REVIEW

Review of therapy for relapsed/refractory multiple myeloma: focus on lenalidomide

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Purpose of review
Multiple myeloma is a malignant neoplasm of plasma cells, for which there is no known cure. This article examines the efficacy and tolerability of lenalidomide, a potent structural analogue of thalidomide, for the treatment of patients with relapsed/refractory multiple myeloma.

Recent findings
Lenalidomide, a thalidomide analogue, was designed to provide increased efficacy, while avoiding the adverse effects associated with thalidomide therapy. Studies assessing lenalidomide as therapy for relapsed/refractory multiple myeloma have shown promising beneficial effects. Lenalidomide–dexamethasone is associated with significantly longer median time to disease progression and overall survival, as well as a significantly higher proportion of patients who respond to treatment compared with dexamethasone alone. Lenalidomide (with dexamethasone) was associated with a high rate of myelosuppression in clinical trials; neutropenia, infection, thrombocytopenia, and venous thromboembolism were common grade 3–4 adverse events. However, appropriate management of these adverse events maximizes the clinical benefit of lenalidomide.

Summary
Lenalidomide in combination with dexamethasone is approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of patients with relapsed/refractory multiple myeloma. Lenalidomide is recommended as a treatment option for patients with multiple myeloma in both United States and European treatment guidelines.

Keywords
lenalidomide, multiple myeloma, relapsed/refractory therapy

INTRODUCTION

Multiple myeloma is a neoplasm of plasma cells [1▪]. Although the exact cause of multiple myeloma is unknown, it is characterized by accumulation of malignant plasma cells in the bone marrow, leading to skeletal destruction, bone marrow failure, anemia, renal failure, hypercalcemia, and increased susceptibility to infection [1▪,2]. Bone pain, recurrent infections, and fatigue, typically related to anemia, are common symptoms at first presentation [3]. A number of biological parameters, including serum β_2-microglobulin, C-reactive protein, lactate dehydrogenase, and albumin, are important prognostic factors, as are cytogenetic abnormalities, which are detected by fluorescent in-situ hybridization (FISH) or conventional karyotyping [4]. Indeed, FISH-defined cytogenetic alterations have been identified in 90% of patients with newly diagnosed multiple myeloma [5]. Notably, the chromosomal alterations del(13), t(4;14), and del(17p) have been observed in 48, 14, and 11% of patients, respectively, and are associated with poor overall survival (OS) [5].

The estimated incidence of multiple myeloma in Europe is six cases per 100 000 individuals/year [4]. The European Network of Cancer Registries estimates there are 21 420 new cases of multiple myeloma in Europe each year and 15 000 associated deaths [6]. Multiple myeloma occurs more commonly in middle-aged and older individuals, with

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the mean age of diagnosis being approximately 60 years [7].

There is presently no cure for multiple myeloma. In a study by the European Cancer Registry, only approximately one-third of all patients with multiple myeloma lived longer than 5 years [8]. However, the recent introduction of new therapeutic agents such as bortezomib, thalidomide, and lenalidomide and increased use of autologous stem cell transplantation (ASCT), along with increased participation in clinical trials have led to major improvements in the survival of younger patients, both in Europe [9,10,11▪,12▪] and the United States [13,14]. For example, 5-year relative survival rates increased from 33.8 to 55.7% between 1989–1992 and 2001–2005 in patients with multiple myeloma aged 65 years or less in a population-based study in the Netherlands [11▪].

LENALIDOMIDE

The immunomodulatory drug lenalidomide is a structural analogue of thalidomide, with a modified backbone and different adverse event profile to the parent compound [15]. Immunomodulatory agents are potent tumor necrosis factor-α inhibitors, and have anti-inflammatory, antiangiogenic, immunomodulatory, and antiproliferative properties [16▪].

The molecular target of lenalidomide is currently under active investigation and is thought in part to be related to modulation of E3 ubiquitin ligase activity through binding to cereblon [17–20]. In-vitro studies of human multiple myeloma cells show that lenalidomide induces apoptosis or cell cycle arrest at G1 and is able to overcome cytokine and bone marrow stromal cell-mediated drug resistance [21,22]. The drug inhibited angiogenesis in a beige-nude-xid mouse tumor model [23] and in a rat model in a dose-dependent manner following oral administration [24]. It also modulates the immune response, enhancing T, natural killer (NK), and NKT cell function [25–27].

Lenalidomide inhibits the proliferation of dexamethasone-resistant human multiple myeloma cells and augments the antiproliferative effect of dexamethasone *in vitro* [21]. Therefore, a regimen of lenalidomide–low-dose dexamethasone may inhibit myeloma cell proliferation, while still allowing lenalidomide to enhance T and NK cell activity [28▪].

Lenalidomide in combination with dexamethasone received US Food and Drug Administration and European Medicines Agency approval for the treatment of patients with multiple myeloma who had received at least one prior therapy; approval was on the basis of two pivotal phase III studies (MM-009 and MM-010) [29,30]. The aim of this review is to examine the efficacy and tolerability of lenalidomide for the treatment of patients with multiple myeloma, with particular focus on the relapsed/refractory setting.

Therapy for newly diagnosed multiple myeloma

According to the National Comprehensive Cancer Network (NCCN) 2010 treatment guidelines for multiple myeloma, the initial treatment of patients presenting with active (symptomatic) multiple myeloma is induction therapy followed by high-dose chemotherapy and ASCT in selected patients [1▪].

For patients who are eligible for ASCT, induction therapy options include thalidomide/dexamethasone, bortezomib/dexamethasone and related bortezomib-based regimens, and lenalidomide/dexamethasone. For patients ineligible for ASCT, options include melphalan/prednisone in combination with thalidomide, bortezomib or lenalidomide.

Although multiple myeloma is typically sensitive to a variety of cytotoxic drugs, it is not considered curable with current approaches [1▪]. The natural history of multiple myeloma is relapse leading to second-line therapy.

Therapy for relapsed/refractory multiple myeloma

According to the NCCN 2010 treatment guidelines for multiple myeloma, second-line therapies with the highest level of supportive evidence include bortezomib ± pegylated liposomal doxorubicin (in patients who have received at least one prior non-bortezomib therapy), or lenalidomide/dexamethasone [1▪]. Recommendations with a lower level of evidence include bortezomib/dexamethasone, or single-agent dexamethasone or lenalidomide. Thalidomide ± dexamethasone and/or chemotherapy are also an option. Alternatively, patients can be treated with high-dose cyclophosphamide, cyclophosphamide-VAD (vincristine, doxorubicin, and dexamethasone), or cyclophosphamide–dexamethasone/chemotherapy, or retreated with primary induction therapy if relapse occurs after more than 6 months after its completion.

Clinical recommendations by the European Society for Medical Oncology (ESMO) for the treatment of relapsed or refractory multiple myeloma include thalidomide (± dexamethasone and/or chemotherapy); bortezomib (± dexamethasone or chemotherapy); or lenalidomide/dexamethasone [4]. VAD is not considered to be a standard salvage treatment option by the ESMO [4].

Efficacy of lenalidomide in clinical studies

The efficacy of lenalidomide in the treatment of relapsed/refractory multiple myeloma has been evaluated in six clinical studies. Lenalidomide was administered in combination with dexamethasone in two pivotal phase III studies (MM-009 and MM-010), as monotherapy in two phase II studies, and in combination with chemotherapy in two phase I/II studies. In addition, three subgroup analyses, a post-hoc review of an expanded access program, and a retrospective review have been published. These studies are summarized in Table 1 [29–36]. Patients included in these studies had relapsed or refractory multiple myeloma and were often heavily pretreated.

Lenalidomide–dexamethasone has also been studied in the treatment of newly diagnosed multiple myeloma [28▪], but the following section will focus on its use in the treatment of relapsed or refractory multiple myeloma.

LENALIDOMIDE AS MONOTHERAPY

In a preliminary study, lenalidomide 30 mg once daily appeared to be more effective than 15 mg twice daily, and the addition of dexamethasone appeared to increase response rates in patients who progressed on, or did not respond to, 2 cycles of lenalidomide therapy [31]. The primary endpoint, overall response rate (ORR) [complete response (CR) + partial response (PR) + minor response (MR)], was similar between once and twice-daily treatment groups (24 vs. 29%), as was median OS; there was a trend toward longer median progression-free survival (PFS) with once-daily dosing (Table 2) [29,30,33,34]. The addition of dexamethasone increased response rates in 29% of patients [33].

LENALIDOMIDE–DEXAMETHASONE

The addition of lenalidomide to dexamethasone significantly increased time to disease progression (TTP) compared with dexamethasone alone in patients with relapsed or refractory multiple myeloma treated with at least one prior therapy [29,30]. Patients receiving lenalidomide–dexamethasone experienced a significantly longer median TTP (11.3 [29] and 11.1 [30] months) than dexamethasone recipients (4.7 months [29,30]; both $P < 0.001$) (Table 2). Similarly, median OS and ORR were significantly longer in the lenalidomide–dexamethasone cohort than dexamethasone alone (Table 2). The comparative median time to progression between lenalidomide-dexamethasone versus placebo-dexamethasone is represented in Fig. 1 [29,30].

Patients in both trials were heavily pretreated with more than 60% of patients having received at least two previous therapies, and more than 50% had undergone stem cell transplantation. Notably, both trials were halted early after interim analyses showed that the O'Brien–Fleming boundary for the superiority of lenalidomide–dexamethasone over dexamethasone had been crossed [29,30].

Lenalidomide–dexamethasone significantly improved median TTP compared with dexamethasone alone, irrespective of previous treatment with thalidomide. In a subgroup analysis of the two phase III studies, median TTP and PFS (both 8.4 vs. 4.6 months; $P < 0.001$) as well as ORR (53.5 vs. 14.3%; $P < 0.001$) were significantly higher in patients with prior exposure to thalidomide who had been treated with lenalidomide–dexamethasone than dexamethasone alone [37]. Patients who were thalidomide-refractory also achieved a significantly higher ORR and longer median TTP and PFS when treated with lenalidomide–dexamethasone compared with dexamethasone alone (all $P < 0.05$) [37]. Notably, ORR was significantly higher in thalidomide-naive patients treated with lenalidomide–dexamethasone than in thalidomide-exposed patients (65 vs. 54%; $P = 0.04$), as were median TTP (13.9 vs. 8.4 months; $P = 0.004$) and PFS (13.2 vs. 8.4 months; $P = 0.02$); however, median OS was similar regardless of prior exposure to thalidomide (36.1 vs. 33.3 months) [37]. In thalidomide-exposed patients there are differences in TTP according to previous response to thalidomide and the progression under therapy. The patients that had response and never progressed while on therapy had better outcome [37].

Lenalidomide–dexamethasone was significantly more effective in patients who had received one prior therapy than those who received at least two prior therapies. In a second subgroup analysis of the MM-009 and MM-010 phase III studies, significantly more patients achieved a CR or a very good PR (VGPR) if they had received only one prior treatment vs. at least two prior therapies (VGPR + CR 39.8 vs. 27.7%; $P = 0.025$). Median TTP (17.1 vs. 10.6 months, $P = 0.026$), PFS (14.1 vs. 9.5 months, $P = 0.047$), and OS (42.0 vs. 35.8 months, $P = 0.041$) were also significantly longer in patients who had received one vs. at least two prior therapies [38]. Thus, evidence suggests that early use of lenalidomide/dexamethasone has superior efficacy [39].

In a third subgroup analysis of the phase III trials, patients who received lenalidomide–dexamethasone for more than 10 months after achieving their first best response had a significantly longer median OS than those who received treatment for

Table 1. Summary of lenalidomide studies in patients with relapsed or refractory multiple myeloma

Study	Design	Treatment regimens	Evaluable patients[b]	Primary endpoint	Other treatment details
Phase I/II studies					
Baz *et al.* (dose-escalation study)[c] [31]	OL	Lenalidomide 10, 15, 20, or 25 mg + DVd	62	Response rate and PFS	DVd (PLD 40 mg/m^2 iv on day 1; VCR 2 mg iv on day 1; DEX 40 mg po on days 1–4) was administered for every 4 weeks for 4 cycles and 2 cycles beyond best response in the induction phase. Patients also received amoxicillin 250 mg bid po, aciclovir 400 mg bid po, and low-dose aspirin 81 mg/day po
Knop *et al.*[c] [32]	OL, MC	Lenalidomide 10–25 mg od + DOX + DEX	69	Response (CR + VGPR + PR)	DOX was administered as a continuous iv infusion over 96 h at 4–9 mg/m^2/day on day 1 and DEX 40 mg od was given on days 1–4 and 17–20 for 6 or less cycles
Phase II clinical studies					
Richardson *et al.* (dose-finding study) [33]	R, OL, MC	Lenalidomide 30 mg od + DEX	67	Best overall response (CR, PR, or MR)	Patients who had progressive or stable disease after 2 cycles continued lenalidomide treatment and received DEX 40 mg/day po for 4 days every 14 days
		Lenalidomide 15 mg bid + DEX	35		
Richardson *et al.* [34]	OL, MC	Lenalidomide 30 mg od	222	At least PR (defined as best response including CR or PR at any time during the first 6 cycles)	
Phase III clinical studies					
Dimopoulos *et al.* (MM-010 study) [29]	R, DB, MC	Lenalidomide 25 mg + DEX	176	Time to disease progression	For the first 4 cycles, DEX 40 mg od was administered on days 1–4, 9–12, and 17–20; thereafter, DEX 40 mg was administered on days 1–4 only
		Placebo + DEX	175		
Weber *et al.* (MM-009 study) [30]	R, DB, MC	Lenalidomide 25 mg + DEX	177	Time to disease progression	For the first 4 cycles, DEX 40 mg od was administered on days 1–4, 9–12, and 17–20; thereafter, DEX 40 mg was administered on days 1–4 only
		Placebo + DEX	176		
Expanded access program					
Chen *et al.* [35]	OL, MC	Lenalidomide 25 mg + DEX	1438	To provide lenalidomide to patients who were highly likely to benefit from treatment; to obtain additional safety data	For the first 4 cycles, DEX 40 mg od was administered on days 1–4, 9–12, and 17–20; thereafter, DEX 40 mg was administered on days 1–4 only
Retrospective analysis (RA)					
Morgan *et al.* [36]	RA	Lenalidomide 25 mg po + cyclophosphamide + DEX	21	Efficacy and safety	Cyclophosphamide 500 mg po was administered on days 1, 8, 15, and 21, and DEX 40 mg po was given on days 1–4 and 12–15 for 9 or less cycles

bid, twice daily; CR, complete response; DB, double-blind; DEX, dexamethasone; DOX, doxorubicin; DVT, deep vein thrombosis; iv, intravenous; LMWH, low molecular-weight heparin; MC, multicenter; MR, minor response; od, once daily; OL, open-label; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; po, oral; PR, partial response; R, randomized; VCR, vincristine; VGPR, very good partial response.
[a]Lenalidomide was administered orally on days 1–21 of a 28-day cycle; treatment was continued until disease progression or unacceptable adverse effects.
[b]Intention-to-treat population.
[c]Data for the phase II portion of the study only are shown.

Table 2. Efficacy of lenalidomide taken on days 1±21 of a 28-day cycle in patients with relapsed or refractory multiple myeloma

Study	Treatment regimen	Median TTP (mo)	Median PFS (mo)	Median OS (mo)	Response rate (% pts)				
					Overall	CR	nCR	PR	CR + PR
Phase II clinical studies									
Richardson *et al* [33]	Lenalidomide 30 mg od		7.7	28	24.0[d]	6.0		12.0	
	Lenalidomide 15 mg bid		3.9	27	29.0[d]	0		14.0	
Richardson *et al.* [34]	Lenalidomide 30 mg od	5.2	4.9	23.2	44.0	2.0		24.0	26.0[d]
Phase III clinical studies[e]									
Dimopoulos *et al.* [29]	Lenalidomide + DEX	11.3[d]*		nr*	60.2*	15.9*	8.5	35.8	
	PL + DEX	4.7[d]		20.6	24.0	3.4	1.7	18.9	
Weber *et al.* [30]	Lenalidomide + DEX	11.1[d]*		29.6*	61.0*	14.1*	10.2	36.7	
	PL + DEX	4.7[d]		20.2	19.9	0.6	1.1	18.2	

bid, twice daily; CR, complete response; DEX, dexamethasone; mo, months; nCR, near complete response; nr, not reached; od, once daily; OS, overall survival; PL, placebo; PFS, progression-free survival; PR, partial response; TTP, time to disease progression.
*$P < 0.001$ vs. PL + DEX. [d] primary end point, [e] identical trials in different continents.

10 months or less (not reached vs. 23.4 months; $P < 0.0001$) [40]. The value of continuous therapy with lenalidomide and dexamethasone was confirmed by several studies, namely the ECOG trial [28▪]; at 3 years, 79% of the patients on continuous lenalidomide therapy were alive vs. an OS of 55% for patients that stop therapy after 4 cycles. Available data suggest that treatment with lenalidomide and dexamethasone should continue on responding patients until disease progression [39].

An expert panel recommends that responding patients continue treatment with the best-tolerated dose of lenalidomide/dexamethasone until there is evidence of disease progression [39].

Together, these subset analyses suggest that lenalidomide–dexamethasone is effective in the treatment of patients with relapsed/refractory multiple myeloma, regardless of prior thalidomide exposure, and substantiate the need to continue lenalidomide/dexamethasone therapy until disease progression in order to optimize patient outcome [38,39].

LENALIDOMIDE IN PATIENTS WITH A POOR PROGNOSIS

Certain cytogenetic abnormalities have been linked to poor outcomes in multiple myeloma, such as del

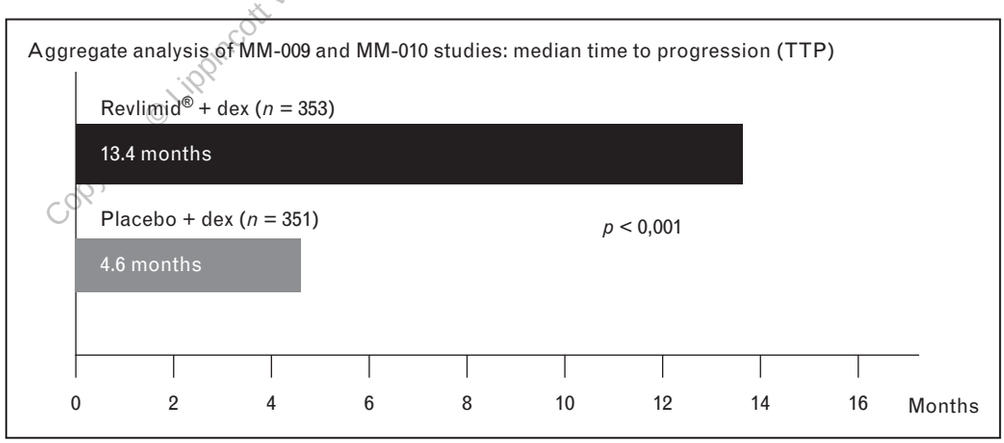

FIGURE 1. Aggregate analysis for time to progression (TTP) among patients in the intention-to-treat population treated with lenalidomide in combination with dexamethasone vs. dexamethasone alone from the MM-009 & MM-010 pivotal studies as for time to progression (TTP). Data from Dimopoulos MA, Chen C, Spencer A, *et al.* Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia 2009; 23:2147–2152.

(13q), t(4;14) and del(17p). In a post-hoc subanalysis of an expanded access program [35], treatment with lenalidomide–dexamethasone overcame poor prognosis conferred by deletions of chromosome 13q or t(4;14) with similar median TTP and OS to patients without these cytogenetic abnormalities. These results were confirmed by another group [41]; however, lenalidomide–dexamethasone had poor activity in patients with multiple myeloma and del(17p13), with significantly shorter median TTP and OS (both $P < 0.001$ vs. patients without this cytogenetic abnormality). In contrast, the French group [42] published a lower response rate as well as PFS and OS in patients presenting with high risk cytogenetics. Conflicting results may be attributed to differences in study populations (age, number of previous therapies). In the upfront setting, patients with high-risk cytogenetic abnormalities treated with lenalidomide and dexamethasone have worse outcome compared with standard-risk patients [43]. Most of the available data are based on small populations with limited follow-up, and patient characteristics and methodology vary widely among studies. These findings highlight the need for prospective clinical trials to further investigate this issue.

LENALIDOMIDE IN COMBINATION WITH CHEMOTHERAPEUTICS

Lenalidomide in combination with chemotherapeutics may be beneficial in the treatment of patients with relapsed or refractory multiple myeloma. Lenalidomide–pegylated liposomal doxorubicin-based chemotherapy was associated with high response rates; median PFS was 12 months and ORR (CR + near-complete remission + PR) was 75%; 29% of patients achieved CR or near-complete remission [31]. Similarly, lenalidomide in combination with doxorubicin and dexamethasone induced substantial and durable remission rates in which 73% of patients achieved an ORR (CR + VGPR + PR) with 15% of patients achieving a CR; the overall median TTP and PFS were 45 and 40 weeks, respectively [32]. Interestingly, a subanalysis of 36 patients for whom cytogenetic data were available showed that the ORR was similar for patients with or without the del(13q) or t(4;14) cytogenetic abnormalities; however, the presence of del(17p) was associated with a significantly poorer response to treatment with lenalidomide–doxorubicin and dexamethasone (20 vs. 87%; $P = 0.001$) and a significantly shorter median TTP (20 vs. 45.5 weeks; $P = 0.025$) than in patients without this cytogenetic abnormality [32].

The addition of bortezomib to lenalidomide and dexamethasone (RVD) proved to be very active and well tolerated in patients with relapsed and refractory multiple myeloma, despite prior therapy with novel agents [44]. This triplet regimen has been investigated in small cohorts of patients with newly diagnosed multiple myeloma. In a phase I/II study [45] with a median follow-up of 21 months, estimated 18-month PFS and OS were 75 and 97%, respectively.

In a retrospective analysis of lenalidomide with cyclophosphamide and dexamethasone, 75% of patients responded to therapy with one patient achieving a CR and three patients achieving a VGPR; the ORR (CR + PR) was 65% and patients showed a rapid response to treatment with a median time to response of 31 (range 15–68) days [36,46]. A phase I/II trial of oral cyclophosphamide, lenalidomide, and prednisone in the setting of advanced disease, was presented at ASH 2010 [47]. The objective response rate (CR + PR + MR) in all patients was 94%. Another study of oral cyclophosphamide and prednisone administrated continuously, associated with lenalidomide [48] has demonstrated better PFS than the study by Morgan [36]. It seems that the continuous exposure of tumor cells to antimyeloma drugs prevents the emergence of resistant clones [49]. Another report of 14 patients showed significant activity in relapse/refractory myeloma with a combination of lenalidomide, dexamethasone and continuous low-dose oral cyclophosphamide, with an overall response of 64.3%, including two CRs [50].

Together, these studies suggest a beneficial effect of lenalidomide in combination with chemotherapeutics in patients with relapsed or refractory multiple myeloma, warranting further clinical trials.

Tolerability of lenalidomide

The most common grade 3–4 adverse events in patients with multiple myeloma treated with lenalidomide–dexamethasone in two phase III studies were neutropenia (35.4%), infection (16.4%), venous thromboembolism (VTE; 13%), thrombocytopenia (13%), and anemia (10.8%; Table 3) [29,30].

The use of lenalidomide is associated with significant myelosuppression, which may require dose interruption or reduction [29,30,51,52]. Indeed, in the MM-009 study, 19.8% of grade 3 or 4 adverse events resulted in study discontinuation [30]. Moreover, adverse event-related dose reductions or treatment interruptions were more common in patients treated with lenalidomide–dexamethasone than dexamethasone alone in both phase III studies (76.1 vs. 56.9%; $P < 0.001$ [29]; 76.8 vs. 57.7% [30]). In addition, in an analysis of pooled tolerability data from the two phase III trials, the incidence

Table 3. Grade 3±4 adverse events [*n* (%)] occurring in 2% or less of patients in either treatment group from pivotal phase III trials of patients with relapsed or refractory multiple myeloma

	Lenalidomide + dexamethasone ($n = 353$)	Placebo + dexamethasone ($n = 350$)
Gastrointestinal disorder		
Constipation	8 (2.3)	2 (0.6)
Diarrhea	11 (3.1)	4 (1.1)
Nausea	7 (2.0)	2 (0.6)
General disorder		
Asthenia	17 (4.8)	16 (4.6)
Fatigue	23 (6.5)	17 (4.9)
Pyrexia	5 (1.4)	12 (3.4)
Hematologic disorder		
Anemia	38 (10.8)	21 (6.0)
Febrile neutropenia	12 (3.4)	0
Neutropenia	125 (35.4)	12 (3.4)
Thrombocytopenia	46 (13.0)	22 (6.3)
Infection		
Any infection	58 (16.4)	32 (9.1)
Metabolism disorder		
Hyperglycemia	19 (5.4)	15 (4.3)
Hypokalemia	11 (3.1)	2 (0.6)
Musculoskeletal disorder		
Arthralgia	2 (0.6)	7 (2.0)
Muscle weakness	20 (5.7)	11 (3.1)
Neurological disorder		
Dizziness	7 (2.0)	3 (0.9)
Respiratory		
Dyspnea	10 (2.8)	10 (2.9)
Vascular disorder		
Deep-vein thrombosis	28 (7.9)	12 (3.4)
Pulmonary embolism	14 (4.0)	3 (0.9)
Venous thromboembolism	46 (13.0)	14 (4.0)

Adapted from [33,37].

of grade 3–4 neutropenia, thrombocytopenia, or deep vein thrombosis (DVT) was highest within the first 3 months of treatment in both arms, and then declined in frequency [53]. It is possible that this observed trend occurred because of dose modifications and/or early discontinuation of patients susceptible to adverse events [53]. The same conclusions are present in a further analysis of patients who obtained at least PR in these two phase III trials [54]. This suggests that clinicians should monitor the initial cycles of lenalidomide/dexamethasone in order to prevent and/or manage adverse events and avoid treatment discontinuation [39]. Recently, a consensus statement recommended optimal starting dose of lenalidomide, when used in combination with dexamethasone in relapsed or refractory multiple myeloma and taking into account cytopenia and renal function, as well the age-adjusted starting dose of dexamethasone [33,37,39].

An expanded access trial, initiated in 2005 to provide access to lenalidomide prior to its approval, demonstrated that the type and frequency of adverse events experienced by 1438 patients in this real-life setting were consistent with those reported in the pivotal studies that led to the approval of lenalidomide in this patient population [35]. The frequency of thromboembolic events in the expanded access program was lower than in the pivotal phase III studies (4.5 vs. 7.9% for grade 3–4 DVT), which may have been due to the recommendation of prophylactic antithrombotic therapy with daily aspirin in the expanded access program [35]. Interestingly, despite an incidence of VTE of 15% or less in patients treated with

lenalidomide–dexamethasone in the pivotal phase III studies [29,30], no increased risk of VTE has been reported with single-agent lenalidomide [33,55].

Lenalidomide was developed to increase the efficacy demonstrated by thalidomide while attempting to minimize some of the adverse effects that have been associated with thalidomide treatment. Although no clinical trials directly comparing these agents have been performed, lenalidomide appears to have a lower incidence of constipation, peripheral neuropathy, and somnolence than thalidomide [52,56]. VTE events may also be commonly associated with thalidomide, especially when thalidomide is administered with dexamethasone or other chemotherapeutic agents (incidence 3–34% in newly diagnosed patients and 2–15% in those with relapsed/refractory disease) [57]. As the effects of myelosuppression associated with lenalidomide-dexamethasone use on stem cell mobilization remain unresolved [58,59], more studies are required to determine a neutral or negative impact.

Impact of lenalidomide on peripheral blood stem cell collection

The combination of lenalidomide and dexamethasone in the upfront treatment of multiple myeloma patients resulted in very high response rates as well as deeper responses [60,61] which translates to a 55% reduced risk of disease progression for the patients submitted to ASCT [62]. However, the most common adverse effect of lenalidomide is neutropenia. This indicated that the use of lenalidomide in front-line therapy could adversely affect the mobilizing and collection of adequate numbers of CD 34+ cells in the ASCT setting [63]. In fact, in two large retrospective studies [58,64], the most significant factor affecting the ability to collect adequate numbers of stem cells is initial therapy with lenalidomide and in particular, the duration of therapy. The recommended number of prior cycles of lenalidomide-based therapy before collection of stem cells is four, and mobilization regimens incorporating cyclophosphamide or plerixafor should be used [65].

CONCLUSION

Lenalidomide is an immunomodulatory agent with both direct tumoricidal and immunomodulatory effect in multiple myeloma. Lenalidomide has been approved in the United States and Europe in combination with dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma, and is listed in US and European treatment guidelines as a recommended treatment option. Recent evidence indicates that continuous therapy with lenalidomide can improve the quality of response, and prolong time to relapse and OS.

The addition of lenalidomide to dexamethasone is efficacious in the treatment of relapsed/refractory multiple myeloma, with a recent consensus panel highlighting the importance of using lenalidomide–dexamethasone early in the course of the disease, and continuing therapy in responding patients until disease progression.

Lenalidomide in combination with dexamethasone is associated with significant myelosuppression, with the most common grade 3 or 4 adverse events being neutropenia, infection, thrombocytopenia, as well as VTE. Importantly, the risk of adverse events appear to be highest during the initial cycles of treatment and decreases thereafter. Clinicians should, therefore, monitor patients to prevent or manage any adverse events so that treatment can be maintained.

Lenalidomide is an important addition to the treatment armamentarium for relapsed or refractory multiple myeloma. Increasing understanding of the disease process and identification of well defined prognostic factors will help to further refine risk-adapted approaches to patient management in the future.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
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