Expert Opinion

Pomalidomide therapy for myeloma

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Introduction: The Office of National Statistics (London, UK) has reported 4040 new patients in the year 2007, with an annual age standardized incidence rate of 4.8 per 100,000 population (range 4.7–5.0). Overall survival (OS) in the last decade has improved from 2–3 years to 7–8 years in the UK. The introduction of IMiDs for the treatment of myeloma has had a significant impact on outcomes in this life-threatening disease.

Areas covered: Pomalidomide, a thalidomide analogue, is a promising anti-myeloma agent with encouraging responses in relapsed/refractory myeloma patients. Pomalidomide has a potent anti-myeloma activity in vitro and in vivo, acting both directly on myeloma cells and on the cells in the bone marrow microenvironment. We have reviewed the chemistry and mechanisms of action of pomalidomide and the literature on pre-clinical and early Phase I and II clinical trials that demonstrates significant clinical efficacy in the relapsed setting and in lenalidomide refractory myeloma patients.

Expert opinion: Pomalidomide has shown significant activity in relapsed/refractory disease and is now being taken into Phase III trials in combination with dexamethasone. The exact place of pomalidomide in the management of myeloma, however, is evolving as more clinical experience is gained with this agent and further data published from clinical trials.

Keywords: IMiD, immunomodulation, myeloma, pomalidomide

1. Introduction

Pomalidomide (CC-4047; 4-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione; Box 1), is a novel immunomodulatory drug initially developed for the treatment of multiple myeloma (MM) and used more recently in the treatment of myelofibrosis. Thalidomide, following initial teratogenic reports [1,2], was withdrawn in the 1960s and subsequently revived for clinical use in lepra reactions [3]. Identification of its immunomodulatory [4], anti-inflammatory [5] and antiangiogenic [6] effects were resulted in the development of analogues with enhanced activity and less toxicity, ultimately leading to the development initially of lenalidomide (CC-5013) and later pomalidomide.

2. Multiple myeloma

Myeloma was first described by Solly [7] in 1844, but more than 100 years elapsed before effective treatment became available in the form of melphalan [8]. Combination chemotherapy improved outcomes for younger patients, but until recently melphalan and prednisolone remained the most effective treatment for patients aged > 65 years [8,9]. All patients will ultimately relapse and finally will become refractory to all agents including melphalan, bortezomib and lenalidomide. Myeloma is a heterogeneous disease with variable genetic, phenotypic and clinical features. Better classification of hematological malignancies has made it possible to identify...
2.1 Treatment of relapsed/refractory multiple myeloma

Treatment options for primary resistant or relapsed MM include combination therapies of glucocorticoids and cytotoxic chemotherapeutic agents [13-15] and autologous stem cell transplantation (ASCT) [16,17].

2.1.1 Dexamethasone

Dexamethasone, a synthetic adrenal corticosteroid, used alone or in combination with other agents, has been used for relapsed MM as the comparator in several relapsed/refractory and newly diagnosed myeloma studies [18]. Responses range from 18 to 28% [18,19] in large Phase III trials, and it is particularly useful in patients with renal impairment or myelosuppression.

2.1.2 Lenalidomide

Lenalidomide in combination with dexamethasone is approved in the United States and Europe for the treatment of patients with MM who have received at least one prior therapy. This combination is associated with the overall response rates (ORRs) ranging from 43 to 82%, depending on the number and type of prior therapies [20,21].

2.1.3 Bortezomib

Bortezomib monotherapy is approved in the EU for the treatment of patients with MM who have received at least one prior treatment and have already undergone or are unsuitable for bone marrow transplantation [18]. It is also approved in combination with melphalan and prednisone in the United States and Canada for the treatment of patients with relapsed or previously untreated MM and is currently being appraised by NICE (National Institute for Clinical Excellence) in the UK. In combination with pegylated liposomal doxorubicin, it is approved in the United States for patients who have not previously received bortezomib and have received at least one prior therapy [22].

Experimental treatment regimens of 3 and 4 licensed drug combinations with alkylating agents, steroids and each other are being evaluated in the setting of relapsed/refractory disease [23]. Other combinations with (liposomal) doxorubicin bendamustine and with histone deacetylase (HDACs) inhibitors and heat shock protein (HSP) inhibitors are underway in an attempt to enhance their activity and overcome resistance.

The second-generation proteasome inhibitor, carfilzomib has been shown to be safe and effective for patients failing to respond to velcade [24]. Ongoing studies are evaluating carfilzomib in velcade-naïve patients [25] and in combination with lenalidomide and dexamethasone [26]. Bendamustine is a bifunctional purine analogue/alkylator, containing a chloroethylamine alkylating group, a butyric acid side chain and a unique purine and amino acid antagonist benzimidaazole ring. It is licensed by the EMEA (European Medicines Agency) for myeloma in combination with prednisone for patients older than 65 years who are not eligible for ASCT and cannot be treated with thalidomide or bortezomib. Studies assessing the impact of combination therapies in the relapsed/refractory setting are ongoing.

The most appropriate salvage regimen in an individual patient is dependent upon the initial therapy regimen, the depth and duration of response to that therapy, toxicity of the treatment, patient comorbidities and the treatment options in that individual [27]. Treatment options include rechallenge of a previous chemotherapy regimen provided 6 – 12 months has elapsed since last therapy or a trial of a new chemotherapy regimen. Until recently, the median survival following relapse after induction therapy was approximately 1 year [28].

3. Pomalidomide

Thalidomide, the parent compound, is a synthetic glutamic acid derivative (Figure 1 Panel A) [29]. Pomalidomide is a thalidomide analogue with an additional amino group in the fourth carbon of the pthaloyl ring. Pomalidomide differs from
lenalidomide in its chemical structure by having an additional carbonyl group in the pthaloyl ring (Figure 1 Panel B).

3.1 Immunomodulatory activity
Myeloma patients have a defective immune response and immune surveillance. Studies of antigen-processing machinery in myeloma patients show reduction in expression of proteasome subunits and peptide transporters at the transcriptional level. These results allude to antigen-processing aberration as one of the mechanisms of impaired immune surveillance in myeloma patients [30]. Cancer testis antigens are aberrantly expressed by myeloma cells and are a potential immunotherapeutic target. CD4+ T cell immunity and cytotoxicity against MAGE (melanoma antigen gene)-positive myeloma cell lines was observed more in monoclonal gammopathy of undetermined significance (monoclonal gammopathy of uncertain significance; MGUS) than MM patients, suggesting that once the patients progress, they lose their ability to mount a T-cell response. CD8+ memory T cell response was seen exclusively in myeloma patients but was poorly recruited into the bone marrow [31]. Increased frequency of naturally occurring functional CD4(+)CD25(+)FoxP3(+) T cells called T regulatory cells (Tregs) is reported in patients with myeloma as well as MGUS, in comparison with age-matched, healthy control. But their role in disease progression remain unclear [32]. Expression of MIC-A and NKG2D in myeloma patients were lower in comparison to MGUS patients and could potentially be linked to disease progression [33]. Defective B7:CD28 costimulation has also been described in myeloma patients [34].

Pomalidomide has T cell costimulatory activity, thereby enhancing durable, antigen-specific Th1 type response in vivo [35]. In a colon cancer murine model, mice challenged with tumor cells, not expressing the costimulatory molecule with pomalidomide, showed enhanced production of IL-2 and IFN-γ. This response continued to last for 2 further rounds of live tumor challenges [35]. NK and NK T cell populations were increased when prostate cancer, myeloid and lymphoid cancer cells were cocultured in the presence of pomalidomide with peripheral blood mononuclear cells (PBMCs) of patients. Pomalidomide dose dependently induced NK-mediated tumor cell apoptosis [36] in these cocultures and in myeloma cell lines in vitro [37]. Pomalidomide and lenalidomide also suppress T-reg cell function and proliferation. Treatment with pomalidomide decreased T-reg numbers in mice, although no direct cytotoxicity was demonstrated in vitro [38]. Pomalidomide decreased IL-2-mediated generation of T-reg cells from PBMCs by half and inhibited T regulatory cell function. The reduction in function was not mediated by TGF-β or IL-10 production (Figure 2) [38].

3.2 Angiogenesis
Angiogenesis in myeloma bone marrow is mediated by plasma cells, stromal cells and endothelial cells in the microenvironment. Bone marrow biopsies from MGUS and early and advanced myeloma were stained with factor VIII (FVIII) antigen, showing significantly increased microvascular density in relapsed myeloma [39]. VEGF secreted by plasma cells acts on cognate receptors on stromal cells releasing soluble factors

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**Figure 1. Chemical structure of thalidomide and its analogues.** A. Thalidomide with pthaloyl ring, part of its chemical structure modified in the analogues highlighted in gray. B. Chemical structure of CC-4047, pomalidomide with additional amino group and CC-5013, lenalidomide with additional amino group but missing carbonyl group in the pthaloyl ring.

Adapted with permission from [29].
that drive plasma cell proliferation in a paracrine manner (Figure 2) [40]. Thalidomide also possesses antiangiogenic properties that significantly reduced microvascular density in bone marrows of responding myeloma patients, with no reduction in angiogenesis in nonresponders [41]. Treatment with pomalidomide in SCID mice carrying lymphoma tumors from Raji cell line, significantly inhibited angiogenesis as evidenced by decreased CD31 staining in the tumors, as compared to placebo controls [42]. Pomalidomide showed greater inhibition of endothelial sprout formation in a human umbilical artery explant assay compared to lenalidomide and blocked VEGF-induced endothelial cell cord formation in hypoxic and normoxic conditions (Figure 2). In hypoxic conditions, hypoxia inducible factor (HIF) proteins enhance angiogenesis. In hypoxic conditions, pomalidomide downregulated HIF-1α but not HIF-2α in endothelial cell cultures [43].

3.3 Direct anti-myeloma activity
Pomalidomide has significant anti-myeloma activity in vitro and in vivo. Pomalidomide causes cell cycle arrest in plasma cells by p21 WAF activation which is p53 independent [44]. Pomalidomide induces plasma cell apoptosis by inducing caspase 8 activation and downregulating the NFκB pathway which is universally activated in myeloma cells [49]. The enhanced antitumor responses in combination with dexamethasone are explained by the fact that dexamethasone activates caspase 3 that synergizes with apoptotic cell death induced by pomalidomide [46]. Pomalidomide apart from direct proapoptotic activity inhibits adhesion to stromal cells and secretion of cytokines such as IL-6, thereby promoting tumor cell death [47].

3.4 Bone disease
Skeletal abnormalities are observed in up to 90% of patients with myeloma during the course of their disease [48]. In a population-based retrospective cohort study, 16 times more fractures, mostly of the vertebrae and ribs, were observed than expected in the year before diagnosis. Patients with a pathological fracture had poor survival [49]. Pomalidomide inhibits lineage commitment required for early differentiation of osteoclasts under the influence of cytokines due to the downregulation of PU.1 resulting in the inhibition of osteoclast production and function [50]. The lack of differentiation completely inhibited
bone resorption. Osteoclasts are motile dynamic cells switching from resorptive to non-resorptive phases, depending on the surface that they are cultured on. This phenotypic switch is dependent on the regulation of the actin cytoskeleton. Pomalidomide-modulated Rho GTPases affecting actin cytoskeleton in osteoclasts results in increased cell migration and lack of bone resorption [51].

3.5 Anti-inflammatory property
Pomalidomide is a potent anti-inflammatory agent. Pomalidomide, significantly decreased TNF-α production by lipopolysaccharide (LPS)-induced monocyte activation in vitro, and endotoxic shock when delivered in large doses in vivo [52]. Cyclooxygenase-2 (COX-2) is highly expressed in myeloma patients and is associated with a poor outcome [53]. A dose-escalating trial of celecoxib administered with thalidomide showed an improved progression free and OS with higher dose of COX-2 inhibitor [54]. Pomalidomide also inhibits COX-2 production reducing COX-2 levels and production of prostaglandins in human LPS-stimulated monocytes. The inhibition of COX-2 occurs at the level of gene transcription, by reducing the LPS-stimulated transcriptional activity at the COX-2 gene [55]. Because of this specific activity, the toxic side effects observed with other COX-2 inhibitors can be safely avoided.

4. Pomalidomide - clinical trials in myeloma
Pomalidomide has undergone extensive preclinical testing, but clinical experience in relapsed and/or refractory MM is limited (Table 1).

4.1 Relapsed myeloma
4.1.1 Phase Ia study (CDC-407 – 00-001 / CC-4047-MM-001)
This was a Phase Ia, first in man, single-center, dose-escalation (1, 2, 5 and 10 mg), open-label study of pomalidomide given continuously [56] (cohort 1) or on alternate days [57] (cohort 2) to a total of 45 subjects relapsing or considered refractory to treatment after at least two cycles of treatment. Patients were excluded an absolute nucleated cell count (ANC) > 1000, platelets 20,000 and a serum creatinine < 200 µmol/l. The median age in Cohorts 1 and 2 was 58 years and 66 years, respectively (range 49 – 82), and the median number of prior regimens was 3 (range 1 – 6) and 4 (range 1 – 7), respectively. Of the 45 patients, 18 (40%) had previously received an autologous stem cell transplant and 24 (53%) had received prior thalidomide therapy.

Median time to reach maximum serum concentration (tmax) was 2.5 – 2.75 h, while the mean half-life (t½) was 6 – 8 h. Two-thirds of the drug is excreted in the urine and there was minimal accumulation by day 28 of administration. The maximum tolerated dose (MTD) was 2 mg continuously and 5 mg on alternate days. The most common dose-limiting toxicity (DLT) was grade 4 neutropenia but no grade 3/4 neutropenia occurred on cycle 4 or later, no patients required growth factor support and no neutropenic sepsis was observed. The most common adverse events (AEs) were neutropenia (58% G3/4), thrombocytopenia, cough, dyspnea and lethargy. National Cancer Institute Clinical Toxicity Criteria (NCI CTC) grade 1 – 2 nonhematological toxicity was reported in 2 patients (8%) who experienced a deep vein thrombosis (DVT; grade 3) at 5 and 8 months, respectively. One further patient developed a DVT at 3 weeks, but this was secondary to inguinal lymphadenopathy on the same side as the thrombus secondary to an undiagnosed melanoma at the time of study entry, giving an overall incidence of 12.5%. No DVTs were experienced in the alternate day Cohort 2 group. There were three cases of grade 1 neuropathy, not necessitating discontinuation from study; all cases resolved without further intervention. Overall, 23 (51%) of 45 subjects had partial response (PR) or better including 6 (13%) complete response (CR) and 12 (27%) very good partial response (VGPR). Progression free survival (PFS) and OS was 9.75 and 22.5 months and 10.5 months and 35.9 months in Cohorts 1 and 2, respectively.

4.1.2 Celgene-initiated Phase Ib/Ill study (CC-4047-MM-002)
A Phase I/Ib multicenter, randomized, open-label, dose-escalation (2, 3, 4 and 5 mg) study is evaluating the MTD and the safety and efficacy of pomalidomide alone using a cyclic regimen (21 of 28 days) and in combination with low-dose dexamethasone in subjects who have received ≥ 2 prior regimens and do not achieve at least a partial response to bortezomib and lenalidomide [58]. Thirty-eight subjects have been enrolled in Phase I cohort. The MTD was 4 mg which is the dose selected for the Phase II cohort. The safety profile was similar across cohorts except for grade 4 neutropenia, which increased in the 5 mg cohort. In 26 evaluable subjects, minimal response (MR) or better was reported in 17 subjects (65%) including 1 CR and 6 PR. As of September 22, 2010, 221 subjects have been enrolled in the Phase II segment.

4.1.3 Phase II study (PO-MM-PI-0010)
This was a Phase II open-label study of pomalidomide (2 mg continuous) plus low-dose dexamethasone (40 mg/day on days 1, 8, 15 and 22) in subjects with relapsed/refractory MM who had received 1 – 3 prior regimens [59]. Pomalidomide was given as 2 mg/day orally on days 1 – 28 with dexamethasone 40 mg p.o. on days 1, 8, 15 and 22 (Cohort 1). Patients were allowed to increase the dose to 4 mg/day if nonresponding or progressing, provided there was no grade 3/4 toxicity (Cohort 2). Patients received aspirin 325 mg/day for thromboprophylaxis. A total of 60 subjects were enrolled. The most common grade 3/4 hematological toxicity was neutropenia reported in 21 patients (35%) and the most common nonhematological grade 3/4 toxicities were fatigue and pneumonia. Thirty-eight (63%) of the 60 subjects responded, including 3 (5%) CR, 17 (28%) VGPR and 18 (30%) PR.
A total of 82% of patients who remained on treatment for a minimum of 12 weeks demonstrated a 25% or greater decrease in measurable paraprotein. Responses were seen in 8 (40%) of 20 lenalidomide-refractory subjects, 6 (37%) of 16 thalidomide-refractory subjects, and 6 (60%) of 10 bortezomib-refractory subjects, suggesting noncross resistance between these agents. Five patients had previously received and were refractory to both bortezomib and lenalidomide, of whom 2 had a PR and 1 a VGPR. In all, 19 patients were considered high risk with adverse cytogenetics or a high plasma cell-labeling index of whom, 14 (74%) had responses including 1 (5%) CR, 5 (26%) VGPRs and 8 (42%) PRs. The median age was 62 years (range: 39 – 77). The median number of previous regimens was 4. Twenty-eight, 37 and 35% of the patients had 1, 2 and 3 previous regimens, respectively, while 68% had received a previous autologous stem cell transplant and 1 patient had received both an autologous and an allogeneic stem cell transplant. All patients had previous lenalidomide therapy; 19 (58%) previous thalidomide and 20 (59%) previous bortezomib. Preexisting baseline peripheral neuropathy was present in 20 patients (59%). Fourteen (41%) were classified as high risk. Median follow-up is 8.3 months. VGPR was seen in 3 (9%), PR in 8 (23%) and MR in 5 (15%) patients, giving an ORR of 47%. The different response rates reported between the studies may be related to the differing entry criteria; patients had a median of 4 prior lines of therapy in the IFM study, while it was 6 in the Mayo study.

### 4.2 Lenalidomide-refractory myeloma

The Mayo group conducted a further single-stage, Phase II study of patients shown to be refractory to previous treatment with lenalidomide [60]. Lenalidomide refractoriness was defined as relapsing on or within 60 days of stopping lenalidomide. In all, 34 patients were entered into the study. Subjects received pomalidomide at a dose of 2 mg/day on days 1–28 of a 28-day cycle. Dexamethasone was given at a dose of 40 mg/day on days 1, 8, 15 and 22 of each cycle. Patients received aspirin 325 mg for thromboprophylaxis. The median age was 62 years (range: 39 – 77). The median number of previous regimens was 4. Twenty-eight, 37 and 35% of the patients had 1, 2 and 3 previous regimens, respectively, while 68% had received a previous autologous stem cell transplant and 1 patient had received both an autologous and an allogeneic stem cell transplant. All patients had previous lenalidomide therapy; 19 (58%) previous thalidomide and 20 (59%) previous bortezomib. Preexisting baseline peripheral neuropathy was present in 20 patients (59%). Fourteen (41%) were classified as high risk. Median follow-up is 8.3 months. VGPR was seen in 3 (9%), PR in 8 (23%) and MR in 5 (15%) patients, giving an ORR of 47%. Twelve (35%) patients had stable disease. The median time to response is 2 months (range: 0.7 – 3.9). Of the 14, 8 (57%) high-risk patients responded; 4 (14%) PR and 4 (14%) MR. Responses were seen in 8 (42%) of 19 patients who received previous thalidomide and 9 (45%) of the 20 patients who had previous bortezomib. The dose of pomalidomide was increased from 2 to 4 mg/day in 8 patients; only 1 patient improved their response from SD to PR. The median

### Table 1. Pomalidomide clinical trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of participants</th>
<th>Drugs</th>
<th>Specific inclusion criteria</th>
<th>Response</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase Ia Study (CDC-407-00-001/CC-4047-MM-001), open-label dose-escalation study</td>
<td>45</td>
<td>Pomalidomide</td>
<td>Relapsed/refractory</td>
<td>ORR 65% in Phase Ia (evaluable patients)</td>
<td>MTD – 2 mg daily or 5 mg alt days</td>
</tr>
<tr>
<td>Celgene-Initiated Phase lb/II Study (CC-4047-MM-002):</td>
<td>221</td>
<td>Pomalidomide (21/28 days) + Dex</td>
<td>&gt; 2 lines of therapy and &lt; PR to thalidomide and bortezomib</td>
<td>ORR 63%</td>
<td>MTD – 4 mg, used in Phase II cohort</td>
</tr>
<tr>
<td>Phase II study (PO-MM-P1-0010)</td>
<td>60</td>
<td>Pomalidomide (2 mg continuous) + Dex weekly</td>
<td>Relapsed/refractory</td>
<td>ORR 47%</td>
<td>Responses seen in Len, Bort and Thal refractory patients</td>
</tr>
<tr>
<td>Phase II study (Mayo)</td>
<td>34</td>
<td>Pomalidomide (2 mg continuous) + Dex weekly</td>
<td>Lenalidomide refractory</td>
<td>ORR 47%</td>
<td>41% high-risk disease, median PFS 4.8 months</td>
</tr>
<tr>
<td>Randomized Phase II study (IFM 2009-02) IFM group</td>
<td>84</td>
<td>Pomalidomide (4 mg continuous) vs Pomalidomide (21/28 days) + Low dose Dex</td>
<td>Patients resistant or refractory to lenalidomide and bortezomib</td>
<td>ORR 47 vs 30%</td>
<td>All patients had high-risk cytogenetics</td>
</tr>
<tr>
<td>Mayo study in double-refractory myeloma</td>
<td>70</td>
<td>Pom (2 mg continuous) + 40 mg Dex weekly vs Pom 4 mg continuous + 40 mg Dex weekly</td>
<td>Patients resistant or refractory to lenalidomide and bortezomib</td>
<td>ORR 49 vs 40%</td>
<td>4 mg/day pomalidomide not superior to 2 mg/day of pomalidomide in combination with dex</td>
</tr>
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</table>
duration of response in the 11 patients achieving PR or greater was 9.1 months. The median PFS was 4.8 months, and this was not significantly different in the high-risk disease compared with those with standard risk disease. The median OS time is 13.9 months for all the patients.

4.3 Lenalidomide- and bortezomib-resistant disease

4.3.1 Investigator-initiated Phase II study (IFM 2009-02; ongoing)

This is a multicenter, randomized Phase II, open-label study of pomalidomide plus dexamethasone in 84 subjects with relapsed and refractory MM who have previously received bortezomib and lenalidomide, conducted by Intergroupe Francais du Myelome (IFM). Subjects received a 4-mg dose of pomalidomide, given either as a cyclic (21-day out of 28-day cycles) regimen in combination with low-dose dexamethasone (Arm A) or continuously (28-day) (Arm B). The primary end point was response rate and the secondary end points were safety, time to response, time to disease progression and OS. At the 2010 American Society of Haematology (ASH) meeting, 83 subjects had been entered, all of whom had poor risk cytogenetics (loss of 17p and/or t (4:14) translocation). In Arm A, 30% of patients achieved a PR or greater (1 VGPR), while in Arm B 47% had a PR or greater (1 VGPR). Median duration of response was 77 and 89 days, respectively, with a median follow-up of 119 days. The drug was well tolerated, with no thromboembolic or neuropathy complications reported [61].

4.3.2 Investigator-initiated study comparing 2 dosing strategies (Mayo clinic)

Mayo clinic presented a study at ASH 2010 comparing 2 dosing strategies in patients refractory to both lenalidomide and bortezomib. Pomalidomide given orally 2 mg/day (Cohort A) or 4 mg/day (Cohort B) on days 1 – 28 of a 28-day cycle with oral dexamethasone given 40 mg/per on days 1, 8, 15 and 22. All patients received aspirin 325 mg daily for thromboprophylaxis. In all, 35 patients with relapsed and resistant/refractory to both lenalidomide and bortezomib were enrolled in each cohort. The median age was 62 years (range, 39 – 77) in Cohort A and 61 (range, 45 – 77) years in Cohort B. The median duration on treatment was 5 (1 – 13) and 2 (0 – 6) cycles in cohorts A and B, respectively. The median follow-up on alive patients was 7.5 months and 3 months in Cohorts A and B, respectively. Toxicity observed was primarily myelosuppression: grade 3/4 neutropaenia (37% Cohort A vs 55% Cohort B); grade 3/4 thrombocytopaenia (11% Cohort A vs 13% Cohort B); and grade 3/4 anemia (9% Cohort A vs 16% Cohort B). Grade 3/4 nonhematologic toxicities occurred in 23% Cohort A vs 13% Cohort B. Hematological responses in Cohort A consisted of VGPR 14%, PR 11% and MR 24% (ORR 49%, 95% CI: 31 – 66), and responses in Cohort B consisted of VGPR 9%, PR 20% and MR 12% (ORR 40%, 95% CI: 23 – 58). The median PFS in Cohorts A and B were 6.4 months (95% CI: 4.7 - no response [NR]) and 3.3 months (95% CI: 2.3 - NR), respectively. This study confirms therapeutic benefit for Pom/dex in patients relapsing after lenalidomide and bortezomib. This study did not demonstrate an advantage of using a higher dose of pomalidomide 4 mg/day on days 1 – 28 of each 28-day cycle [62].

4.4 Toxicity

Toxicity from pomalidomide is primarily due to myelosuppression. Neutropenia is the commonest complication, but grade 1 and 2 thrombocytopaenia and anemia are reported in < 5% of patients. Nonhematological complications are rare and tend to be grade 1 – 2 only. Hypoglycemia, constipation and diarrhea are also reported in < 5% of patients. Throughout the studies, neuropathy either is not reported or occurs in < 5% of patients, and venous thromboembolic disease is not increased above that reported in patients treated with conventional chemotherapy. However, thromboprophylaxis was given in the Phase I and II studies.

4.5 Other combination studies

A Phase III randomized study of pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone for patients relapsed after being shown to be refractory to both lenalidomide and bortezomib is being planned to open in 2011 in the UK and Europe.

5. Conclusion

Pomalidomide a new IMiD has significant activity in relapsed/refractory myeloma with potent immunomodulatory effect. Manageable toxicities observed in clinical trials and the ease of use would provide a valuable addition to the increasing list of available agents that can be used for resistant/refractory disease to induce remissions and as a maintenance agent to improve durability of response.

6. Expert opinion

There are an increasing number of patients who are refractory, respond suboptimally or experience significant toxicity to either bortezomib or lenalidomide therapy. Gertz et al. in a retrospective analysis reported that patients who never respond or relapse on treatment with a thalidomide- or lenalidomide-containing regimen have a significantly shorter PFS and OS following stem cell transplantation than those who achieve at least a PR [63]. Furthermore, although by combining lenalidomide and bortezomib, up to 100% of de novo patients achieved at least a PR, patients continue to relapse and significantly less respond at the time of relapse [64,65]. There remains, therefore, a clinical need for new agents. Pomalidomide has been shown to be effective in overcoming resistance to both bortezomib and lenalidomide. The 40% response rate in lenalidomide-refractory patients reported in early Phase II trials implies non-cross-resistance for pomalidomide, suggesting a role for this drug in the treatment of relapsed patients, supporting the laboratory results observed in lenalidomide-resistant
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cells [66]. Also notable is the high remission rate (74%) seen in patients from a Phase II relapse study [59] with high-risk disease. The median progression-free survival was 11.6 months and was not significantly different in the patients with high-risk disease compared to those with standard risk disease, which supports the use of pomalidomide.

Data is now emerging for thalidomide and lenalidomide that maintenance prolongs both PFS and OS [67-70]. The low incidence of significant nonhematological toxicity with pomalidomide means that the drug is well tolerated and can be given over prolonged periods. This raises the possibility of utilizing pomalidomide as a maintenance agent or perhaps in the treatment of high-risk precursor conditions such as smouldering myeloma [71]. Furthermore, the potent in-vitro and in-vivo immunomodulatory activity of this agent makes it an ideal candidate to use as an adjuvant for immunotherapeutic strategies such as vaccine therapies for the treatment of myeloma [35,72,73] and other malignancies.

Pomalidomide has also shown activity in upregulating fetal erythropoiesis by causing a switch in lineage commitment [74]. Fetal hemoglobin (HbF) has higher oxygen affinity than normal adult hemoglobin (HbA,) and could potentially be effective in improving fatigue and lethargy in patients with dysregulated erythropoiesis such as hereditary hemoglobinopathies.

Declaration of interest

The authors declare no conflict of interest and have received no payment in preparation of this manuscript.

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