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Supportive care in multiple myeloma

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Abstract

Multiple myeloma is one of the most commonly diagnosed blood cancers. Due to the introduction of new therapies in recent years, there has been significant progress in treating myeloma. Even so, with the introduction of new groups of drugs, there have been some adverse events. In addition to anti-myeloma treatment, patients require supportive therapies. This article presents the principles of supportive treatment in emergencies and discusses the toxicity associated with the use of new groups of drugs.

Key words: adverse events, management, multiple myeloma, supportive care

Introduction

Multiple myeloma (MM) is one of the most frequently diagnosed hematological neoplasms [1]. In Poland, c.2,600 new MM cases are reported annually, and it is the third most frequently

diagnosed hematological neoplasm [2]. The introduction of thalidomide, bortezomib and lenalidomide to therapy has prolonged the survival of patients with myeloma [3, 4]. The more recent use of pomalidomide, carfilzomib, ixazomib, daratumumab, isatuximab, selinexor, belantamab, mandolin, and chimeric antigen receptor-T (CAR-T) will most likely prolong the survival of patients with MM. In addition to anti-MM therapy, the standard of care requires supportive therapies to prevent and treat organ damage early.

The method of treating MM has been changing dynamically in recent years. In Europe, patients qualified for high-dose (HD) chemotherapy followed by autologous stem cell transplantation (ASCT) are treated with 3–4 cycles of remission-inducing chemotherapy, followed by high-dose (HD) chemotherapy followed by ASCT. As recommended by the European Hematology Association–European Society for Medical Oncology (EHA-ESMO), first-line chemotherapy protocols include VRd (bortezomib, lenalidomide, dexamethasone) and DaraVTD (daratumumab, bortezomib, thalidomide, dexamethasone). Other methods of induction therapy include the VTD (bortezomib, thalidomide, dexamethasone) and the VCD (bortezomib, cyclophosphamide, dexamethasone) protocols.

However, in patients not qualified for ASCT, the following chemotherapy protocols are recommended for treating newly diagnosed myeloma (NDMM): DaraRd (daratumumab, lenalidomide, dexamethasone); DaraVMP (daratumumab, bortezomib, melphalan, prednisone); and VRd. Other first-line treatment options include the VMP (bortezomib, melphalan, prednisone) and the Rd (lenalidomide, dexamethasone) protocols. Figure 1 shows the treatment algorithm for patients with newly diagnosed myeloma recommended by the EHA-ESMO [5]. After achieving remission, all patients are expected to relapse. The duration of remission decreases with each subsequent relapse. Treating relapsed/refractory MM (RRMM) depends on many factors, including time of remission, treatment applied, response to previous therapy, the aggressiveness of the relapse, and the patient’s performance status. . Among the newest options for treating RRMM are belantamab mafodotin (BM) and CAR-T [5].

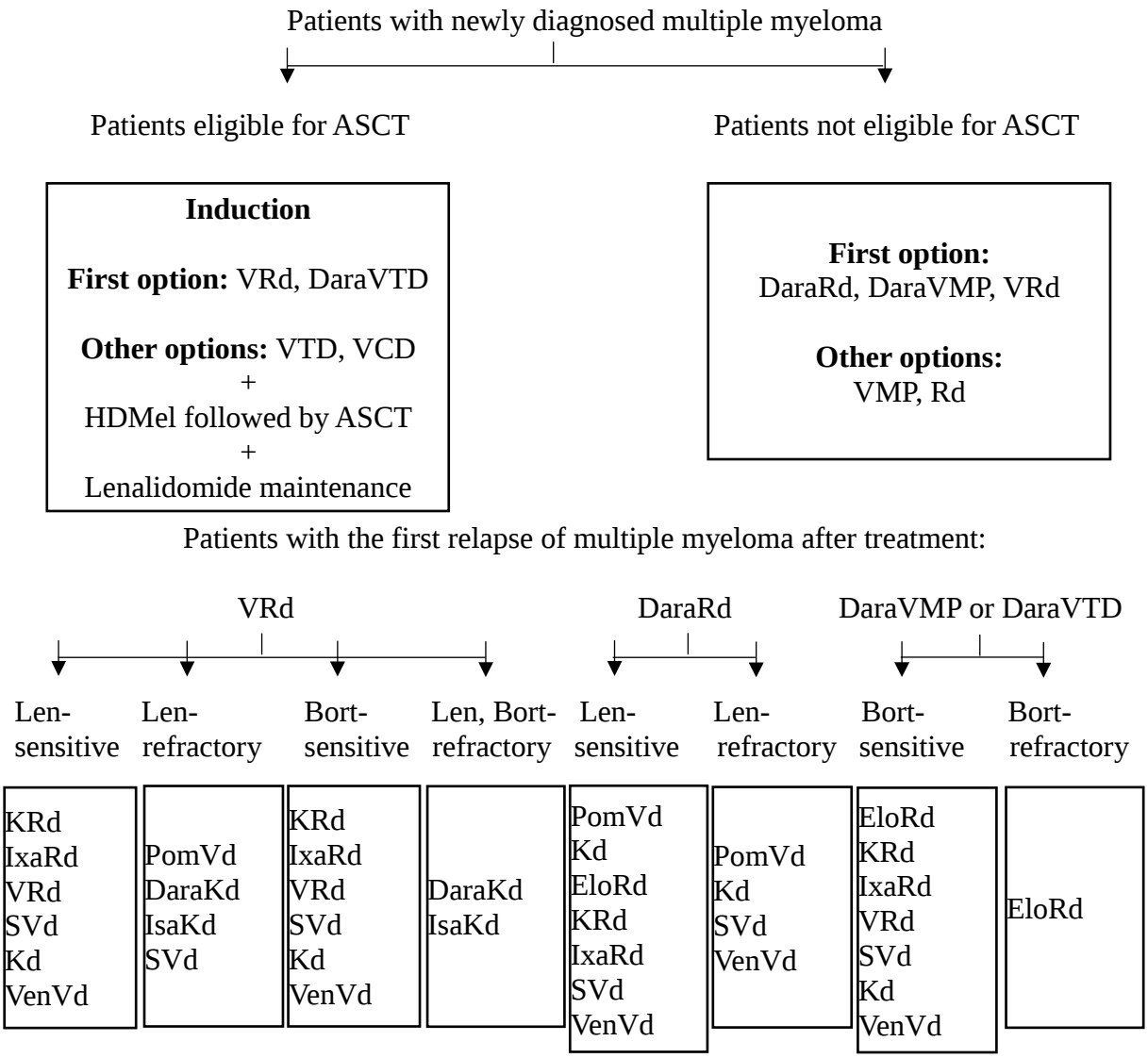

Figure 1. Multiple myeloma treatment recommendations according to European Hematology Association–European Society for Medical Oncology; ASCT — autologous stem cell transplantation; Bort — bortezomib; DaraKd — daratumumab, carfilzomib, dexamethasone; DaraRd — daratumumab, lenalidomide, dexamethasone; DaraVMP — daratumumab, bortezomib, melphalan, prednisone; DaraVTD — daratumumab, bortezomib, thalidomide, dexamethasone; EloRd — elotuzumab, lenalidomide, dexamethasone; HDMel — high-dose melphalan; IsaKd — isatuximab, carfilzomib, dexamethasone; IxaRd — ixazomib, lenalidomide, dexamethasone; Kd — carfilzomib, dexamethasone; KRd — carfilzomib, lenalidomide, dexamethasone; Len — lenalidomide; PomVd — pomalidomide, bortezomib, dexamethasone; Rd — lenalidomide, dexamethasone; SVd — selinexor, bortezomib, dexamethasone; VCD — bortezomib, cyclophosphamide, dexamethasone; VenVd —

venetoclax, bortezomib, dexamethasone; VMP — bortezomib, melphalan, prednisone; VRd — bortezomib, lenalidomide, dexamethasone; VTD — bortezomib, thalidomide, dexamethasone

Multiple myeloma is a malignant tumor that worsens patients' quality of life due both to the disease itself and to the consequences of adverse events (AEs) associated with the treatment used. Clinical symptoms of MM include impaired immune system function, impaired hematopoiesis, diseases of the skeletal system, and organ failure including kidney, heart, and nervous system [6]. Depending on the symptoms, patients with MM often require supportive treatment, including renal replacement therapy, treatment of hypercalcemia, analgesic treatment, and treatment of pathological bone fractures. An additional component of treating patients with MM is the treatment of the AEs that develop during anti-MM therapy.

In this article, we summarize the principles of supportive treatment and the principles of the prevention and treatment of the adverse events observed in the most commonly used methods of anti-MM treatment. Table I lists the most common AEs observed during the treatment of NDMM [7–11]. Tables II [12–19] and 3 [20-24] summarize the most common AEs observed in treating RRMM.

Table I. Incidence of serious adverse events (grade: ≥3) in treatment of newly diagnosed multiple myeloma identified in pivotal phase III clinical trials

Trial	**IFM2013-04 [7]**		**CASSIOPEIA [8]**		**SWOG S0777 [9]**		**MAIA [10]**		**ALCYONE [11]**	
Regimen	**VCD**	**VTD**	**VTD**	**Dara VTD**	**Rd**	**VRd**	**Dara Rd**	**Rd**	**DaraVMP**	**VMP**
Hematological adverse events, grade ≥3 [%]										
Neutropenia	33	19	15	28	21	19	50	35	40	39
Thrombocytopenia	11	5	7	11	14	18	NA	NA	34	38
Anemia	9	4	NA	NA	16	13	12	20	16	20
Non-hematological adverse events, grade ≥3 [%]										
Infections	NA	NA	20	22	14	19	32	23	23	15
Peripheral neuropathy	Grade 2–4:	Grade 2–4: 22	9	9	11	35	NA	NA	<2	4

	13									
Venous thromboembolism	2	2	NA	NA	9	8	NA	NA		
Skin rash	NA	NA	NA	NA	4	4	NA	NA	NA	NA
Secondary malignancy (any grade)	NA	NA	2	2	3	3	9	7	NA	NA
IRR (all grades)				4			3		4	

DaraRd — daratumumab, lenalidomide, dexamethasone; DaraVMP — daratumumab, bortezomib, melphalan, prednisone; DaraVTD — daratumumab, bortezomib, thalidomide, dexamethasone; IRR — infusion-related reactions; NA — not available; Rd — lenalidomide, dexamethasone; VCD — bortezomib, cyclophosphamide, dexamethasone; VMP — bortezomib, melphalan, prednisone; VRd — bortezomib, lenalidomide, dexamethasone; VTD — bortezomib, thalidomide, dexamethasone

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

Trial	**MM-003 [20]**		**OPTIMISM M [21]**		**APOLLO [22]**		**ICARIA-MM [23]**		**ELOQUENT-3 [24]**	
Regimen	**Dex**	**Pd**	**Vd**	**PVd**	**Pd**	**DaraPd**	**Pd**	**IsaRd**	**Pd**	**EloPd**
Hematological adverse events, grade ≥3 [%]										
Neutropenia	16	48	9	41	51	68	71	85	27	13
Thrombocytopenia	26	21	29	28	18	17	25	34	5	8
Anemia	37	33	14	14	21	17	29	35	21	20
Non-hematological adverse events, grade ≥3 [%]										
Febrile neutropenia	0	10	NA	NA	3	9	NA	NA	20	10
Infections	10	14	1	1	23	28	<1	5	22	13
Pneumonia			7	11	7	13	21	23	9	5
Peripheral neuropathy	NA	NA	4	9	NA	NA	NA	NA	NA	NA
Venous thromboembolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Skin rash	NA	NA	NA	NA	NA	NA	NA	NA	2	0
Cardiac disorders	NA	NA	NA	NA	NA	NA	NA	NA	4	7
IRR (all grades)						2		3		1

DaraPd — daratumumab, pomalidomide, dexamethasone; Dex — dexamethasone; EloPd — elotuzumab, pomalidomide, dexamethasone; IRR — infusion-related reactions; IsaRd —

isatuximab, pomalidomide, dexamethasone; NA — not available; Pd — pomalidomide, dexamethasone; PVd — pomalidomide, bortezomib, dexamethasone; Vd — bortezomib, dexamethasone

Prevention and supportive treatment in patients with MM

Treatment of hyperviscosity syndrome

Hyperviscosity syndrome (HVS) is a life-threatening condition found in c.2–6% of MM patients [25]. Clinical symptoms are most often seen when the concentration of monoclonal (M) protein in the immunoglobulin (Ig) M class is at least 30 g/L, IgA — 40 g/L, and IgG — 60 g/L (mean concentration of M protein: >40 g/L). The most common clinical symptoms of HVS are neurological symptoms including headache, dizziness, impaired consciousness, visual disturbances, central nervous system bleeding, somnolence, and coma. Other symptoms include coronary pain, dyspnea, pulmonary hypertension, and bleeding disorder symptoms. The treatment of HVS in MM involves plasmapheresis. In addition, anti-MM therapy should start as soon as possible, and be repeated for 3-5 consecutive days [26, 27].

Prevention and treatment of MM anemia

Anemia develops due to direct AE of clonal plasmacytes, chronic inflammation, kidney disease, and myelosuppressive effects of drugs. Anemia is found in at least 60–70% of NDMM patients and in more than 40% of patients who are RRMM [28]. Treatment of MM-related anemia includes red blood cell (RBC) transfusions and the use of erythropoiesis-stimulating agents (ESAs; epoetin, darbepoetin alfa). Red blood cell transfusions cause a rapid but transient increase in hemoglobin (Hb) level; therefore, this is recommended for the acute treatment of symptomatic anemia or in high-risk patients with asymptomatic anemia [29]. Importantly, the use of ESAs increases the risk of thromboembolic events, especially in patients treated with immunomodulatory drugs (IMiDs) combined with dexamethasone [30, 31]. On the other hand, a sustained increase in Hb concentration and a reduction in the need for RBC transfusion is achieved after using ESA [30]. For this reason, treatment with ESA should be administered only in accordance with international guidelines and having carried out a risk-benefit assessment.

Infection prevention while treating MM

Patients with MM have an increased risk of infection, especially in the early stages of diagnosis. This is due to the impairment of both humoral immunity (functional hypogammaglobulinemia) and cellular immunity and the applied anti-MM therapy, which has a myelosuppressive effect [32]

Bacterial infections

The risk of bacterial infections in patients with MM is significantly greater than in the healthy population [33]. This mainly concerns active NDMM patients, especially the elderly and people with recurrent infections. According to the ESMO and the European Myeloma Network (EMN), all MM patients should receive prophylactic antibiotic therapy during the first three months of anti-MM therapy. This is especially true for patients treated with lenalidomide and pomalidomide. As part of antibacterial prophylaxis, trimethoprim–sulfamethoxazole (TMP/SMX), amoxycillin, or quinolone is recommended [34–36]. The guidelines of the Stratification for Myeloma and Risk-Adapted Therapy (mSMART) and the International Myeloma Working Group (IMWG) also recommend prophylactic use of TMP/SMX during induction therapy of MM.

Viral infections

An increased risk of reactivation of Varicella-Zoster virus (VZV) is observed in patients with MM. Prophylaxis with acyclovir or its derivatives (famcyclovir, pencyclovir, and valacyclovir) is recommended in all MM patients treated with proteasome inhibitors (PIs) and monoclonal antibodies (MoAbs) [37, 38]. It is recommended to use prophylactic doses, usually 50% of the therapeutic dose.

The outcomes of treating MM patients with coronavirus disease 2019 (COVID-19) are relatively poor, with mortality ranging from 30% to 55% [39, 40]. Survival rates have improved with the advent of vaccines and new drugs including remdesivir, dexamethasone, and anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies. Nevertheless, the immune response to the applied vaccines in patients with MM is inconsistent, and is generally lower than in the general population [41].

Vaccinations

Vaccinations are essential in protecting immunocompromised MM patients from common pathogens such as influenza and pneumococcus. Vaccination against the influenza virus,

Streptococcus pneumonia, and Hemophilus influenza is recommended in patients with MM [42]. Patients undergoing ASCT should be revaccinated [43].

Prophylactic use of intravenous immunoglobulins

In severe humoral immunodeficiency, one may consider treatment with intravenous immunoglobulins (IVIg) at 0.4 g/kg body weight every four weeks. This applies to selected patients with recurrent bacterial infections and Ig deficiency [44–47].

Prophylaxis of neutropenia during MM treatment

Prophylactic use of granulocyte colony stimulating factor (G-CSF) is recommended in patients with MM treated with chemotherapy protocols associated with a high risk of febrile neutropenia (FN) and in patients with additional risk factors [48]. Additionally, G-CSF is recommended in patients who develop grade 3/4 neutropenia and/or FN due to treatment [49]. In clinical practice, G-CSF's intermittent or short-term use at an amount of 30 MU is usually sufficient. After an increase in the absolute neutrophil count (ANC) ≥1.0 G/L, treatment with the current doses may continue; if not, the start of treatment should be delayed until an increase in the ANC ≥1.0 G/L and the quantity of the drug should be reduced accordingly [50].

Prevention and treatment of venous thromboembolism in patients with MM

Venous thromboembolism (VTE) is a common complication. It is usually observed in the initial phase of MM treatment, and decreases in the period of MM remission or recurrence. VTE risk factors are presented in Table IV [51].

Table IV. Thrombosis risk factors and recommendations for use of antithrombotic prophylaxis according to International Myeloma Working Group guidelines

Risk factors		
Treatment-specific	**Patient-specific**	**Myeloma-specific**
Immunomodulatory drugs	Age	Active uncontrolled disease
High-dose dexamethasone	Previous VTE	Hyperviscosity
Erythropoietin	Infection	

Anthracyclines	Surgical procedures	
Multiagent chemotherapy	Cardiovascular comorbidities	
	Immobilization	
	Inherited thrombophilia	
	Central venous catheter	
Recomendations for thromboprophylaxis		
Risk factor	**Number of risk factors**	**Therapy**
Treatment-specific	≥1	LMWH or warfarin
Patient-specific	1	ASA
Myeloma-specific	1	ASA
Patient- or myeloma-specific	≥2	LMWH or warfarin

VTE — venous thromboembolism; LMWH — low molecular weight heparin; ASA — acetylsalicylic acid

An increased risk of VTE has been observed during treatment with IMiDs used both as monotherapy and combined with dexamethasone and other drugs such as carfilzomib and adriamycin or ESA [52, 53]. According to the IMWG recommendations, in patients with at least one treatment-specific, or at least two patient-specific or MM, risk factors for VTE, treatment with low-molecular-weight heparin (LMWH) or warfarin (target international normalized ratio 2–3) is recommended. However, acetylsalicylic acid (ASA) treatment is recommended in lower-risk patients. The optimal duration of antithrombotic prophylaxis has not yet been established. It is often recommended for 4–6 months, while ASA can be used chronically. The risk of developing VTE with lenalidomide maintenance treatment is low, and thromboprophylaxis is not required [52, 54, 55].

If a thromboembolic complication occurs, anti-MM treatment may be temporarily interrupted and restarted with concomitant therapy with warfarin or LMWH. New oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) are valuable in VTE treatment [56, 57].

Application of dialysis therapy in patients with MM

Renal impairment (RI) is diagnosed in 20–40% of patients with MM, with 2–4% requiring renal dialysis [58]. Kidney involvement occurs due to excessive secretion of serum-free light chains (sFLC) leading to foundry nephropathy, hypercalcemia, acute tubular necrosis, or acquired Fanconi syndrome. Current data supports high-cutoff hemodialysis (HCO-HD)

combined with anti-MM therapy. In combination with anti-MM therapy, HCO-HD leads to a sustained reduction in FLC concentration in 67% of patients and leads to independence from dialysis in 63% of patients [59].

Prevention and treatment of bone disease in course of MM

Osteolytic lesions can cause skeletal-related severe events (SREs) such as hypercalcemia, pain, and fractures requiring surgery or radiotherapy. Osteolytic changes are detected by X-ray examination of the skeletal system in at least 80% of MM patients [60]. SREs are found in 40% of NDMM patients and in more than 20% of patients with RRMM. At MM diagnosis, pathological fractures and compression fractures are diagnosed in 26% and 22% of patients, respectively. In 58% of patients with NDMM, pain is present during bone disease [28]. As a result of compression of the nerves in the spinal cord, neurological symptoms may develop, including decreased sensation or numbness in the extremities. Spinal cord compression caused by a MM tumor or bone fractures that compress the spinal cord can occur. Local and systemic treatment is used in the treatment of bone changes. Radiotherapy can treat pain or pressure on the spinal cord. In the case of compression fractures of the vertebrae, kyphoplasty is performed, and surgery is performed in the case of fractures of long bones or instability of the spine. Two groups of drugs are used to treat systemic treatment and prevent the occurrence of SREs: bisphosphonates (BP) and denosumab, an inhibitor of the kappa-B nuclear ligand–receptor RANKL (receptor activator for nuclear factor κB ligand). Pamidronic acid (PA) and zoledronic acid (ZA) are the BPs used to treat bone disease [61]. Particular caution should be exercised when treating BPs in patients with MM and RI (creatinine clearance: 30–60 mL/min). Zoledronic acid is a BP recommended for use in all MM patients, regardless of the presence of bone disease in imaging tests. In addition, this drug is recommended for use in patients with asymptomatic biochemical recurrence of MM. The use of ZA is limited in patients with RI [62, 63]. In such cases, an alternative may be denosumab, a MoAb that inhibits RANKL activation. The effectiveness of denosumab is comparable to that of ZA at the time of the first SRE [64]. Hypocalcemia is more frequent with denosumab treatment than with ZA treatment (17% vs. 12%), but conversely renal adverse events are less frequent (10% vs. 17%). For this reason, denosumab is recommended for treating MM patients with RI [65–67]. Another indication for denosumab treatment is BPs-resistant hypercalcemia.

It is worth noting that since its approval the use of denosumab in MM has increased rapidly, irrespective of renal function or BP intolerance, mainly due to the advantages of

subcutaneous administration. Denosumab, like ZA, does not show anti-MM activity in the case of disease recurrence, but is effective in inhibiting bone resorption markers.

Other treatments for bone disease in the course of MM include surgery, vertebroplasty, and radiotherapy.

Surgical treatment is indicated in the case of high-risk long bone fractures and compression fractures of the vertebrae. Vertebroplasty and balloon kyphoplasty effectively reduce pain resulting from compression fractures of the vertebrae. Radiotherapy is the treatment of choice for solitary plasmacytoma. More than 90% of patients respond to topical therapy. Low-dose radiotherapy (8 Gy × 1 fx or 10–30 Gy × 2–3 fx) can be used for uncontrolled bone pain, impending spinal compression, and pathological fractures [67].

Prevention and treatment of peripheral neuropathy in course of MM

Peripheral neuropathy (PNP) can be seen in MM and can also develop with IMiDs, PIs, and histone deacetylase inhibitor (HDACi) treatment, an incidence rising to 19% in NDMM [68]. Thalidomide can cause severe and, in most cases irreversible, PNP, especially in patients with existing PNP. Thalidomide-induced PNP appears to be cumulative and persistent toxicity, unlike bortezomib-induced PNP, which typically occurs within the first five treatment cycles and is rarely observed later [69]. PNP development is more likely to occur during treatment with intravenous bortezomib than with subcutaneous administration. The most common PNP is sensory, very rarely motor. We have clearly defined guidelines for dose reduction of bortezomib based on the intensity of PNP. Anticonvulsants (gabapentin and pregabalin), antidepressants, and analgesics mainly treat PNP and neuropathic pain symptoms.

Other anti-MM agents, including other PIs (ixazomib, carfilzomib), and other IMiDs (lenalidomide, pomalidomide), are less likely to cause neurotoxicity [70].

Occurrence and treatment of skin lesions during MM therapy

Skin changes, including rashes, are among the most commonly observed AEs during treatment with IMiDs. Rash (of any grade) has been reported in approximately a quarter of lenalidomide-treated patients and most often develops within the first month of treatment [71]. Such rashes have been rarely observed and are primarily mild during treatment with bortezomib. In combination with antihistamines, topical corticosteroids treat mild and moderate rash [72]. In contrast, the discontinuation of lenalidomide treatment and the

initiation of systemic corticosteroid therapy is recommended to treat a severe rash. The changes usually go away after one or two weeks, and most patients tolerate re-treatment with lenalidomide and switching from dexamethasone to prednisone. The reappearance of rash is a contraindication to lenalidomide treatment [72].

Prophylaxis and treatment of cardiovascular complications

Cardiovascular diseases are diagnosed in over 60% of patients at the time of MM diagnosis, the most common being cardiac arrhythmias, ischemic disease, and congestive heart failure. Additionally, more than 70% of patients develop cardiac complications during the treatment of newly diagnosed and recurrent MM [73]. Drugs used in treating MM with AEs on the heart are anthracycline antibiotics, IMiDs, or PIs. Acute cardiac events during treatment with doxorubicin include arrhythmias and ECG abnormalities. Left ventricular failure and the development of congestive heart failure occur in c.1–2% of patients and increase with cumulative dose of the drug [74]. The pegylated liposomal form of doxorubicin reduces cardiotoxicity compared to the classic form. In contrast, using pegylated liposomal doxorubicin in combination with bortezomib causes cardiac severe adverse events in 2% of patients [75].

Immunomodulatory drugs can induce cardiac arrhythmias, including sinus bradycardia and atrioventricular block, and increase the risk of thromboembolic events. Thalidomide causes sinus bradycardia in 5% of patients [76]. Another serious complication of treatment with thalidomide is the development of pulmonary arterial hypertension (PAH), which occurs in 4.8% of patients and correlates with structural heart disease and PAH [77]. In phase III clinical trials with IMiDs (lenalidomide, pomalidomide) in combination with dexamethasone, heart failure (grade ≥3) was found in 2–8% of patients [12–15, 24]. On the other hand, the use of thalidomide in combination with bortezomib and dexamethasone in inducing treatment causes serious cardiac events (grade ≥3) in 8% of patients [78].

The causes of cardiotoxicity caused by PIs are still not fully understood. One of the mechanisms may be the inhibition of the sarcomeric turnover protein, resulting in the death of myocytes [79]. The incidence of heart failure (all grades) in patients treated with bortezomib ranges from 2% to 17.9%, depending on the clinical trial [80]. Carfilzomib is a PI used in Europe to treat RRMM. In phase III studies, heart failure (grade ≥3) was observed in 2–4% of carfilzomib-treated patients [12, 16, 81] and in 0–7.5% of bortezomib-treated patients [9, 82–84]. In the ENDEAVOR study, heart failure (grade ≥3) was observed in 2.8% of patients

treated with carfilzomib in combination with dexamethasone and in 0.7% of patients treated with bortezomib plus dexamethasone [16]. In patients treated with ixazomib, the development of arterial hypertension has been found in 5% of patients [85]. In the TOURMALINE-MM1 study, in a group of patients treated with Ixa-Rd (ixazomib, lenalidomide, dexamethasone) versus Rd, heart failure, arrhythmias, hypertension, and myocardial ischemia were found in 4% of both groups, 16% versus 15%, 6% versus 5%, and 1%, respectively versus 2% of patients [13].

In Europe, bortezomib is approved for the treatment of both NDMM and RRMM, while carfilzomib and ixasomib are used to treat RRMM.

Angiotensin-converting enzyme (ACE) inhibitors and beta-blockers are drugs recommended for treating symptomatic heart failure with reduced ejection fraction. An additional option is using a mineralocorticoid receptor antagonist; an angiotensin receptor nepresin inhibitor, and ivabradine. If optimal pharmacological treatment is not practical, cardioverter-defibrillator implantation may be considered [86].

Arterial hypertension is diagnosed in 38% of patients at the time of myeloma diagnosis [87]. It is found relatively often in patients treated with PIs. In phase III studies, in a group of patients with RRMM, the development of arterial hypertension (grade ≥3) was found in 0–4% of patients treated with bortezomib, in 3–15% of patients treated with carfilzomib [12, 16, 81], and in 5% of patients treated with ixasomib in combination with Rd [85].

Arterial hypertension develops in 5% of patients treated with daratumumab and in less than 7% of patients treated with daratumumab plus bortezomib and dexamethasone [88]. In the treatment of grade I hypertension, thiazides are recommended, and grade II a diuretic plus an ACE inhibitor or an angiotensin receptor blocker or a beta-blocker is the recommendation [89].

Prevention and treatment of most common AEs observed during treatment with MoAbs

In 2015, the US Food and Drug Administration (FDA) approved the first anti-CD38 monoclonal antibody for treating MM, daratumumab. Another anti-CD38 MoAb is isatuximab. Isatuximab, based on the results of the phase III ICARIA-MM study, has been approved by the FDA and European Medicines Agency (EMA) for use in combination with Pd in the therapy of RRMM. The anti-SLAM7 monoclonal antibodies (elotuzumab) and anti-B-cell maturation antigen are also used to treat MM (anti-BCMA, belantamab mafodotin).

Many clinical trials have been carried out with these drugs in recent years, and they are currently used to treat NDMM and RRMM.

Reactions related to infusion of MoAbs

Daratumumab treatment in monotherapy and combination therapy has a favorable safety profile. Most infusion-related reactions (IRR, 96%) are observed with the first infusion. The most commonly observed AEs are fatigue, nausea, anemia, back pain, cough, upper respiratory tract infection, thrombocytopenia, and neutropenia. Reactions related to daratumumab infusion have been observed in 48% of patients and include nasal congestion, cough, allergic rhinitis, throat irritation, and dyspnea. Antihistamines, corticosteroids, and acetaminophen have been used to treat infusion-related reactions [90]. In the POLLUX clinical trial, daratumumab IRR were observed in 47.7% of patients; they were most often mild and occurred during the first infusion [14]. A similar incidence of IRR was seen in the CASTOR study, which used daratumumab in combination with bortezomib and dexamethasone (DVd). Daratumumab IRR occurred in 45.3% of patients and occurred mainly during the first infusion [17]. In both the POLLUX and the CASTOR studies, dexamethasone 20 mg intravenously/orally or an equivalent long-acting corticosteroid, acetaminophen 650–1,000 mg intravenously/orally, and an intravenous/oral antihistamine (diphenhydramine in 25–50 mg or equivalent) were used.

Rarely, mild (grade I/II) AEs develop during treatment with elotuzumab. The most common symptoms are chills, fatigue, fever, cough, headache, anemia, nausea, and back pain. One of the most frequently reported AEs is an IRR, found in fewer than 60% of patients during the first elotuzumab infusion in a Phase I study. With subsequent infusions of elotuzumab, IRRs were observed in half of them. No severe IRR was observed after changing the infusion rate of elotuzumab and using methylprednisolone, diphenhydramine, and acetaminophen. Grade I/II infusion reactions resolved spontaneously, usually within 24 hours [91].

In the Phase III clinical trial, ELOQUENT-2, which compared EloRd (elotuzumab, lenalidomide, dexamethasone) to Rd, diphenhydramine (dose: 25–50 mg) or its equivalent, ranitidine (dose: 50 mg) or equivalent, and acetaminophen (dose: 650–1,000 mg) were used before starting the elotuzumab infusion. Infusion-related reactions were reported in 33 patients, including 29 with grade I/II. Most infusion-related reactions (70%) were observed after the first dose of elotuzumab [15]. To prevent an IRR to elotuzumab, the administration

of diphenhydramine and ranitidine or their equivalents, as well as acetaminophen, is recommended c.30–60 minutes before the start of elotuzumab infusion and administration of elotuzumab 10 mg/kg body weight (in 250 mL), starting with flow 0.5 mL/min [92].

Infusion-related reactions with belantamab mafodotin (BM) are rare and usually grade I/II. If grade II or higher infusion reactions occur during the BM infusion, the infusion rate should be reduced or stopped, depending on the severity of the symptoms. If a grade II or higher IRR occurs, premedication should be initiated before the next infusion. If a grade II IRR occurs, the infusion should be interrupted, supportive treatment started, and when symptoms resolve, infusion should be continued at a rate reduced by at least 50%. However, if grade III/IV IRRs occur, the infusion should be stopped and supportive care given. After symptoms have resolved, the infusion can be continued at a reduced rate of at least 50%. If an anaphylactic or life-threatening infusion-related reaction occurs, the infusion should be stopped and appropriate emergency measures started [93].

Prevention and treatment of keratopathy during BM therapy

Belantamab mafodotine is an antibody-drug conjugate approved for the treatment of RRMM. It is an agent against the B-cell maturation antigen (BCMA). Treatment with BM is associated with a high incidence of ocular complications, including keratopathy (≥20%) [85]. In the Phase I DREAMM-1 clinical trial, 53% of patients in the first part, and 63% of patients with MM in the second part of the study, had corneal AEs [94]. In contrast, in the randomized phase II clinical trial, DREAMM-2, keratopathy (grade III/IV) was observed in 31% of RRMM patients treated with BM 2.5 mg/kg body weight monotherapy and 34% of RRMM patients treated with BM in 3.4 mg/kg body weight [95, 96]. In the DREAMM-6 study, 83% of patients experienced keratopathy in the combination of BM with bortezomib and dexamethasone in RRMM [97]. To reduce the risk of keratopathy incidence, an ophthalmological examination to assess vision is recommended before initiating treatment with BM and then again during treatment (assessment of AEs). Dose reduction or interruption of therapy with BM depends on the severity of ocular toxicity, including blurred vision, dry eyes, and corneal ulceration. BM should be discontinued if ocular toxicity is severe. BM dose modifications based on AEs in the cornea are summarized in Table V [93].

Table V. Belantamab mafodotin dose modifications based on corneal adverse events

Category	**Eye examination findings**		**Belantamab mafodotin dose modification**
	Corneal examination finding(s)	**Change in BCVA**	
Mild	Mild superficial keratopathy	Decline from baseline of 1st-line on Snellen Visual Acuity	Continue treatment at current dose
Moderate	Moderate superficial keratopathy	Decline from baseline of 2 or 3 lines (and Snellen Visual acuity not worse than 20/200)	Withhold treatment until improvement in examination findings and BCVA to mild severity or better Consider resuming treatment at a reduced dose of 1.9 mg/kg body weight
Severe	Severe superficial keratopathy Corneal epithelial defect	Change in BCVA: decline from baseline of more than three lines	Withhold until improvement in examination findings and BCVA to mild severity or better For worsening symptoms that are unresponsive to appropriate management, consider discontinuation

BCVA — best corrected visual acuity

Adverse events in CAR-T therapy

The introduction to therapy of CAR-T has significantly changed the prognosis of patients with B-cell malignances, including patients with MM. CAR-T can cause numerous AEs, including life-threatening ones such as cytokine-release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) [98]. CRS (grade III/IV) is found in 6–38% of patients and ICANS (grade III/IV) in 3–12% of patients [99–102]. The main symptoms of CRS include pyrexia, hypotension, hypoxia, and organ toxicity, which may result in organ failure. However, the main symptoms of ICANS are a disturbance in concentration, cognitive

impairment, confusion, agitation, tremors, lethargy, aphasia, delirium, somnolence, convulsions, motor weakness, and paresis or signs of intracerebral pressure. ICANS development most often occurs during or after CRS and in c.10% of cases up to four weeks after CAR-T infusion.

For early detection, it is recommended to perform a neurological assessment at least twice daily using the Immune Effector Cell-Associated Encephalopathy (ICE) screening tool [98]. It is currently believed that pro-inflammatory interleukin-6 (IL-6) plays a crucial role in the pathogenesis of CRS [103]. A recent study identified mbaIL-6 expression on the surface of T cells that was associated with the rapid clearance of IL-6 from the cell culture supernatant. T lymphocytes co-expressing mbaIL-6 and anti-CD19 CAR neutralized macrophage-derived IL-6, retaining antitumor activity *in vitro* and the xenograft model. Another strategy is to turn on 'suicidal' switches such as constructs containing CAR and inducible caspase 9. The administration of a small molecule that dimerizes inducible caspase 9 resulted in CAR-T specific apoptosis and depletion [104].

Other side effects during CAR-T treatment are hemophagocytosis and prolonged cytopenia. Neutropenia (grade III/IV) has been reported in 85–100% of patients and thrombocytopenia (grade III/IV) in 28–69% of patients [99–102].

Conclusions

In the past, dosages of anti-MM drugs and durations of treatment were determined by AEs, especially myelosuppression or PNP. The introduction of new anti-MM drugs has led to the development of highly effective treatment regimens for MM. Better understanding of the role of drug toxicity in early and late AEs is important due to the shift from short-term to chronic treatment. Treatment of a patient with MM should be based not only on the characteristics of the disease, but also on patient factors including age, general condition, comorbidities, and AEs of previous treatment.

In the treatment of MM, a very important role is played by the management of AEs, including regular monitoring and prompt and appropriate intervention in the event of treatment-related AEs, based on scientific knowledge, applicable guidelines, and clinical experience.

Conflicts of interest

None.

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Ethics

The work described in this article has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; and Uniform Requirements for manuscripts submitted to biomedical journals.

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Table 2. Incidence of serious adverse events (grade: ≥3) in treatment of relapsed/refractory multiple myeloma in pivotal phase III clinical trials

Trial	**ASPIRE [12]**		**TOURMALINE-MM1 [13]**		**POLLUX [14]**		**ELOQUENT-2 [15]**		**ENDEAVOR [16]**		**CASTOR [17]**		**CANDOR [18]**		**CLARION [19]**	
Regimen	Rd	KRd	Rd	IxaRd	Rd	DaraRd	Rd	EloRd	Kd	Vd	Vd	DaraVd	Kd	DaraKd	KMP	VMP
Hematological adverse events, grade ≥3 [%]																
Neutropenia	27	31	24	23	42	55	45	36	NA	NA	5	14	6	8	23	29
Thrombocytopenia	13	17	9	19	16	15	21	21	9	9	33	46	16	24	15	21
Anemia	17	19	13	9	21	18	21	20	14	10	16	15	14	17	17	14
Non-hematological adverse events, grade ≥3 [%]																
Pneumonia	12	16	NA	2	10	15	26	33	6	7	10	10	8	13	10	7
Peripheral neuropathy	3	3	2	2	NA	NA	NA	NA	1	5	7	4	0	1	<1	8
Diarrhea	4	5	NA	NA	4	10	5	6	0	<1	1	4	<1	4		
Cardiac disorders	4	7	2	3	NA	NA	8	5	6	<3	NA	NA	11	7	10	4
Hypertension	2	4	1	3	NA	NA	NA	NA	9	3	<1	7	14	18	9	3
IRR (all grades)						5		1				9				

DaraKd — daratumumab, carfilzomib, dexamethasone; DaraRd — daratumumab, lenalidomide, dexamethasone; DaraVd — daratumumab, bortezomib, dexamethasone; EloRd — elotuzumab, lenalidomide, dexamethasone; IRR — infusion-related reactions; IxaRd — ixazomib, lenalidomide, dexamethasone; Kd — carfilzomib, dexamethasone; KMP — carfilzomib, melphalan, prednisone; KRd — carfilzomib,

lenalidomide, dexamethasone; NA — not available; Rd — lenalidomide, dexamethasone; Vd — bortezomib, dexamethasone; VMP — bortezomib, melphalan, prednisone