBN depletion is initially cytotoxic to human myeloma cells, but that surviving cells with stable CRBN depletion become highly resistant to both lenalidomide and pomalidomide, but not to the unrelated drugs bortezomib, dexamethasone, and melphalan. Acquired depletion of CRBN was described to be the primary genetic event of myeloma cell lines cultured to be sensitive or resistant to lenalidomide or pomalidomide. Gene expression changes induced by lenalidomide were substantially suppressed in the presence of CRBN depletion, demonstrating that CRBN is required for lenalidomide activity. Downstream targets of CRBN-included interferon regulatory factor 4 (IRF4) previously reported to be a target of lenalidomide. Patients exposed and resistant to lenalidomide had lower CRBN levels in paired samples before and after therapy, suggesting that CRBN is an essential requirement for IMiD activity and a useful biomarker for the clinical assessment of IMiDs' antimyeloma efficacy. Other recent studies have confirmed that threshold levels of CRBN expression are required for response to IMiD therapy (Schuster et al. 2012).

3 Clinical Data

The introduction of novel agents and their combination has generated major advances in MM. Nevertheless, their immediate use in first-line and subsequent therapies makes the treatment of subsequent relapses a challenge, since MM remains incurable, and patients will ultimately acquire resistance to prior agents. Once patients are no longer responsive to IMiDs and bortezomib, the prognosis is grave and new agents are needed. This outcome of relapsed disease in the current era of novel drugs has recently been described by Kumar et al.: 286 patients with relapsed MM were studied, who were refractory to bortezomib. The date, patients satisfied the entry criteria, was defined as time zero ($T(0)$). The median age at diagnosis was 58 years, and time from diagnosis to $T(0)$ was 3.3 years. Following $T(0)$, 74 % of patients ($n = 213$; Table 1) had a treatment recorded with one or more regimens (median = 1; range 0–8). The first regimen contained bortezomib in 26 % and an IMiD in 33 % of patients. A minor response or better was seen to at least one therapy after $T(0)$ in 44 %, including ≥ partial response in 32 %. The median OS and event-free survival from $T(0)$ were 9 and 5 months, respectively. This study impressively confirmed the poor outcome, once patients become treatment refractory and currently provides the context for interpreting trials of newer agents, such as pomalidomide combined with antimyeloma agents (Kumar et al. 2012) (Table 1).

Pomalidomide as the newest IMiD suggests at least incomplete cross-resistance among thalidomide or lenalidomide and albeit all 3 IMiDs have similar structures, they differ markedly in their potency and side effects (Fig. 1). Phase I pomalidomide results have shown tolerable side effects (Streetly et al. 2008) and phase II clinical trials for MM and MF reported promising results (Richardson et al. 2013; Leleu et al. 2013; Lacy et al. 2012; Tefferi 2011).

4 MM

In February 2013, the Food and Drug Administration (FDA) granted accelerated approval to pomalidomide for the treatment of patients with MM, who have received at least two prior therapies, including lenalidomide and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy. The approval was based on the results of the CC-4047-MM-002 trial; a multicenter, randomized, open-label study in 221 patients with RRMM, who had previously received lenalidomide and bortezomib and were refractory to the last myeloma therapy (Richardson et al. 2009). The treatment arms were pomalidomide alone or pomalidomide plus low-dose dexamethasone. The efficacy results demonstrated an overall response rate of 7 % in patients treated with pomalidomide alone, and 29 % in those treated with pomalidomide plus low-dose dexamethasone. The median response duration was not evaluable in the pomalidomide monotherapy arm and was 7.4 months in the pomalidomide plus low-dose dexamethasone arm.

Table 1 Outcome after IMiDs and bortezomib (Bz; Kumar SK; Leukemia) versus pomalidomide, cyclophosphamide, and prednisone (PCP) in relapsed/refractory MM (RRMM)

	Best response				
	≥VGPR (%)	≥PR (%)	≥MR (%)	1-y PFS (%)	1-y OS (%)
Outcome after IMiDs and Bz ($n = 213$) Kumar et al. Leukemia 2012;26:149–157	7	24	34	25	50
All PCP patients ($n = 52$)	19	54	75	52	78
Relapsed after Len ($n = 18$)	28	67	78	63	89
Refractory to Len ($n = 23$)	15	47	73	48	72
Refractory to Bz ($n = 15$)	33	67	80	62	78
Double refractory to both Len+Bz ($n = 11$)	18	63	81	64	69

Abbreviations
IMiDs Immunomodulatory agents, *Len* Lenalidomide, *Bz* Bortezomib

A phase 1 dose-escalation study recently determined the maximum tolerated dose (MTD) of pomalidomide on days 1–21 of a 28-day cycle in 38 patients with RRMM (Richardson et al. 2013). Pretreatment had been substantial with a median of 6 prior therapies; including 63 % who were refractory to both lenalidomide and bortezomib. There were 4 dose-limiting toxicities (grade 4 neutropenia) at 5 mg/d, so that the MTD was specified with 4 mg/d. Among the 38 patients enrolled (including 22 with added dexamethasone), 42 % achieved minimal response or better, 21 % PR or better, and 3 % CR. Median duration of response, PFS, and OS were 4.6, 4.6, and 18.3 months, respectively.

The subsequent multicenter, phase 2 randomized study assessed 2 different pomalidomide dose schedules [4 mg for 21 vs. 28 days (21/28 vs. 28/28 cycles)] combined with dexamethasone in 84 advanced MM patients. The median number of prior therapy lines was again substantial with 5 and the overall response rate was 35 % (arm 21/28) and 34 % (arm 28/28), irrespective of the number of prior lines and level of refractoriness. Median duration of response, time to disease progression and PFS was 7.3, 5.4, and 4.6 months, respectively. At 23 months of follow-up, median OS was 14.9 months (Leleu et al. 2013). This phase 2 trial suggested that 4 mg pomalidomide—given on days 1–21 of a 28-day cycle and combined with dexamethasone—should be investigated further.

Recent results of the phase III trial, that randomized pomalidomide and low-dose dexamethasone to high-dose dexamethasone alone, have shown significant extension of PFS (median 3.6 months vs. 1.8 months; $p < 0.001$), and OS in patients taking pomalidomide and dexamethasone (Dimopoulos et al. 2012).

Moreover, the large comparative analysis of 6 sequential phase 2 trials at Mayo in 345 patients receiving pomalidomide at doses of 2 or 4 mg/d demonstrated excellent activity in relapsed MM patients (Table 2). The six cohorts consisted of: cohort 1 ($n = 60$): relapsed MM with 1–3 prior regimens, 2 mg dose; cohort 2 ($n = 34$): lenalidomide (Len)-refractory, 2 mg dose; cohort 3 ($n = 35$):

Table 2 Pomalidomide and low-dose dexamethasone (Pom/Dex) in relapsed MM: long-term follow-up and factors predicting outcome in 345 patients

	Pomalidomide schedule					
	2 mg relapse <3reg	2 mg Len ref	2 mg Bz/ Len ref	4 mg relapse <3 reg	4 mg relapse Bz/Len ref	4 mg relapse d1–21
	$n = 60$	$n = 34$	$n = 35$	$n = 60$	$n = 35$	$n = 120$
Confirmed response (≥PR) (%)	63	32	26	38	29	21
# of responders	39	11	9	23	10	25
Median time to response (ms)	1.7	2.0	1	1.1	1.4	1.1
Duration of response (ms)	21.3	8.2	15.6	NR	3.1	8.3
PFS (ms)	13	5	6.4	7.7	3.3	4.3
6-ms PFS (%)	73	44	54	63	37	34
OS (ms)	NR	33	16	NR	9.2	NR
6-ms OS (%)	95	85	74	92	67	74

Abbreviations
NR not reached, *ref* refractory, *reg* regimens, *d* day, *ms* months

bortezomib (Bz)/Len-refractory, 2 mg dose; cohort 4 ($n = 35$): Bz/Len-refractory, 4 mg dose; cohort 5 ($n = 60$) Len-refractory, 1–3 prior regimens, 4 mg dose; and cohort 6 ($n = 120$) Len-refractory, 4 mg dose. Pomalidomide was given orally 2 mg daily or 4 mg daily on days 1–28 (cohorts 1–5) or 1–21 (cohort 6) of a 28-day cycle with oral dexamethasone given 40 mg daily on days 1, 8, 15, and 22. 1/345 patient was ineligible and excluded from the analysis. The median age was 64 years (32–88). The median time since diagnosis was 53 months. The median number of prior therapies was 3 (1–14) and 44 % had high-risk molecular markers by mSMART criteria. Prior therapies consisted of thalidomide (52 %), lenalidomide (87 %), bortezomib (75 %), autologous stem cell transplant (70 %), and allogeneic transplant (3 %). The median follow-up was 10.4 months (5.4–34 months), with 67 % being alive and 32 % remaining progression free. The authors concluded that response rates and toxicity were similar between the 2 mg and 4 mg pomalidomide doses (Lacy et al. 2012) (Table 2).

The combination of pomalidomide and dexamethasone with cyclophosphamide in RRMM was also reported at ASH (Palumbo et al. 2012): 52 patients had received 1–3 prior lines, their median time from diagnosis was 55 months (range 15–203) and pomalidomide was administered at doses ranging from 1 to 2.5 mg/day on days 1–28, cyclophosphamide with 50 mg on alternate days and prednisone at 50 mg also every other day for 6 cycles, followed by maintenance therapy with

pomalidomide/prednisone. The MTD of pomalidomide was defined as 2.5 mg/day, with impressive responses as depicted in Table 1. Other combination schedules with oral cyclophosphamide at doses of 300 or 400 mg on days 1, 8, and 15 applied with pomalidomide/dexamethasone (Baz et al. 2012), pegylated liposomal doxorubicin (Berenson et al. 2012), or carfilzomib (Shah et al. 2012) further enlarge the options to treated RRMM patients. At least one study also suggested that the addition of clarithromycin may enhance antimyeloma activity of pomalidomide plus dexamethasone: Mark et al. reported a phase 2 study that used clarithromycin 500 mg twice daily, pomalidomide 4 mg for day 1–21 of a 28-day cycle, and dexamethasone 40 mg weekly in 97 relapsed MM patients, many of whom were refractory to lenalidomide or both lenalidomide and bortezomib. They reported responses of PR or better in 53 % (Mark et al. 2012).

Albeit the dose of pomalidomide, that should be used, is a recurring question, current data suggest that either 2 mg/d continuously or 4 mg for 21 of 28 days is effective and well tolerable (Lacy 2013).

5 AL Amyloidosis

Pomalidomide/dexamethasone has shown activity in patients with immunoglobulin light-chain AL amyloidosis where patients were eligible for the prospective phase 2 trial if they had at least 1 prior regimen and reasonably preserved organ function (Dispenzieri et al. 2012): 33 patients were enrolled, with a median age of 66 years and median time from diagnosis to on study of 37 months. 82 % had cardiac involvement. The confirmed hematological response rate was 48 %, with a median time to response of 1.9 months. Organ improvement was observed in 5 patients. The median PFS and OS were 14 and 28 months, respectively. The results demonstrated the activity of pomalidomide/dexamethasone even among lenalidomide and bortezomib failures and that pomalidomide may be a beneficial treatment option in patients with previously treated AL amyloidosis.

6 Myelofibrosis

In Myelofibrosis (MF), thalidomide and lenalidomide, with or without prednisone, have shown comparable activity in alleviating anemia, splenomegaly and thrombocytopenia, with responses being induced in ~20 % each (Tefferi 2011). Treatment may be complicated by peripheral neuropathy (PNP) or severe myelosuppression in patients receiving thalidomide or lenalidomide, respectively. Therefore, another IMiD, pomalidomide, was assessed in a phase 2 trial, where ~25 % of patients with anemia responded to pomalidomide alone (2 mg/d) or pomalidomide (0.5 or 2 mg/d) combined with prednisone (Tefferi et al. 2009). In a subsequent phase 2 study of pomalidomide monotherapy (0.5 mg/d; Begna et al. 2011), anemia response was observed only in the presence of JAK2V617F (24 vs. 0 %) and was predicted by the presence of pomalidomide-induced basophilia (38

vs. 6 %) or the absence of marked splenomegaly (28 vs. 11 %). Platelet response was seen in 58 %, but the drug had limited activity on spleen size reduction. Unlike thalidomide and lenalidomide, drug-induced PNP and myelosuppression were infrequent. However, higher doses (>2 mg/d) were myelosuppressive and not necessarily better in terms of efficacy. Therefore, for MF in choosing between the 3 IMiDs, lenalidomide seems preferable in the presence of del(5q) because of the possibility of obtaining hematological and cytogenetic remission (Tefferi et al. 2007). In the absence of del(5q), pomalidomide represents an option in patients with JAK2V617F positivity without marked splenomegaly; otherwise, thalidomide plus prednisone is a reasonable alternative; albeit, of note, all 3 IMiDs should not be used in the absence of symptomatic anemia.

7 Toxicity

The most common side effects of pomalidomide reported in clinical trials have been fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upper respiratory tract infections, back pain, and pyrexia. In the comparative analysis of 6 sequential phase 2 trials at Mayo in 345 patients receiving pomalidomide at doses of 2 or 4 mg/d, most common toxicities (grade ≥3) were neutropenia (31 %), anemia (16 %), thrombocytopenia (12 %), pneumonia (8 %), and fatigue (8 %; Fig. 1). VTE was seen in 10 patients (3 %; Lacy et al. 2012). Moreover, a brief review on 2 patients who developed pulmonary toxicity related to pomalidomide was consistent with previously published reports on pulmonary toxicity related to thalidomide and lenalidomide. It was suggested that this very rare toxicity should readily be recognized by clinicians in patients with pulmonary complaints and no identifiable infectious source and that timely withdrawal of the medication leads to rapid resolution of symptoms without long-term sequelae (Geyer et al. 2011). In general, pomalidomide induces less aesthesia and neuropathy than thalidomide and is more likely to induce neutropenia than thalidomide, but this side effect is usually well manageable with a dose reduction. Subsets of MM patients, who are sensitive to the myelosuppressive effect of lenalidomide and have trouble tolerating even low doses, may do well with pomalidomide, suggesting that its myelosuppressive effect is less pronounced. Skin rash which might be observed with lenalidomide (Wäsch et al. 2012) is rarely seen with pomalidomide (Lacy 2013) (Fig. 1).

Pomalidomide is approved by the FDA and EMA with a Boxed Warning alerting patients and healthcare professionals that the drug can cause embryo-fetal toxicity and venous thromboembolism. Because of this embryo-fetal risk, pomalidomide is available only through a restricted distribution program called the POMALYST Risk Evaluation and Mitigation Strategy (REMS) Program. Prescribers must be certified with the POMALYSTREMS Program by enrolling and complying with the REMS requirements. Patients must sign a patient–physician agreement form and comply with the REMS requirements. Female patients of reproductive potential who are not

pregnant must comply with the pregnancy testing and contraception requirements. Males must comply with contraception requirements. Pharmacies must be certified with the POMALYSTREMS program, must only dispense to patients who are authorized to receive pomalidomide, and comply with REMS requirements http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm339286.htm.

8 Drug Interactions

Pomalidomide is metabolized by CYP1A2 and CYP3A and is a substrate for p-glycoprotein. CYP1A2 and CYP3A4 inhibitors may increase the serum concentrations of pomalidomide, whereas inducers of these enzymes may decrease pomalidomide concentrations. Current data have shown that CYP1A2 and CYP3A4 are the primary isozymes responsible for the CYP450-mediated metabolism (Hoffmann et al. 2013). Coadministration of pomalidomide with strong inhibitors of CYP1A2 (e.g., ciprofloxacin, enoxacin, and fluvoxamine), CYP3A (e.g., clarithromycin, ketoconazol, and grapefruit juice), or p-glycoprotein (e.g., azithromycin, amiodarone, and itraconazol) may increase pomalidomide exposure and should be avoided. Strong inducers of CYP1A2 (e.g., broccoli, modafinil, and nafcillin), CYP3A (carbamazepine, phenytoin, and rifampicin), or p-glycoprotein (avasimibe, rifampicin, and St.John's wort) may decrease pomalidomide plasma levels and should likewise be avoided. Cigarette smoking may reduce pomalidomide exposure via CYP1A2 induction; therefore, patients should be advised that smoking may reduce the efficacy of pomalidomide.

9 Biomarkers

Acquired depletion of CRBN has been demonstrated to be the primary genetic event of myeloma cell lines cultured to be sensitive or resistant to IMiDs. Gene expression changes induced by lenalidomide were substantially suppressed in the presence of CRBN depletion, demonstrating that CRBN is required for IMiD activity. Zhu et al. also showed that patients exposed and resistant to lenalidomide had lower CRBN levels in paired samples before and after therapy, suggesting that CRBN is an essential requirement for IMiD activity and a useful biomarker for the clinical assessment of IMiDs' antimyeloma efficacy (Zhu et al. 2011). Other recent studies have confirmed that threshold levels of CRBN expression are required for response to IMiD therapy (Schuster et al. 2012).

Across the 6 cohorts—of the sequential phase 2 trials at Mayo in 345 patients receiving pomalidomide at doses of 2 or 4 mg/d—confirmed responses of PR or better in 34 % of patients. Responses and duration of response (DOR) in those with high-risk molecular markers included the following: 17p-: 19 of 56 (34 %): DOR 8.2 months; *t*(4;14): 6 of 24 (25 %): DOR 4.8 months; *t*(14;16): 7 of 11 (64 %): DOR 9.5 months; deletion 13 by cytogenetics: 13 of 37 (35 %): DOR

8.2 months. In a multivariate analysis, LDH >ULN, number of prior regimens, and prior bortezomib therapy were predictive of a shorter time to progression and factors associated with a poor OS following initiation of pomalidomide therapy included ß2-micoglobuline levels >5.5 mg/l, LDH >ULN, number of prior regimens and prior bortezomib therapy. In general and as true for almost all anti-myeloma agents, number and types of prior regimens are the strongest predictors of pomalidomide response and survival, with best responses in patients who are the least heavily pretreated (Lacy 2013).

10 Summary and Perspectives

Although new agents have significantly improved the prognosis in MM, novel therapies are constantly needed. Pomalidomide is effective and well tolerated in patients with advanced, refractory myeloma and potentially provides an unmet clinical need in patients with previously treated MM. The use of pomalidomide and low-dose dexamethasone, and their combination with other active agents, warrants further clinical testing. Moreover, response in cytogenetically high-risk patients (Richardson et al. 2012) and those with organ impairment, such as renal insufficiency (Siegel et al. 2012), are currently confounded by low patient numbers and need to be further investigated.

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