VIA MEDICA

Review article

NOWOTWORY Journal of Oncology
2022, volume 72, number 4, 231–241
DOI: 10.5603/NJO.a2022.0031

ISSN 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

Principles of prevention and management of adverse events of immunomodulatory drugs in the treatment of multiple myeloma

Grzegorz Charliński[1], David H. Vesole[2, 3], Artur Jurczyszyn[4]

[1]*Department of Hematology, Medical Faculty, University of Warmia and Mazury in Olsztyn, Olsztyn, Poland*
[2]*Department of Hematology/Oncology, Medstar Georgetown University Hospital, Washington, United States*
[3]*John Theurer Cancer Center at Hackensack Meridian School of Medicine, Hackensack, United States*
[4]*Plasma Cell Dyscrasias Center, Department of Hematology, Faculty of Medicine, Jagiellonian University Medical College, Krakow, Poland*

Over the past 15 years, significant progress has been made in understanding the biology and treatment of multiple myeloma (MM). This is due to the introduction of new therapies and new applications of known drugs associated with a better understanding of how to optimize treatment to patient and disease characteristics. Indeed, 15 new drugs have been approved over this time period. Immunomodulatory drugs (IMiDs) have been used in the treatment of MM for over 20 years. Initially, it was thalidomide, then analogues lenalidomide and pomalidomide; in the future, cereblon E3 ligase modulators CelMoDs, such as iberdomide and CC-480. Currently, IMiDs are mainly used as the backbone of multi-drug protocols, including in combination with monoclonal antibodies and proteasome inhibitors. Given the common utilization of IMiDs in the management of MM, it is relevant to review the safety profile of IMiDs and the management of adverse events (AEs).

Key words: adverse events, immunomodulatory drugs, lenalidomide, management, multiple myeloma, pomalidomide, thalidomide, treatment

Introduction

Immunomodulatory drugs (IMiDs) have significantly improved survival in patients with multiple myeloma (MM) over the past 20 years. That said, only 10–15% of MM patients meet or exceed life expectancy compared to the matched general population [1]. There are three IMiDs commonly used in clinical practice: thalidomide, lenalidomide, and pomalidomide. Immunomodulating drugs are oral drugs that have unique mechanisms of action, including anti-cancer and anti-inflammatory effects, and affect the human immune system [2].

The mechanism of action of IMiDs in MM cells was initially considered a process of anti-angiogenesis [3]. After that, direct and indirect anti-tumor activity was demonstrated by immunomodulation. In 2010, the anti-MM activity of the IMiDs was mediated by the inhibition of cereblon (CRBN), a protein that dictates the substrate specificity of CRL4CRBN E3 ubiquitin ligase [4–6]. By binding the CRL4CRBN E3 ligase, the proteins associated with the disease are ubiquitinated and degraded. The key neosubstrates in plasma cells (PCs) are transcription factors – the Ikaros (IKZF1) and Aiolos (IKZF3) proteins [7, 8].

How to cite:
Charliński G, Vesole DH, Jurczyszyn A. ***Principles of prevention and management of adverse events of immunomodulatory drugs in the treatment of multiple myeloma.*** *NOWOTWORY J Oncol* 2022; 72: 231–241.

IMiDs degrade Ikaros and Aiolos *via* CRBN-dependent ubiquitination, leading to the downregulation of IRF4 and MYC [9]. In addition to their direct anti-MM activity, IMiDs show indirect anti-MM activity, inhibiting the secretion of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin (IL) – 1, IL-6, IL-12, and IL-16, which leads to the inhibition of proliferation and migration of neoplastic PCs and apoptosis [10]. Lenalidomide and pomalidomide induce malignant PCs apoptosis more potently by activating tumor suppressor genes than thalidomide. In preclinical studies, lenalidomide and pomalidomide were 300–1200 times more potent than thalidomide in T-cell costimulation [11, 12]. Both lenalidomide and pomalidomide increase the action of NK cells in destroying PCs. Lenalidomide additionally activates NKT cells [13, 14]. Cereblon E3 ligase modulators (CELMoDs), compared to IMiDs, have a greater affinity for CRBN and a more decisive influence on the degradation of Ikaros and Aiolos, which results in a stronger anti-MM and immunomodulatory effect [15, 16]. This is the fundamental difference between the two groups of drugs.

Despite the similarities in their chemical structure, the IMiDs differ in their adverse event (AE) profile and exhibit only moderate cross-reactivity, and can be used sequentially in subsequent lines of MM treatment. Currently, these drugs are considered a standard backbone in the induction therapy of transplant and non-transplant eligible patients, post-autologous stem cell transplantation (ASCT) consolidation and maintenance therapy, and in the treatment of relapsed/refractory MM (RRMM).

Thalidomide (α-N-phthalimido-glutarimide) has been used to treat MM for over 20 years [17]. Thalidomide shows synergy *in vitro* with other drugs and has become an integral component of many combinations of MM treatment. In the European Union (EU), the European Medicines Agency (EMA) approved thalidomide in combination with melphalan and prednisone (MPT), MPT with daratumumab (Dara-MPT), and with daratumumab, bortezomib, and dexamethasone (Dara-VTD) for the treatment of newly diagnosed MM (NDMM). The AEs observed during treatment with thalidomide favored the development of thalidomide analogs with greater immunomodulatory activity and a better safety profile [18]. A modification of the chemical structure led to the formulation of lenalidomide and pomalidomide.

Lenalidomide is an analogue of thalidomide that is commonly used in the treatment of MM. In the EU, the EMA approved lenalidomide in combination with dexamethasone (Rd), daratumumab and dexamethasone (Dara-Rd), bortezomib and dexamethasone (VRd), and melphalan and prednisone (MPR) for the treatment of NDMM. In Poland, lenalidomide can treat NDMM under the Ministry of Health drug program criteria based on the Rd and VRd chemotherapy protocols [19]. Lenalidomide monotherapy for maintenance treatment after ASCT is also EMA approved. In addition, the EMA approved lenalidomide for the treatment of RRMM, in combination with dexamethasone, and Rd in combination with carfilzomib (KRd), ixasomib (Ixa-Rd), Dara-Rd, and elotuzumab (Elo-Rd). In Poland, in the treatment of RRMM, lenalidomide treatment is approved following the criteria of the Ministry of Health drug program under the Rd, KRd, Ixa-Rd chemotherapy protocols [19].

Pomalidomide is another thalidomide analogue with direct antiproliferative, pro-apoptotic, and anti-angiogenic effects. It has a modulating effect on bone resorption and the immune system [20]. The EMA has approved pomalidomide and dexamethasone (Pd) remove for the treatment of RRMM in combination with bortezomib (PVd), isatuximab (Isa-Pd), and elotuzumab (Elo-Pd). In Poland, in the treatment of RRMM, the combination of Pd and PVd is approved under the Ministry of Health drug program [19]. A comparison of the chemical structure, dosing, and mechanism of action of IMiDs is presented in table I [21].

The AEs observed in patients with MM result from both the neoplastic disease and the anti-MM treatment used and comorbidities. For this reason, it is not easy to ascribe specific AEs to specific drugs. In clinical practice, the Common Terminology Criteria (CTC) for AEs classification is most often used to identify AEs [22]. Common to all IMiDs is their potential teratogenic effect, which can result in severe, life-threatening congenital malformations (e.g., phocomelia). For this reason, unless there is reliable evidence that they cannot become pregnant, all patients must meet the conditions of the pregnancy prevention program before starting treatment with IMiDs [23].

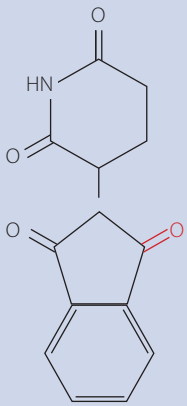
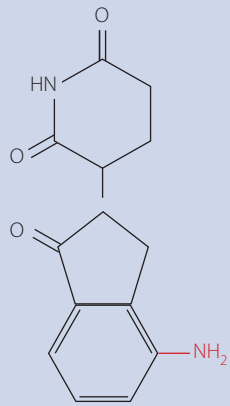
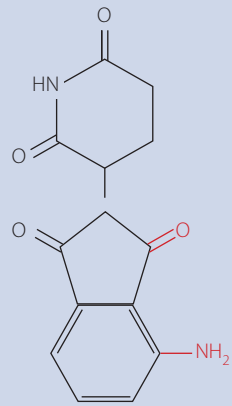
Due to the results of phase 3 clinical trials, IMiDs are currently used mainly in multi-drug combinations with new drugs, including monoclonal antibodies (daratumumab, elotuzumab, isatuximab) and proteasome inhibitors (bortezomib, carfilzomib, ixazomib). We review the AEs reported in the latest phase 3 clinical trials and their management principles.

Thalidomide

So far, thalidomide has been the main IMiD used in the treatment of patients with NDMM in Poland. In ASCT eligible patients, thalidomide is used with bortezomib and dexamethasone (VTD) and VTD in combination with daratumumab. In the most recent EHA-ESMO recommendations issued in 2021, thalidomide is not recommended for patients with NDMM who are ineligible for ASCT [24].

The AEs of thalidomide depend on the dose and duration of treatment and the presence of comorbidities. The most common serious AEs of thalidomide include constipation, peripheral neuropathy (PN), somnolence, depression, and venous thromboembolism (VTE). Depending on the treatment regimen (monotherapy versus multi-drug combinations), the frequency of AEs is variable [25]. In randomized phase 3 clinical trials utilizing VTD induction therapy for NDMM before ASCT, the most common causes of hematological AEs, include neutropenia (15–19% of patients). In contrast, the most com-

Table I. Comparison of the mechanisms of action and chemical structure of immunomodulatory drugs

	Thalidomide	Lenalidomide		Pomalidomide
chemical structure				
daily dose	50–200 mg	2.5–25 mg		1–4 mg
dose modification depending on RI	no dose modification needed	CrCl (ml/min)	daily dose	no dose modification needed
		>60	25 mg	
		30–59	10 mg	
		15–29	15 mg every other day	
		<15	5 mg	
		on dialysis	5 mg	
relative potency ± potency factor of 10				
CD4+ and CD8+ T-cell co-stimulation	+	++++		+++++
tregs suppresion	–	+		+
Th1 cytokine production	+	++++		+++++
NK and NKT cell activation	+	++++		+++++
antibody-dependent cellular cytotoxicity	–	++++		++++
anti-angiogenesis	++++	+++		+++
anti-inflammatory properties	+	++++		+++++
anti-proliferative activity	+	+++		+++

CrCl – creatinine clearance; RI – renal impairment

mon non-hematological AEs are infections and PN [26, 27]. The combination of VTD and Dara-VTD in induction therapy before ASCT compared to VTD increases the incidence of serious hematological AEs, including neutropenia (grade 3–4: 28% *vs.* 15%) and thrombocytopenia (grade 3–4: 11% *vs.* 7%). There was no increase in the frequency of non-hematological serious AEs in the Dara-VTD group compared to the VTD group [28].

In patients not eligible for ASCT in first-line treatment, thalidomide is most often used in combination with melphalan and prednisone (MPT). The most common hematological AE was neutropenia, whereas the non-hematological AEs included infections, PN, VTE, and skin lesions (Stevens-Johnson syndrome and toxic epidermal necrolysis) [29, 30]. In some countries, thalidomide combined with cyclophosphamide and dexamethasone (CTD) was used as first-line treatment. The most frequently observed AEs in the phase 3 study, MRC Myeloma IX, were neutropenia (grade 3–4: 11%), infections (grade 3–4: 13%), and PN (grade 3–4: 7%) [31]. Table II summarizes the incidence of serious AEs from pivotal phase 3 clinical trials of thalidomide for the treatment of NDMM. Thalidomide has been well studied as post ASCT maintenance therapy. The most common AEs are PN and constipation [32, 33], thus limiting their *se* for long term treatment.

Currently, the role of thalidomide in the treatment of RRMM is limited. In this indication, thalidomide has been used as monotherapy, combined with dexamethasone (TD) and triplet regimens. Regardless of the regimen, the most common side effects AE's were somnolence (11–57%), constipation (16–75%), PN (6–23%), skin rashes (3–21%), cardiovascular disorders (bradycardia, arrhythmias, 2%), and VTE (3–7%) [34, 35].

Table II. Incidence of serious adverse events of thalidomide in treatment of newly diagnosed multiple myeloma identified in pivotal phase 3 clinical trials

Trial	Cavo et al. [26]		IFM2013-04 [27]		CASSIOPEIA [28]		Myeloma MRC IX [31]		The metanalysis of 6 randomized trials [30]	
regimen	TD	VTD	VCD	VTD	VTD	Dara-VTD	CTD	MP	MPT	MP
hematological adverse events, grade ≥3 (%)										
neutropenia	NA	NA	33	19	15	28	11	15	overall: 32	overall: 29
thrombocytopenia	0	5	11	5	7	11	NA	NA		
anemia	NA	NA	9	4	NA	NA	NA	NA		
non-hematological adverse events, grade ≥3 (%)										
febrile neutropenia										
infections	3	1	NR	NR	20	22	13	7	13	9
peripheral neuropathy	0	<1	grade 2–4: 12.9	grade 2–4: 21.9	9	9	7	2	15	3
venous thromboembolism	<1	<1	2	2	NA	NA	0	0	6	2
constipation	<1	<1	NA	NA	1	1	3	1.2	NA	NA
skin rash	<1	<1	NA	NA	NA	NA	2	<1	3	1
secondary malignancy (any grade)	NA	NA	NA	NA	2	2	NA	NA	NA	NA

CTD – cyclophosphamide, thalidomide, dexamethasone; Dara-VTD – daratumumab, bortezomib, thalidomide, dexamethasone; MP – melphalan, prednisone; MPT – melphalan, prednisone, thalidomide; NA – not available; TD – thalidomide, dexamethasone; VCD – bortezomib, cyclophosphamide, dexamethasone; VTD – bortezomib, thalidomide, dexamethasone

Thalidomide when combined with cyclophosphamide has the additional hematologic AEs including neutropenia (grade 3–4: 86%), thrombocytopenia (grade 3–4: 30%), infection (grade 3–4: 26%) [36].

Management of AEs during treatment with thalidomide

The most common hematological AE in treatment with thalidomide is neutropenia. Anemia and thrombocytopenia are observed less frequently than neutropenia [23, 37]. For this reason, it is recommended to perform a blood count. When the absolute neutrophil count (ANC) is 0.5–1.0 G/L, reduce the thalidomide dose by 50% and consider the use of granulocyte colony-stimulating factor (G-CSF) when the ANC < 0.5 G/L treatment with thalidomide should be discontinued; if the ANC is more than 1.0 G/L, start treatment with a dose reduced by 50% with or without G-CSF [23]. Anemia and thrombocytopenia are less frequently observed than neutropenia [23, 37].

The most severe non-hematological undesirable effect of thalidomide treatment is PN. The incidence of PN is variable and is dependent on the dose and duration of therapy [38]. Some authors recommend treatment with thalidomide be limited to no more than six months [39]. Unfortunately, thalidomide-associated PN is often slow to resolve, if ever, and a substantial proportion of patients have some level of persistent PN. Therefore, during therapy with thalidomide, it is necessary to monitor for PN. Grade 1 PN does not require a reduction of the thalidomide dose; in grade 2, the dose of thalidomide should be reduced by 50%, and in grades 3 and 4, treatment with thalidomide should be discontinued until symptoms resolve or decrease to grade 1 [40].

The treatment for neuropathic pain is variable and challenging to manage, and the best management is to avoid the development of PN. One option is using agents which reduce neurotransmitter release: gabapentin (titrated up to 1200 mg three times daily) or pregabalin (titrated up to 300 mg twice daily). Alternative options include amitriptyline (10–100 mg daily), serotonin and norepinephrine reuptake inhibitors (venlafaxine, duloxetine), or anti-epileptic drugs (carbamazepine) [41]. Only 25% of patients completely recover from thalidomide-induced PN within 4–6 years [42].

Another non-hematological AEs of thalidomide (and all other IMiDs) treatment is VTE, which most often develops in the first three months and decreases after approximately 12 months [43]. During treatment with an IMiD, it is necessary to use anticoagulation prophylaxis adapted to the presence of risk factors, which include: age, immobility, obesity, history of VTE, presence of a central venous catheter, presence of comorbidities, hereditary thrombophilia, a large mass of MM tumor and treatment of high doses of dexamethasone, an anthracycline, or multi-drug chemotherapy [44]. According to the SAVED Score, the finding of at least two risk factors is an indication for treatment with enoxaparin 40 mg/day or warfarin (target International Normalized Ratio [INR]: 2–3). According to the SAVED Score, treatment with acetylsalicylic acid (ASA) 81–325 mg daily is recommended in patients with one risk

factor [45–47]. Other drugs recommended are rivaroxaban 10 mg daily, apixaban 2.5 mg twice daily, and fondaparinux 2.5 mg daily.

A common side effect of thalidomide treatment is constipation, reported in 80–90% of patients. It develops early after initiation of thalidomide treatment and most often affects elderly patients concomitantly treated with opioid analgesics. In patients starting thalidomide treatment, prophylactic use of low doses of stool softeners and/or laxatives is recommended. Should be adjusted treatment according to the severity of constipation. In the case of grade 3 or 4 constipation a 50% reduction in the daily dose of thalidomide is recommended. In constipation requiring the use of an enema, thalidomide treatment should be withheld until symptoms resolve. Prophylactic laxatives should be taken when treatment with thalidomide is resumed at a reduced dose [48, 49].

Common AEs of thalidomide include somnolence and fatigue. Mild drowsiness occurs in more than 75% of patients and severe (grade 3–4) in 5–10%. Daytime drowsiness may be reduced by taking the total daily dose of thalidomide in the evening. Hazardous tasks and the concomitant use of alcohol and medications that may make you feel drowsy should be avoided. If grade 3 somnolence interferes with normal activities of daily living, or if dementia, or a coma occurs, one should discontinue treatment until the toxicity has resolved. When re-treating, the daily dose of thalidomide should be reduced by 50%. Additionally, patients may report fatigue, weakness, difficulty concentrating, and mood changes [48].

Other non-hematological AEs include skin lesions observed in approximately 15% of patients, including about 1.5% of patients with grade $\geq$3 skin lesions [23]. The most common symptoms are pruritis and maculopapular rash. Alveolar lesions develop in 25% of patients treated with thalidomide in a dose >400 mg/day. Once the skin lesions have resolved, re-treatment of thalidomide may be considered at a reduced dose [23, 37]. After the skin lesions have resolved, may resume treatment with thalidomide at a reduced dose. If grade 1–2 dermatological AEs develops, treatment with thalidomide should be discontinued until the toxicity resolves or decreases to grade 1. Thalidomide should be suspended indefinitely in the event of severe exfoliative, macular, or bullous rash, or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected. Medicines that may cause severe skin reactions, such as trimethoprim/sulfamethoxazole or allopurinol, should be avoided during treatment with thalidomide [23].

Renal impairment

Dexamethasone protocol is a highly effective and widely used treatment of NDMM with renal impairment (RI), mainly in Europe. The use of thalidomide in combination with a high dose of dexamethasone (TD) improves renal function in 55–75% of patients with NDMM and about 60% of patients with RRMM [50, 51]. The use of thalidomide in the treatment of MM with RI does not increase the incidence of AEs. Therefore, there is no need to adjust the dose of thalidomide depending on RI [52]. This also applies to patients requiring dialysis. Patients undergoing dialysis require close monitoring as they may develop hyperkalemia. It is necessary to remember the necessity to use antithrombotic prophylaxis in this group of patients [43]. Thalidomide dosing by creatinine clearance (CrCl) is presented in table I.

Lenalidomide

Lenalidomide is an IMiD that is approved for both NDMM and RRMM. Despite the high structural similarity to thalidomide, the two drugs have different safety profiles. The dominant AEs are hematological AEs resulting from the myelosuppressive effects of lenalidomide on the bone marrow [25]. Lenalidomide, unlike thalidomide, is renally cleared; therefore, RI increases the myelosuppressive effect of lenalidomide [53]. Unlike thalidomide, PN, constipation, and somnolence are rarely observed with lenalidomide treatment.

Lenalidomide may be associated with an increased risk of VTE. In a randomized phase 3 trial comparing Rd with lenalidomide in combination with high-dose dexamethasone (RD) in patients with NDMM, thromboprophylaxis was not mandatory until the first 266 patients were enrolled. More AEs were observed in the Rd group except grade 3–4 VTE, which was more common in the RD group (12% *vs.* 26%, respectively) [54]. Lenalidomide, when incorporated into multi-drug protocols, including in combination with dexamethasone and cyclophosphamide or liposomal doxorubicin, resulted in VTE in 14% and 9%, respectively) [55, 56].

The phase 3 FIRST study in NDMM compared lenalidomide in combination with dexamethasone for 18 cycles (Rd18) with continuous Rd – Rd(cont), and MPT [57]. In the group of patients treated with lenalidomide, hematological serious (grade 3–4) AEs were reported in the following proportion of patients: neutropenia in 26% and 30% of patients treated with Rd18 and Rd(cont), respectively; thrombocytopenia in 8% and 9% of patients, respectively, and neutropenia in 26%, and 30% of patients, respectively. The most common non-hematological serious (grade 3–4) AEs were infection (22% *vs.* 32%, respectively), VTE (4% *vs.* 5%, respectively) and pulmonary embolism (3% *vs.* 4%, respectively), thromboprophylaxis was included in the study), peripheral sensory neuropathy (<1% *vs.* 1%, respectively), diarrhea (3% *vs.* 5%, respectively) [57].

The use of VRd in NDMM compared to Rd does not increase serious (grade 3–4) hematological AEs but increases the risk of PN (grade 3–4: 35% *vs.* 11%, respectively) [58].

In the phase 3 MAIA trial, comparing Dara-Rd with Rd in transplant-ineligible NDMM, serious AEs were reported in 77% and 70% of patients, respectively. It is known that daratumumab is associated with neutropenia as a single agent. The most common serious (grade 3–4) AEs are neutropenia (54% *vs.* 37%, respectively), anemia (17% *vs.* 22%, respectively),

lymphopenia (16% *vs.* 11%, respectively), and infections (32% *vs.* 23%, respectively) [59]. MPR compared with MPR with lenalidomide in maintenance therapy (MPR-R) in the treatment of NDMM is associated with a higher incidence of myelosuppression: neutropenia (grade 3–4) was found in 65% patients, thrombocytopenia in more than 33%, and anemia in 25% patients [60]. Table III summarizes the incidence of serious AEs from pivotal phase 3 clinical trials of lenalidomide for the treatment of NDMM.

In RRMM, two randomized phases 3 trials reported grade 3–4 AEs, including neutropenia (35%), anemia (11%), thrombocytopenia (13%), and infections (16%), atrial fibrillation (3%), and VTE (13%) The duration of use of lenalidomide in second-line treatment did not generally worsen the safety profile [61, 62].

There are several phase 3 studies comparing triplets with an Rd backbone to an Rd doublet, including combinations with carfilzomib, ixazomib, daratumumab, or elotuzumab. Most of the additions of a third drug, in general, resulted in a higher incidence of AEs [63–66]. In contrast, in these phase 3 studies which included mild to moderate RI, the myelosuppressive effect of lenalidomide was more pronounced, a significantly higher incidence of thrombocytopenia (grade 3–4) was found in patients with CrCl < 50 ml/min compared to CrCl ≥ 50 ml/min (14% *vs.* 5%) with no difference in grade 3 or 4 neutropenia [67]. Table IV summarizes the incidence of serious AEs from pivotal phase 3 clinical trials of lenalidomide for the treatment of RRMM.

It is worth adding that the development of secondary neoplasms is observed in the treatment with lenalidomide in the context of recent melphalan therapy (e.g., MPR, or ASCT), post-ASCT, lenalidomide-maintenance therapy). In the treatment of NDMM, secondary primary malignancy were reported in 3–9% of NDMM and 4–17% of RRMM [61–66].

Management of AEs during treatment with lenalidomide

The myelosuppressive effect of lenalidomide is the most serious AE. Blood counts (CBCs) need to be routinely monitored, minimum monthly, to avoid severe infections and discontinuation of lenalidomide treatment. You should follow the EMA product information for dose restrictions, resumptions, and dose reductions. When the platelets (PLT) count drops to <25 G/L, should discontinue lenalidomide treatment until the PLT count has improved to ≥50 G/L, and lenalidomide should be given at a reduced dose of 15 mg/day. With each successive decrease in the PLT count <25 G/L, lenalidomide treatment should be discontinued and restarted when the PLT count increases ≥50 G/L, at a dose reduced by 5 mg compared to the previously used dose [68]. When the ANC < 0.5 G/L, lenalido-

Table III. Incidence of serious adverse events of lenalidomide in treatment of newly diagnosed multiple myeloma identified in pivotal phase 3 clinical trials

Trial/author	MM-015 [60]			Rajkumar et al. [54]		FIRST [57]		SWOG S0777 [58]			MAIA [59]	
regimen	MPR-R	MPR	MP	RD	Rd	Rd(cont)	Rd18	MPT	Rd	VRd	Dara-Rd	Rd
hematological adverse events, grade ≥3 (%)												
neutropenia	67	64	29	12	20	30	26	45	21	19	50	35
thrombocytopenia	35	38	12	6	5	9	8	11	14	18	NA	NA
anemia	24	26	14	8	7	19	16	19	16	13	12	20
non-hematological adverse events, grade ≥3 (%)												
febrile neutropenia	5	1	0	NA	NA	1	3	3	NA	NA	NA	NA
infections	9	13	7	16	9	32	22	17	14	19	32	23
pneumonia												
peripheral neuropathy	NA	NA	NA	2	2	1	<1	9	11	35	NA	NA
venous thromboembolism	1	4	1	26	12	5	4	3	9	8	NA	NA
constipation	NA	NA	NA	NA	NA	2	2	5	NA	NA	2	<1
diarrhea	2	1	0	NA	NA	5	3	1	NA	NA	7	4
skin rash	5	5	1	NA	NA	NA	NA	NA	4	4	NA	NA
secondary malignancy (any grade)	NA	NA	NA	NA	NA	7	7	9	3	3	9	7

Dara-Rd – daratumumab, lenalidomide, dexamethasone; MP – melphalan, prednisone; MPR – melphalan, prednisone, lenalidomide; MPR-R – melphalan, prednisone, lenalidomide and maintenance lenalidomide; NA – not available; Rd – lenalidomide, low dose dexamethasone; RD – lenalidomide, high dose dexamethasone; Rd18 – lenalidomide, dexamethasone (18 cycles); Rd(cont) – lenalidomide, dexamethasone continues therapy; VRd – bortezomib, lenalidomide, dexamethasone

Table IV. Incidence of serious adverse events of lenalidomide in treatment of relapsed/refractory multiple myeloma identified in pivotal phase 3 clinical trials

Trial	ASPIRE [63]		TOURMALINE-MM1 [64]		POLLUX [65]		ELOQUENT-2 [66]	
regimen	Rd	KRd	Rd	Ixa-Rd	Rd	Dara-Rd	Rd	Elo-Rd
hematological adverse events, grade ≥3 (%)								
neutropenia	27	31	24	23	42	55	45	36
thrombocytopenia	13	17	9	19	16	15	21	21
anemia	17	19	13	9	21	18	21	20
non-hematological adverse events, grade ≥3 (%)								
febrile neutropenia	NA	NA	NA	NA	3	6	NA	NA
infections								
pneumonia	12	16.	NA	2	10	15	26	33
peripheral neuropathy	3	3	2	2	NA	NA	NA	NA
venous thromboembolism	NA	NA	3	2	NA	NA	NA	NA
constipation	<1	<1	<1	<1	<1	1	<1	1
diarrhea	4	5	NA	NA	4	10	5	6
skin rash	NA	NA	2	5	NA	NA	NA	NA
cardiac disorders	2.	4	2	3	NA	NA	8	5
secondary malignancy (any grade)	NA	NA	4	5	9	8	11	17

Dara-Rd – daratumumab, lenalidomide, dexamethasone; Elo-Rd – elotuzumab, lenalidomide, dexamethasone; Ixa-Rd – ixazomib, lenalidomide, dexamethasone; KRd – carfilzomib, lenalidomide, dexamethasone; NA – not available; Rd – lenalidomide, dexamethasone

mide treatment should be discontinued, G-CSF administered, and lenalidomide at the current dose resumed when the ANC increases ≥1.0 G/L. If ANC count returns to <1.0 G/L, lenalidomide treatment should be discontinued and restarted at a dose 5 mg lower when the ANC becomes ≥1.0 G/L [68]. In the case of anemia (hemoglobin [Hb] concentration <9.0 g/dl), treatment with erythropoiesis-stimulating agents (ESA) may be used.

Lenalidomide monotherapy has little effect on the development of VTE. This risk increases when lenalidomide is combined with high-dose dexamethasone and multi-drug combinations [54, 69]. VTE is more commonly found in the treatment of NDMM. Thromboprophylaxis is not recommended during treatment with lenalidomide monotherapy [46]. In other cases, the principles of thromboprophylaxis are the same as in therapy with thalidomide.

Other serious (grade 3–4) non-hematological AEs requiring a dose reduction of lenalidomide are infections (dose reduction 25–50%), asthenia (25–50%), grade 2 skin toxicity (50%), and grade 2 intestinal toxicity (50%). In the case of lenalidomide treatment with a high dose of dexamethasone, antibacterial prophylaxis is recommended in NDMM [67].

Skin rashes are observed in approximately 25% (grade 3–4: 3.5%) of patients, usually appearing in the first month of treatment and may last for several weeks [70]. Discontinuation of lenalidomide treatment and the use of antihistamines and systemic corticosteroids is recommended in the presence of grade 3–4 skin lesions. Retreatment once the rash has resolved is usually well tolerated [71]. The reappearance of skin lesions is a contraindication to further treatment with lenalidomide [72].

Constipation can be managed with a bowel regimen while continuing lenalidomide therapy. Diarrhea (defined as four or more bowel movements) is a common complication of lenalidomide treatment. Loperamide may be used to reduce the frequency of bowel movements [73, 74]. After several months of lenalidomide treatment, diarrhea may occur due to bile salt malabsorption syndrome [74].

Renal impairment

Lenalidomide is mainly eliminated renally. When lenalidomide is used to treat patients with MM with RI, care should be taken in dose selection and monitoring renal function. In patients with moderate, severe, or end-stage renal disease, dose adjustments of lenalidomide are recommended at treatment initiation and during treatment. No dose adjustment of lenalidomide is required during therapy in patients with mild RI [68]. Lenalidomide dosing by CrCl is presented in table I.

Pomalidomide

Pomalidomide is an IMiD currently used to treat RRMM. The safety profile of pomalidomide is similar to that of lenalidomide.

Adverse events resulting from the myelosuppressive effect of pomalidomide dominate, mainly neutropenia, less often thrombocytopenia and anemia. Constipation, infection, fatigue, fever, peripheral edema, confusion, and VTE are the most common non-hematological AEs. Peripheral neuropathy is uncommonly observed [75].

In the phase 3 clinical trial MM-003, patients were treated with Pd or with dexamethasone alone, neutropenia (grade 3–4) was reported in 48% of patients, most often developing in the first treatment cycles. Anemia (grade 3–4) was observed in 33% of patients and thrombocytopenia (grade 3–4) in 24% of patients. Febrile neutropenia was found in <10% of patients [76, 77]. In another phase, three studies in which Pd was combined with a third drug, i.e., bortezomib, daratumumab, isatuximab, elotuzumab, again predominantly hematological AEs were observed, including neutropenia in 41–85% of patients, thrombocytopenia 8–34% and anemia 10–35% of patients. Due to compulsory antithrombotic prophylaxis, VTE was observed in 2–4% of patients treated with Pd [78–81].

In the MM-002 study, although 73% of patients treated with Pd had a history of PN, no grade 3–4 PN was observed [82]. In study MM-003, 15% of Pd-treated patients had PN. Grade 1 PN was diagnosed in 52% of patients at baseline [76]. In the phase 3 study, OPTIMISMM, PN (grade 3–4) was reported in 8.5% of patients with RRMM treated with PVd and 4% of patients treated with bortezomib with dexamethasone (Vd) [78]. Table V summarizes the incidence of serious AEs from pivotal phase 3 clinical trials of pomalidomide for the treatment of RRMM.

Management of AEs during treatment with pomalidomide

Due to the risk of myelosuppression, CBC monitoring weekly is recommended for the first two treatment cycles. When the ANC drops to <0.5 G/L, pomalidomide should be discontinued. G-CSF may be administered until the ANC is ≥1.0 G/L; after that, treatment should be resumed with pomalidomide at a dose reduced by 1 mg/day compared to the previously used dose [83, 84]. Due to the increased risk of infection during treatment with pomalidomide, some authors recommend antimicrobial prophylaxis for at least the first three treatment cycles. In patients at high risk of infection and/or after infection, prophylactic antibiotics may be considered. A reduction in the PLT count <25 G/L indicates discontinuing pomalidomide therapy until the PLT count is increased ≥50 G/L.

Treatment should be resumed at a dose reduced by 1 mg/day compared to previous treatment [83, 84]. The principles of treating anemia with pomalidomide are the same as

Table V. Incidence of serious adverse events of pomalidomide in treatment of relapsed/refractory multiple myeloma identified in pivotal phase 3 clinical trials

Trial	MM-003 [76]		STRATUS [77]	OPTIMISMM [78]		APOLLO [79]		ICARIA-MM [80]		ELOQUENT-3 [81]	
regimen	Dex	Pd	Pd	Vd	PVd	Pd	Dara-Pd	Pd	Ixa-Pd	Pd	Elo-Pd
hematological adverse events, grade ≥3 (%)											
neutropenia	16	48	50	9	41	51	68	71	85	27	13
thrombocytopenia	26	21	24	29	28	18	17	25	34	5	8
anemia	37	33	33	14	14	21	17	29	35	21	20
non-hematological adverse events, grade ≥3 (%)											
febrile neutropenia	0	10	NA	NA	NA	3	9	NA	NA	20	10
infections	10	14	28	1	1	23	28	<1	5	22	13
pneumonia			13	7	11	7	13	21	23	9	5
peripheral neuropathy	NA	NA	<1	4	9	NA	NA	NA	NA	NA	NA
venous thromboembolism	NA	NA	<2	NA	NA	NA	NA	NA	NA	NA	NA
constipation	0.0	2	<1	<1	3	NA	NA	0	0	0	2
diarrhea	1	1	<1	4	7	1	5	1	2	0	0
skin rash	NA	NA	NA	NA	NA	NA	NA	NA	NA	2	0
cardiac disorders	NA	NA	NA	NA	NA	NA	NA	NA	NA	4	7
secondary malignancy (any grade)	NA	NA	2	NA	NA	NA	NA	NA	NA	22	2

Dara-Pd – daratumumab, pomalidomide, dexamethasone; Dex – dexamethasone; Elo-Pd – elotuzumab, pomalidomide, dexamethasone; Ixa-Pd – isatuximab, pomalidomide, dexamethasone; NA – not available; Pd – pomalidomide, dexamethasone; PVd – pomalidomide, bortezomib, dexamethasone; Vd – bortezomib, dexamethasone

those with lenalidomide treatment. Thrombotic prophylaxis is recommended in all patients treated with pomalidomide when combined with dexamethasone, following the same guidelines as for lenalidomide. If grade ≥2, PN develops, withhold pomalidomide treatment until symptoms improve to grades 0–1. After that, pomalidomide should be taken at a reduced dose. The occurrence of PN (grade 4) is an indication for discontinuing treatment with pomalidomide [83, 84]. Treatment of the rash and reduction of the daily dose of lenalidomide by 1 mg is recommended. Rash (grade 4) is an indication of permanent discontinuation of pomalidomide treatment [84]. If constipation and another grade ≥3 non-hematological AEs occur, it is recommended that pomalidomide treatment be interrupted until symptoms resolve to grade ≤2 and that treatment is resumed at a dose reduced by one dose level for the next cycle [83].

Renal impairment

Pomalidomide is metabolized in the liver and, unlike lenalidomide, only 2% of unmetabolized pomalidomide is excreted in the urine [47]. Based on study MM-013, patients with RRMM and moderate or severe RI, including those requiring hemodialysis, benefit from treatment with pomalidomide in combination with low-dose dexamethasone. The use of pomalidomide at a dose of 4 mg daily in combination with dexamethasone is an effective and safe treatment for patients with RRMM and moderate to severe RI, including patients who require hemodialysis [85]. Therefore, no dose reduction of pomalidomide is needed in patients with mild or moderate RI (CrCl ≥ 45 ml/min). Pomalidomide should be taken after hemodialysis on the patient's hemodialysis [47]. Pomalidomide dosing by CrCl is presented in table I.

Conclusions

One of the most important drugs used in the treatment of MM is IMiDs. The combination of IMiD, dexamethasone, and a third drug (proteasome inhibitor, monoclonal antibody, alkylating drug) is the cornerstone of treatment for NDMM and RRMM.

Immunomodulatory drugs have a predictable toxicity profile. The most important AEs of thalidomide are PN and VTE, while lenalidomide and pomalidomide are predominantly myelosuppressive. Close monitoring of their safety profile makes it possible to protect patients from AEs by reducing doses and/or discontinuing treatment with IMiDs. Table V summarizes the most common AEs observed during treatment with IMiDs in patients with MM. Maintaining clinical vigilance and timely dose modifications to AEs with the simultaneous use of the recommended prophylaxis will reduce the development of serious AEs, resulting in improved quality of life and longer treatment duration.

Conflict of interest: none declared

Grzegorz Charliński
University of Warmia and Mazury in Olsztyn
Medical Faculty
Department of Hematology
ul. Wojska Polskiego 37
10-228 Olsztyn, Poland
e-mail: grzegorz.charlinski@uwm.edu.pl

Received: 19 Jan 2022
Accepted: 16 Mar 2022

References

1. Usmani SZ, Hoering A, Cavo M, et al. Clinical predictors of long-term survival in newly diagnosed transplant eligible multiple myeloma - an IMWG Research Project. Blood Cancer J. 2018; 8(12): 123, doi: 10.1038/s41408-018-0155-7, indexed in Pubmed: 30470751.
2. Aragon-Ching JB, Li H, Gardner ER, et al. Thalidomide analogues as anticancer drugs. Recent Pat Anticancer Drug Discov. 2007; 2(2): 167–174, doi: 10.2174/157489207780832478, indexed in Pubmed: 17975653.
3. Davies F, Baz R. Lenalidomide mode of action: linking bench and clinical findings. Blood Rev. 2010; 24 Suppl 1: S13–S19, doi: 10.1016/S0268-960X(10)70004-7, indexed in Pubmed: 21126632.
4. Ito T, Ando H, Handa H, et al. Identification of a primary target of thalidomide teratogenicity. Science. 2010; 327(5971): 1345–1350, doi: 10.1126/science.1177319, indexed in Pubmed: 20223979.
5. Ito T, Handa H. Cereblon and its downstream substrates as molecular targets of immunomodulatory drugs. Int J Hematol. 2016; 104(3): 293–299, doi: 10.1007/s12185-016-2073-4, indexed in Pubmed: 27460676.
6. Sievers QL, Petzold G, Bunker RD, et al. Defining the human C2H2 zinc finger degrome targeted by thalidomide analogs through CRBN. Science. 2018; 362(6414), doi: 10.1126/science.aat0572, indexed in Pubmed: 30385546.
7. Lu G, Middleton RE, Sun H, et al. The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. Science. 2014; 343(6168): 305–309, doi: 10.1126/science.1244917, indexed in Pubmed: 24292623.
8. John LB, Ward AC. The Ikaros gene family: transcriptional regulators of hematopoiesis and immunity. Mol Immunol. 2011; 48(9-10): 1272–1278, doi: 10.1016/j.molimm.2011.03.006, indexed in Pubmed: 21477865.
9. Chanan-Khan AA, Swaika A, Paulus A, et al. Pomalidomide: the new immunomodulatory agent for the treatment of multiple myeloma. Blood Cancer J. 2013; 3: e143, doi: 10.1038/bcj.2013.38, indexed in Pubmed: 24013664.
10. Castelli R, Cassin R, Cannavò A, et al. Immunomodulatory drugs: new options for the treatment of myelodysplastic syndromes. Clin Lymphoma Myeloma Leuk. 2013; 13(1): 1–7, doi: 10.1016/j.clml.2012.09.016, indexed in Pubmed: 23153925.
11. Davies FE, Raje N, Hideshima T, et al. Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. Blood. 2001; 98(1): 210–216, doi: 10.1182/blood.v98.1.210, indexed in Pubmed: 11418482.
12. Hayashi T, Hideshima T, Akiyama M, et al. Molecular mechanisms whereby immunomodulatory drugs activate natural killer cells: clinical application. Br J Haematol. 2005; 128(2): 192–203, doi: 10.1111/j.1365-2141.2004.05286.x, indexed in Pubmed: 15638853.
13. Noonan K, Rudraraju L, Ferguson A, et al. Lenalidomide-induced immunomodulation in multiple myeloma: impact on vaccines and antitumor responses. Clin Cancer Res. 2012; 18(5): 1426–1434, doi: 10.1158/1078-0432.CCR-11-1221, indexed in Pubmed: 22241792.
14. Matyskiela ME, Zhang W, Man HW, et al. A Cereblon Modulator (CC-220) with Improved Degradation of Ikaros and Aiolos. J Med Chem. 2018; 61(2): 535–542, doi: 10.1021/acs.jmedchem.6b01921, indexed in Pubmed: 28425720.
15. Hansen JD, Correa M, Nagy MA, et al. Discovery of CRBN E3 Ligase Modulator CC-92480 for the Treatment of Relapsed and Refractory Multiple Myeloma. J Med Chem. 2020; 63(13): 6648–6676, doi: 10.1021/acs.jmedchem.9b01928, indexed in Pubmed: 32130004.
16. Moreau P, San Miguel J, Sonneveld P, et al. ESMO Guidelines Committee. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017; 28(suppl_4): iv52–iv61, doi: 10.1093/annonc/mdx096, indexed in Pubmed: 28453614.

17. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med. 1999; 341(21): 1565–1571, doi: 10.1056/NEJM199911183412102, indexed in Pubmed: 10564685.
18. Richardson PG, Delforge M, Beksac M, et al. Management of treatment-emergent peripheral neuropathy in multiple myeloma. Leukemia. 2012; 26(4): 595–608, doi: 10.1038/leu.2011.346, indexed in Pubmed: 22193964.
19. https://www.gov.pl/web/zdrowie/choroby-onkologiczne (15.03.2022).
20. Lacy MQ, McCurdy AR. Pomalidomide. Blood. 2013; 122(14): 2305–2309, doi: 10.1182/blood-2013-05-484782, indexed in Pubmed: 23974193.
21. Quach H, Ritchie D, Stewart AK, et al. Mechanism of action of immunomodulatory drugs (IMiDS) in multiple myeloma. Leukemia. 2010; 24(1): 22–32, doi: 10.1038/leu.2009.236, indexed in Pubmed: 19907437.
22. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf (25.11.2021).
23. Ghobrial IM, Rajkumar SV. Management of thalidomide toxicity. J Support Oncol. 2003; 1(3): 194–205, indexed in Pubmed: 15334875.
24. Dimopoulos MA, Moreau P, Terpos E, et al. EHA Guidelines Committee. Electronic address: guidelines@ehaweb.org, ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021; 32(3): 309–322, doi: 10.1016/j.annonc.2020.11.014, indexed in Pubmed: 33549387.
25. Cohen AD, Parekh S, Santomasso BD, et al. KEYNOTE-183 Investigators. Management of treatment-related adverse events in patients with multiple myeloma. Cancer Treat Rev. 2010; 36 Suppl 2(4): S24–S32, doi: 10.1016/S0305-7372(10)70009-8, indexed in Pubmed: 20472185.
26. Cavo M, Pantani L, Petrucci MT, et al. GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) Italian Myeloma Network. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. Blood. 2012; 120(1): 9–19, doi: 10.1182/blood-2012-02-408898, indexed in Pubmed: 22498745.
27. Moreau P, Hulin C, Macro M, et al. VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial. Blood. 2016; 127(21): 2569–2574, doi: 10.1182/blood-2016-01-693580, indexed in Pubmed: 27002117.
28. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019; 394(10192): 29–38, doi: 10.1016/S0140-6736(19)31240-1, indexed in Pubmed: 31171419.
29. Kapoor P, Rajkumar SV, Dispenzieri A, et al. Melphalan and prednisone versus melphalan, prednisone and thalidomide for elderly and/or transplant ineligible patients with multiple myeloma: a meta-analysis. Leukemia. 2011; 25(4): 689–696, doi: 10.1038/leu.2010.313, indexed in Pubmed: 21233832.
30. Palumbo A, Waage A, Hulin C, et al. Safety of thalidomide in newly diagnosed elderly myeloma patients: a meta-analysis of data from individual patients in six randomized trials. Haematologica. 2013; 98(1): 87–94, doi: 10.3324/haematol.2012.067058, indexed in Pubmed: 22875621.
31. Morgan GJ, Davies FE, Gregory WM, et al. National Cancer Research Institute Haematological Oncology Clinical Studies Group. Cyclophosphamide, thalidomide, and dexamethasone as induction therapy for newly diagnosed multiple myeloma patients destined for autologous stem-cell transplantation: MRC Myeloma IX randomized trial results. Haematologica. 2012; 97(3): 442–450, doi: 10.3324/haematol.2011.043372, indexed in Pubmed: 22058209.
32. Stewart AK, Trudel S, Bahlis NJ, et al. A randomized phase 3 trial of thalidomide and prednisone as maintenance therapy after ASCT in patients with MM with a quality-of-life assessment: the National Cancer Institute of Canada Clinicals Trials Group Myeloma 10 Trial. Blood. 2013; 121(9): 1517–1523, doi: 10.1182/blood-2012-09-451872, indexed in Pubmed: 23297129.
33. Donk Nv, Holt Bv, Minnema M, et al. Thalidomide before and after autologous stem cell transplantation in recently diagnosed multiple myeloma (HOVON-50): long-term results from the phase 3, randomised controlled trial. The Lancet Haematology. 2018; 5(10): e479–e492, doi: 10.1016/s2352-3026(18)30149-2.
34. Glasmacher A, Hahn C, Hoffmann F, et al. A systematic review of phase-II trials of thalidomide monotherapy in patients with relapsed or refractory multiple myeloma. Br J Haematol. 2006; 132(5): 584–593, doi: 10.1111/j.1365-2141.2005.05914.x, indexed in Pubmed: 16445831.
35. Terpos E, Christoulas D, Kastritis E, et al. Greek Myeloma Study Group. Thalidomide and dexamethasone combination for refractory multiple myeloma. Ann Oncol. 2001; 12(7): 991–995, doi: 10.1023/a:1011132808904, indexed in Pubmed: 11521808.
36. Kropff MH, Lang N, Bisping G, et al. Hyperfractionated cyclophosphamide in combination with pulsed dexamethasone and thalidomide (HyperCDT) in primary refractory or relapsed multiple myeloma. Br J Haematol. 2003; 122(4): 607–616, doi: 10.1046/j.1365-2141.2003.04473.x, indexed in Pubmed: 12899716.
37. Palumbo A, Facon T, Sonneveld P, et al. Thalidomide for treatment of multiple myeloma: 10 years later. Blood. 2008; 111(8): 3968–3977, doi: 10.1182/blood-2007-10-117457, indexed in Pubmed: 18245666.
38. Schiff D, Wen PY, van den Bent MJ. Neurological adverse effects caused by cytotoxic and targeted therapies. Nat Rev Clin Oncol. 2009; 6(10): 596–603, doi: 10.1038/nrclinonc.2009.128, indexed in Pubmed: 19707193.
39. Reddy GK, Mughal TI, Lonial S. Optimizing the management of treatment-related peripheral neuropathy in patients with multiple myeloma. Support Cancer Ther. 2006; 4(1): 19–22, doi: 10.3816/SCT.2006.n.027, indexed in Pubmed: 18632462.
40. Tariman JD, Love G, McCullagh E, et al. IMF Nurse Leadership Board. Peripheral neuropathy associated with novel therapies in patients with multiple myeloma: consensus statement of the IMF Nurse Leadership Board. Clin J Oncol Nurs. 2008; 12(3 Suppl): 29–36, doi: 10.1188/08.CJON.S1.29-35, indexed in Pubmed: 18490255.
41. Jongen JL, Broijl A, Sonneveld P. Chemotherapy-induced peripheral neuropathies in hematological malignancies. J Neurooncol. 2015; 121(2): 229–237, doi: 10.1007/s11060-014-1632-x, indexed in Pubmed: 25326770.
42. Delforge M, Bladé J, Dimopoulos MA, et al. Treatment-related peripheral neuropathy in multiple myeloma: the challenge continues. Lancet Oncol. 2010; 11(11): 1086–1095, doi: 10.1016/S1470-2045(10)70068-1, indexed in Pubmed: 20932799.
43. Palumbo A, Palladino C. Venous and arterial thrombotic risks with thalidomide: evidence and practical guidance. Ther Adv Drug Saf. 2012; 3(5): 255–266, doi: 10.1177/2042098612452291, indexed in Pubmed: 25083240.
44. Snowden JA, Ahmedzai SH, Ashcroft J, et al. Haemato-oncology Task Force of British Committee for Standards in Haematology and UK Myeloma Forum. Guidelines for supportive care in multiple myeloma 2011. Br J Haematol. 2011; 154(1): 76–103, doi: 10.1111/j.1365-2141.2011.08574.x, indexed in Pubmed: 21517805.
45. Minnema MC, Breitkreutz I, Auwerda JJA, et al. Prevention of venous thromboembolism with low molecular-weight heparin in patients with multiple myeloma treated with thalidomide and chemotherapy. Leukemia. 2004; 18(12): 2044–2046, doi: 10.1038/sj.leu.2403533, indexed in Pubmed: 15470485.
46. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. International Myeloma Working Group. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia. 2008; 22(2): 414–423, doi: 10.1038/sj.leu.2405062, indexed in Pubmed: 18094721.
47. Fouquet G, Bories C, Guidez S, et al. Pomalidomide for multiple myeloma. Expert Rev Hematol. 2014; 7(6): 719–731, doi: 10.1586/17474086.2014.966074, indexed in Pubmed: 25265911.
48. NCCN Clinical Practice Guidelines in Oncology. Multiple myeloma. Version 4.2022.
49. Smith LC, Bertolotti P, Curran K, et al. IMF Nurse Leadership Board. Gastrointestinal side effects associated with novel therapies in patients with multiple myeloma: consensus statement of the IMF Nurse Leadership Board. Clin J Oncol Nurs. 2008; 12(3 Suppl): 37–52, doi: 10.1188/08.CJON.S1.37-51, indexed in Pubmed: 18490256.
50. Dimopoulos MA, Roussou M, Gkotzamanidou M, et al. The role of novel agents on the reversibility of renal impairment in newly diagnosed symptomatic patients with multiple myeloma. Leukemia. 2013; 27(2): 423–429, doi: 10.1038/leu.2012.182, indexed in Pubmed: 22763386.
51. Rizzello I, Cavo M, Dozza L, et al. GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto Italian Myeloma Network), GIMEMA Italian Myeloma Network. Thalidomide alone or in combination with dexamethasone in patients with advanced, relapsed or refractory multiple myeloma and renal failure. Eur J Haematol. 2004; 73(2): 98–103, doi: 10.1111/j.1600-0609.2004.00272.x, indexed in Pubmed: 15245508.
52. Alexander M, Kirsa S, Mellor JD. Thalidomide thromboprophylaxis in multiple myeloma: a review of current evidence. Asia Pac J Clin Oncol. 2012; 8(4): 319–324, doi: 10.1111/j.1743-7563.2011.01511.x, indexed in Pubmed: 22897571.

53. Niesvizky R, Jayabalan DS, Christos PJ, et al. BiRD (Biaxin [clarithromycin]/Revlimid [lenalidomide]/dexamethasone) combination therapy results in high complete- and overall-response rates in treatment-naive symptomatic multiple myeloma. Blood. 2008; 111(3): 1101–1109, doi: 10.1182/blood-2007-05-090258, indexed in Pubmed: 17989313.
54. Rajkumar SV, Jacobus S, Callander NS, et al. Eastern Cooperative Oncology Group. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol. 2010; 11(1): 29–37, doi: 10.1016/S1470-2045(09)70284-0, indexed in Pubmed: 19853510.
55. Morgan GJ, Schey SA, Wu P, et al. Lenalidomide (Revlimid), in combination with cyclophosphamide and dexamethasone (RCD), is an effective and tolerated regimen for myeloma patients. Br J Haematol. 2007; 137(3): 268–269, doi: 10.1111/j.1365-2141.2007.06538.x, indexed in Pubmed: 17408469.
56. Schey S, Morgan G, Ramasamy K, et al. CRD: A Phase 1 Dose Escalation Study to Determine the Maximum Tolerated Dose of Cyclophosphamide in Combination with Lenalidomide and Dexamethasone in Relapsed/Refractory Myeloma. Blood. 2008; 112(11): 3707–3707, doi: 10.1182/blood.v112.11.3707.3707.
57. Facon T, Dimopoulos MA, Dispenzieri A, et al. Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. Blood. 2018; 131(3): 301–310, doi: 10.1182/blood-2017-07-795047, indexed in Pubmed: 29150421.
58. Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017; 389(10068): 519–527, doi: 10.1016/S0140-6736(16)31594-X, indexed in Pubmed: 28017406.
59. Facon T, Kumar S, Plesner T, et al. MAIA Trial Investigators. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. N Engl J Med. 2019; 380(22): 2104–2115, doi: 10.1056/NEJMoa1817249, indexed in Pubmed: 31141632.
60. Palumbo A, Gay F, Cavallo F, et al. MM-015 Investigators. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med. 2012; 366(19): 1759–1769, doi: 10.1056/NEJMoa1112704, indexed in Pubmed: 22571200.
61. Dimopoulos M, Spencer A, Attal M, et al. Multiple Myeloma (010) Study Investigators. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med. 2007; 357(21): 2123–2132, doi: 10.1056/NEJMoa070594, indexed in Pubmed: 18032762.
62. Weber DM, Chen C, Niesvizky R, et al. Multiple Myeloma (009) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med. 2007; 357(21): 2133–2142, doi: 10.1056/NEJMoa070596, indexed in Pubmed: 18032763.
63. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. ASPIRE Investigators. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med. 2015; 372(2): 142–152, doi: 10.1056/NEJMoa1411321, indexed in Pubmed: 25482145.
64. Mateos MV, Masszi T, Grzasko N, et al. TOURMALINE-MM1 Study Group. Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016; 374(17): 1621–1634, doi: 10.1056/NEJMoa1516282, indexed in Pubmed: 27119237.
65. Bahlis NJ, Dimopoulos MA, White DJ, et al. Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study. Leukemia. 2020; 34(7): 1875–1884, doi: 10.1038/s41375-020-0711-6, indexed in Pubmed: 32001798.
66. Dimopoulos MA, Lonial S, White D, et al. Elotuzumab plus lenalidomide/dexamethasone for relapsed or refractory multiple myeloma: ELOQUENT-2 follow-up and post-hoc analyses on progression-free survival and tumour growth. Br J Haematol. 2017; 178(6): 896–905, doi: 10.1111/bjh.14787, indexed in Pubmed: 28677826.
67. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. International Myeloma Working Group. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia. 2008; 22(2): 414–423, doi: 10.1038/sj.leu.2405062, indexed in Pubmed: 18094721.
68. https://www.ema.europa.eu/en/documents/product-information/revlimid-epar-product-information_en.pdf (25.11.2021).
69. Richardson P, Jagannath S, Hussein M, et al. Safety and efficacy of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma. Blood. 2009; 114(4): 772–778, doi: 10.1182/blood-2008-12-196238, indexed in Pubmed: 19471019.
70. Imbesi S, Allegra A, Calapai G, et al. Cutaneous adverse reactions to lenalidomide. Allergol Immunopathol (Madr). 2015; 43(1): 88–91, doi: 10.1016/j.aller.2013.07.005, indexed in Pubmed: 24998775.
71. Barley K, He W, Agarwal S, et al. Outcomes and management of lenalidomide-associated rash in patients with multiple myeloma. Leuk Lymphoma. 2016; 57(11): 2510–2515, doi: 10.3109/10428194.2016.1151507, indexed in Pubmed: 26943456.
72. Tinsley SM, Kurtin SE, Ridgeway JA. Practical Management of Lenalidomide-Related Rash. Clin Lymphoma Myeloma Leuk. 2015; 15 Suppl: S64–S69, doi: 10.1016/j.clml.2015.02.008, indexed in Pubmed: 26297281.
73. Vehreschild MJ, Vehreschild JJ, Hübel K, et al. German Society of Hematology and Oncology. Diagnosis and management of gastrointestinal complications in adult cancer patients: evidence-based guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Ann Oncol. 2013; 24(5): 1189–1202, doi: 10.1093/annonc/mdt001, indexed in Pubmed: 23401037.
74. Pawlyn C, Khan MS, Muls A, et al. Lenalidomide-induced diarrhea in patients with myeloma is caused by bile acid malabsorption that responds to treatment. Blood. 2014; 124(15): 2467–2468, doi: 10.1182/blood-2014-06-583302, indexed in Pubmed: 25301337.
75. Richardson PG, Palumbo A, Schey SA, et al. Pomalidomide – an appraisal of its clinical development and role in the treatment of relapsed/refractory multiple myeloma. Eur Oncol Haematol. 2015; 11: 109–117.
76. Miguel J, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013; 14(11): 1055–1066, doi: 10.1016/s1470-2045(13)70380-2.
77. Dimopoulos MA, Palumbo A, Corradini P, et al. Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUS (MM-010): a phase 3b study in refractory multiple myeloma. Blood. 2016; 128(4): 497–503, doi: 10.1182/blood-2016-02-700872, indexed in Pubmed: 27226434.
78. Richardson PG, Oriol A, Beksac M, et al. OPTIMISMM trial investigators. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. Lancet Oncol. 2019; 20(6): 781–794, doi: 10.1016/S1470-2045(19)30152-4, indexed in Pubmed: 31097405.
79. Dimopoulos MA, Terpos E, Boccadoro M, et al. APOLLO Trial Investigators. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. Lancet Oncol. 2021; 22(6): 801–812, doi: 10.1016/S1470-2045(21)00128-5, indexed in Pubmed: 34087126.
80. Attal M, Richardson PG, Rajkumar SV, et al. ICARIA-MM study group. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet. 2019; 394(10214): 2096–2107, doi: 10.1016/S0140-6736(19)32556-5, indexed in Pubmed: 31735560.
81. Dimopoulos MA, Dytfeld D, Grosicki S, et al. Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma. N Engl J Med. 2018; 379(19): 1811–1822, doi: 10.1056/NEJMoa1805762, indexed in Pubmed: 30403938.
82. Richardson PG, Siegel DS, Vij R, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. Blood. 2014; 123(12): 1826–1832, doi: 10.1182/blood-2013-11-538835, indexed in Pubmed: 24421329.
83. Dimopoulos MA, Leleu X, Palumbo A, et al. Expert panel consensus statement on the optimal use of pomalidomide in relapsed and refractory multiple myeloma. Leukemia. 2014; 28(8): 1573–1585, doi: 10.1038/leu.2014.60, indexed in Pubmed: 24496300.
84. https://www.ema.europa.eu/en/documents/product-information/imnovid-epar-product-information_en.pdf (25.11.2021).
85. Dimopoulos M, Weisel K, van de Donk NW, et al. Pomalidomide Plus Low-Dose Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma and Renal Impairment: Results From a Phase II Trial. J Clin Oncol. 2018; 36(20): 2035–2043, doi: 10.1200/JCO.2017.76.1742, indexed in Pubmed: 29394124.