Chapter 3
Pomalidomide

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Abstract Pomalidomide is the third-generation immunomodulatory imide drug (IMiD) derived from thalidomide, approved for the treatment of multiple myeloma (MM). The exact mechanisms of action of pomalidomide are unclear; however, given the structural similarities between pomalidomide and the second-generation IMiD lenalidomide, it is postulated that the two IMiDs share common effects. Pomalidomide is more potent than lenalidomide and is efficacious in lenalidomide-resistant cases. However, pomalidomide-resistant cases have been observed. This chapter will review data from notable clinical trials of pomalidomide and explore the potential mechanisms of pomalidomide action and resistance.

Keywords Multiple myeloma · Pomalidomide · Immunomodulatory imide drug · Cereblon pathway · Pomalidomide resistance

Abbreviations

EMA	European Medicines Agency
FDA	US Food and Drug Administration
IMiD	Immunomodulatory imide drug

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mRNA	Messenger RNA
NF-κβ	Nuclear factor-kappa B
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PI	Proteasome inhibitor
RRMM	Relapsed/refractory multiple myeloma
TGA	Therapeutic Goods Administration

3.1 Introduction

Pomalidomide is an analog of thalidomide and the third drug to be developed belonging to the immunomodulatory imide drug (IMiD) class. It shares common phthalimide and glutarimide moieties as thalidomide but differs in that it has a substituted amino acid at position 4 on the isoindole ring system [1].

3.2 Clinical Indication of Pomalidomide

In Australia pomalidomide, in combination with dexamethasone, is indicated in relapsed/refractory multiple myeloma (RRMM) patients who have undergone at least two prior lines of therapy, which must include bortezomib and lenalidomide based regimes, and with demonstrated disease progression on their last line of therapy (Therapeutic Goods Administration, 2014). It is licensed for the same indication by the US Food and Drug Administration (FDA) (Food and Drug Administration, 2013) and the European Medicines Agency (EMA).

The combination of pomalidomide and bortezomib is approved by the Therapeutic Goods Administration (TGA) of Australia and the European Medicines Agency (EMA) for the treatment of RRMM patients who have undergone at least one prior line of therapy, including lenalidomide.

The combination of daratumumab, pomalidomide, and dexamethasone has been licensed by the FDA since 2017 for the treatment of RRMM patients who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor (PI). Isatuximab and pomalidomide was approved by the FDA in 2020 for the same indication.

3.3 Efficacy

3.3.1 Efficacy in Relapsed and Refractory Multiple Myeloma

3.3.1.1 Pomalidomide and Dexamethasone

A multicenter, open-label, randomized phase III trial by Miguel et al. set the foundation for TGA and FDA approval of pomalidomide and dexamethasone [2]. In this study patients with RRMM who had failed at least two previous treatment lines including bortezomib and lenalidomide were randomized to either pomalidomide and dexamethasone or high dose dexamethasone without pomalidomide. Pomalidomide was dosed at 4 mg daily on days 1–21 of 28-day cycles, with weekly doses of dexamethasone 40 mg orally. The high dose dexamethasone arm was dosed at 40 mg daily orally on days 1–4, 9–12, and 17–20. For patients older than 75 years of age, dexamethasone was reduced to 20 mg at the same dosing frequency. Four hundred and fifty five patients were enrolled in the study with 302 in the pomalidomide and dexamethasone arm and 153 in the high dose dexamethasone arm. Overall response rates (ORR) in the pomalidomide arm were reported at 31%, with median progression-free survival (PFS) in the intention to treat a population of 16 weeks in the pomalidomide and dexamethasone arm, compared to 8.1 weeks in the high dose dexamethasone arm. Subgroup analysis including age stratified (65 years and younger compared to above 65 years old), lenalidomide refractory, bortezomib intolerant, refractory to both lenalidomide and bortezomib, lenalidomide as last treatment, and bortezomib as last treatment groups demonstrated similar results in favor of the pomalidomide arm. Median overall survival (OS) also favored the pomalidomide arm at 55.4 weeks compared to 35.1 weeks for high dose dexamethasone.

Pomalidomide as a single agent has also been compared to pomalidomide and dexamethasone but was observed to result in both a lower median PFS and median OS [3]. Other variations of pomalidomide and dexamethasone dosing strategies have also been studied, including continuous pomalidomide at 4 mg daily on days 1–28, with weekly dexamethasone [4], and continuous low dose pomalidomide at 2 mg daily on days 1–28 in combination with weekly dexamethasone [5]. These strategies were compared to the standard dosing of pomalidomide 4 mg on days 1–21 and weekly dexamethasone and demonstrated comparable PFS and OS benefits. However, continuous pomalidomide dosing slightly increased the incidence of grade 3 and 4 adverse effects.

3.3.1.2 Pomalidomide + Dexamethasone + Cyclophosphamide

A phase I/II randomized controlled trial compared pomalidomide and dexamethasone in combination with cyclophosphamide to pomalidomide and dexamethasone alone [6]. Cyclophosphamide was dosed at 400 mg on days 1, 8, and 15. Thirty-four

patients were enrolled in the triple therapy arm and 36 patients were enrolled in the pomalidomide and dexamethasone arm. Although an increased ORR was observed in the triple therapy arm (65% vs 39%), this did not translate to a significant improvement in PFS or OS.

3.3.1.3 Pomalidomide, Bortezomib, and Dexamethasone

A randomized, open-label phase III trial by Richardson et al. compared pomalidomide, bortezomib, and dexamethasone to bortezomib and dexamethasone in patients with RRMM who had undergone one to three previous regimens, one of which must have been a lenalidomide-containing regimen for at least two consecutive cycles [7]. Bortezomib was dosed at 1.3 mg/m^2, given either intravenously or subcutaneously on days 1, 4, 8, and 11 for the first eight cycles, and then on days 1 and 8 of subsequent cycles. Each cycle was 21 days in length. Dexamethasone was dosed at 20 mg on the day of and the day after bortezomib administration. The dexamethasone dose was reduced to 10 mg for patients older than 75 years of age. Patients allocated to the pomalidomide arm were given 4 mg pomalidomide orally on days 1–14. In total, 559 patients were enrolled with 281 in the pomalidomide, bortezomib, and dexamethasone arm, and 278 in the bortezomib and dexamethasone arm. An improvement in median PFS was observed with the addition of pomalidomide (11.2 months vs 7.1 months [p value <0.0001]).

3.3.1.4 Pomalidomide, Daratumumab, and Dexamethasone

The addition of daratumumab to the standard dosing of pomalidomide and dexamethasone was evaluated in an open-label, nonrandomized phase Ib trial [8]. The standard dosing of pomalidomide 4 mg daily days 1–21 with weekly dexamethasone was evaluated with the addition of daratumumab at 16 mg/kg intravenously weekly for the first two 28-day cycles, every 2 weeks from cycles 3 to 6, and every 4 weeks in each subsequent cycle. Eligible patients must have received at least two prior lines of therapy which must have included lenalidomide and bortezomib but must also be naïve to daratumumab and pomalidomide. One hundred and three patients were enrolled, with an ORR of 60% and median PFS of 8.8 months. The estimated survival rates at 3, 6, and 12 months were 89%, 79%, and 66%, respectively. These results appear to be improved compared to pomalidomide and dexamethasone alone; however, there is a paucity of phase III trials comparing these regimes.

3.3.1.5 Pembrolizumab, Pomalidomide, and Dexamethasone

A randomized phase trial investigating pembrolizumab combined with pomalidomide and dexamethasone compared to pomalidomide and dexamethasone alone was halted due to risks in the triple therapy arm outweighing benefits [9]. A total of 125 patients were randomized to the pembrolizumab combined with pomalidomide and dexamethasone arm, compared to 124 in the pomalidomide and dexamethasone alone arm. The median PFS was 5.6 months in the triple therapy arm compared to 8.4 months in the pomalidomide and dexamethasone arm, with serious adverse events occurring in 63% of patients in the triple therapy arm compared to 46% in the pomalidomide and dexamethasone arm. Of these serious adverse events, 3% were considered treatment-related in the triple therapy arm, with none in the pomalidomide and dexamethasone arm considered treatment-related. From these early results, there is no current data to support the addition of pembrolizumab with standard dosing of pomalidomide and dexamethasone.

3.4 Mechanisms of Pomalidomide Action

Belonging to the same IMiD class, it is postulated that pomalidomide shares a similar mechanism of action to the other second-generation IMiD lenalidomide. Pomalidomide and lenalidomide have multiple anti-myeloma effects, including induction of cell cycle arrest and apoptosis, inactivation of nuclear factor-kappa β (NF-κβ), downregulation of C/Ebβ, activation of caspase-8, disruption of the interaction between myeloma cells and the bone marrow microenvironment, enhancement of T cell proliferation and modulation of regulatory T cells, and effects on proinflammatory cytokines [10–12]. The same cereblon pathway which lenalidomide affects also seems to be an important factor in the efficacy of pomalidomide. Although the exact molecular mechanisms behind this myriad of changes are not yet known, pomalidomide does appear to be more potent than both thalidomide and lenalidomide with regards to its effect on cereblon [13].

3.5 Potential Mechanism of Pomalidomide Resistance and Overcoming Resistance

The specific mechanism for pomalidomide resistance remains unknown. Given the similar effects of lenalidomide and pomalidomide, it can be assumed that lenalidomide-resistant cases would also be pomalidomide resistant. However, lenalidomide resistance does not translate to pomalidomide resistance, as pomalidomide has clearly been proven to be efficacious in lenalidomide-resistant

populations. Whether this is solely due to its more potent nature compared to lenalidomide or an undescribed effect of pomalidomide is yet to be understood.

Cereblon is the key binding protein of IMiDs. The expression of cereblon protein and its messenger RNA (mRNA) had been shown to correlate with clinical response to pomalidomide. Higher cereblon protein expression was associated with increased depth of response and improved PFS and OS [14].

The mechanism of acquired resistance to lenalidomide and pomalidomide was studied in a xenograft plasmacytoma model. It appeared that there was a differential mechanism of resistance between the two drugs. This was supported by the lack of cross-resistance in vivo and differences in gene expression levels and cereblon expression levels. Cereblon expression was significantly downregulated in pomalidomide-resistant cases but not in lenalidomide-resistant ones. The gene expression profile was also significantly different between cases of lenalidomide resistance and pomalidomide resistance. However, in both situations there was upregulation of the MEK/ERK pathway and MEK inhibition by selumetinib could overcome both lenalidomide resistance and pomalidomide resistance in the animal model. It appears that pomalidomide action is more dependent on cereblon than lenalidomide, whereas lenalidomide may rely more on non-cereblon pathways for its anti-myeloma effect.

3.6 Conclusion

There is little data on pomalidomide-resistant cases given pomalidomide itself is reserved for relapsed/refractory cases. As described previously, the combination of pomalidomide with anti-myeloma agents from different classes such as cyclophosphamide, bortezomib, and daratumumab seem to have benefits, regardless of how small. Unfortunately, this does not appear to be the case with pembrolizumab which appeared to result in detrimental outcomes. Further studies of pomalidomide combinations with current drugs, as well as newly developed drugs will be required to determine the optimum approach to pomalidomide-resistant myeloma.

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