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ORIGINAL PAPER

Multiple myeloma: management of adverse events

F. Gay · A. Palumbo

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Abstract The combination of conventional chemotherapy or dexamethasone with new drugs, such as immunomodulatory agents and proteasome inhibitors, has substantially changed the treatment paradigm of myeloma patients. New drugs have been incorporated in pre-transplant induction regimens and post-transplant consolidation and maintenance strategies for young patients; in elderly patients, standard melphalan and prednisone (MP) plus thalidomide or plus bortezomib are now considered standards of care, and ongoing trials are assessing if lenalidomide plus standard MP or plus low-dose dexamethasone may be other options. The efficacy of these drugs needs to be balanced against their toxicity. Different drugs have a different toxicity profile. The choice for the best treatment strategy for every single patient should be based on results of scientific randomized studies but tailored to account for patient's biological age, comorbidities, and the expected toxicity profile of different regimens. Prompt dose reduction and accurate management of treatment-related toxicity can greatly reduce early discontinuation rate and significantly improve treatment efficacy. This chapter will focus on frequency and management of main adverse events in newly diagnosed and relapsed myeloma patients and will provide guidelines for dose reductions and supportive therapy.

Keywords Myeloma · Adverse events · Therapy · New drugs

F. Gay · A. Palumbo (✉)
Divisione di Ematologia dell'Università di Torino, Azienda Ospedaliera S. Giovanni Battista, Ospedale Molinette, Via Genova 3, 10126 Torino, Italy
e-mail: appalumbo@yahoo.com

F. Gay
e-mail: francescam_gay@yahoo.it

Introduction

In patients eligible for autologous stem cell transplant (ASCT), combination regimens including high-dose dexamethasone plus thalidomide (TD) [1–3], or high-dose dexamethasone plus lenalidomide (RD) [4, 5], or high-dose dexamethasone plus bortezomib (VD) [6] have been used as induction regimens. Randomized trials have demonstrated superior response rate and survival in patients treated with high-dose therapy compared to conventional chemotherapy [7]. In patients not eligible for ASCT, standard melphalan and prednisone (MP) plus thalidomide (MPT) [8, 9] and plus bortezomib (MPV) [10] are both superior to MP alone and are now considered standards of care. Ongoing trials will determine if lenalidomide plus MP (MPR) or plus low-dose dexamethasone (Rd) may be other options. In relapsed patients, RD, VD, and bortezomib plus pegylated-liposomal-doxorubicin have received the Food and Drug Administration (FDA) approval based on the results of randomized trials [11–14]. Preliminary results suggest also the efficacy of TD compared to high-dose dexamethasone [15]. Standard treatment should always be supported by the evidence of improved progression-free survival, provided by randomized trials. Treatment choice should however account for patient's biological age, comorbidities, and the expected toxicity profile of different regimens. Prompt dose reduction in case of adverse events (AEs) can significantly reduce early discontinuation rate and consequently improve treatment efficacy. Besides, dose reduction in elderly patients can be appropriate even in the absence of toxicity, according to patient age (Table 1). This article will provide an overview of the main AEs in multiple myeloma (MM) patients, focusing mainly on AE related to the use of new drugs in combination regimen of consolidate efficacy; furthermore, it will provide indications for management and

Table 1 Dose reductions according to age in elderly myeloma patients

	65–75 years	>75 years	Further dose reduction
Dexamethasone (mg weekly)	40	20	10
Melphalan	0.25 mg/kg on days 1–4	0.18 mg/kg on days 1–4	0.13 mg/kg on days 1–4
Thalidomide (mg/day)	200	100	50
Lenalidomide in combination with dexamethasone	25 mg on days 1–21	15 mg on days 1–21	10 mg on days 1–21
Lenalidomide in combination with melphalan	10 mg on days 1–21	5 mg on days 1–21	5 mg every other day on days 1–21
Bortezomib	1.3 mg/m^2 twice-weekly	1.3 mg/m^2 weekly	1.0 mg/m^2 weekly

dose reductions (Table 2). A brief section on management of bone pain and skeletal complications is included in this article, since these are frequent complications of MM, although not related to therapy.

Hematologic toxicity

Neutropenia

Neutropenia is a common AE of lenalidomide and alkylating agents. The incidence of grade 3–4 neutropenia in relapsed patients treated with RD ranged from 30 to 46% [13, 14, 16] and was significantly higher in patients who had received prior treatment with ASCT [17] and in patients with impaired renal function [16, 18]. In newly diagnosed patients, grade 3–4 neutropenia was reported in 21% of patients receiving RD [19] and raised to 52% of patients receiving MPR, due to the addiction of melphalan [20]. Severe neutropenia is less frequent (15%) in relapsed patients treated with bortezomib alone [11, 12], but increases in combination including chemotherapy agents (30% in relapsed patients treated with bortezomib plus pegylated-liposomal-doxorubicin [12] and 40% in newly diagnosed patients receiving VMP) [10, 21, 22]. Thalidomide itself can induce mild neutropenia in 3–15% of patients [23]; the frequency increases when myelotoxic chemotherapy is added (with MPT treatment in newly diagnosed patients, grade 3–4 neutropenia is reported in 16–48% of cases) [8, 9].

Neutropenic patients are at higher risk of infections. The use of granulocyte-colony stimulating factor (G-CSF) is an effective and safe method to prevent and decrease the occurrence and the severity of neutropenia. In case of grade 4 neutropenia (neutrophilic count $< 500/mm^3$) during the cycle, it is recommended to stop treatment and add G-CSF until the neutrophilic count is $> 1000/mm^3$; in case of repeated grade 4 neutropenia despite G-CSF administration treatment should be withheld until the toxicity resolves to at least grade 2 (neutrophilic count $\geq 1000/mm^3$), when treatment can be restarted after appropriate dose reduction. If the neutrophilic count is $< 1500/mm^3$ on the first day of a new cycle, RD should be withheld and treatment should be restarted at lower dose when at least grade 1 toxicity (neutrophilic count $> 1500/mm^3$) is reached. Prophylaxis with G-CSF is recommended for the prevention of febrile neutropenia in patients at high risk on the basis of age, medical history, disease characteristics, and the expected myelotoxicity of the treatment regimen. In case of multiagent chemotherapy regimens where the expected rate of neutropenia is high, the use of pegylated G-CSF should be considered.

Anemia

Anemia is more commonly related to myeloma and generally improves with disease response to therapy. Incidence of grade 3–4 anemia in different combination regimens, including novel agents plus dexamethasone or plus MP, ranges from 3 to 19% [3, 8–14, 20]. Erythropoiesis stimulating agents (ESAs) can be prescribed to treat chemotherapy-associated anemia, and iron supplements can improve treatment effectiveness. ESAs are recommended when the hemoglobin concentration is < 9 g/dl; for patients with heart disease or those who have difficulties undertaking regular daily activities, treatment can begin earlier (hemoglobin 10–12 g/dl). The ESA dose should be adjusted to maintain a hemoglobin concentration of 11–12 g/dl, to avoid blood transfusion and anemia-related symptoms. Hemoglobin concentration > 12 g/dl in cancer patients creates serious health problems, in particular an increased risk of thrombosis, in patients at high risk for developing clots. The benefits of these drugs need to be carefully weighed against the risks.

Thrombocytopenia

Thrombocytopenia is quite common in patients treated with lenalidomide, bortezomib, and alkylating agents. In relapsed setting, grade 3–4 thrombocytopenia is reported in about 10–12% with RD regimen [13, 14], in 15–30% with bortezomib alone [11, 12], and in 22% of patients receiving bortezomib plus pegylated-liposomal-doxorubicin [12]. In newly diagnosed patients, grade 3–4 thrombocytopenia was reported in 23% of patients receiving MPR [20], and in 21–38% of patients receiving VMP [10, 21, 22]. Thalidomide rarely induce thrombocytopenia [23], that is generally

Table 2 AEs management in myeloma patients treated with novel agents

AE	Anti-myeloma agent	AE grade	Dose reduction	Management
Hematologic toxicity				
Neutropenia	Lenalidomide-based regimens	Uncomplicated grade 4 (ANC $< 500/mm^3$) or grade 2–3 (ANC: 500–$1000/mm^3$) complicated by infection	25–50% reduction	G-CSF until neutrophil recovery
Thrombocytopenia	Bortezomib and lenalidomide-based regimens	Grade 4 (PLTs $< 25000/mm^3$)	25–50% reduction	Platelet transfusion
Anemia	Bortezomib and lenalidomide-based regimens	Grade 2–4 (Hgb $\leq$ 10 g/dl)	25–50% reduction[a]	Erythropoietin or darbepoietin
Extra-hematologic toxicity				
Infection	Bortezomib, lenalidomide, and thalidomide-based regimens	Grade 3–4	25–50% reduction	Prophylaxis: trimetoprin-cotrimoxazole for *Pneumocytis carinii* during high-dose dexamethasone; acyclovir or valacyclovir for HVZ prophylaxis during Bortezomib-based therapy; consider antibiotic prophylaxis
Neurotoxicity	Bortezomib-based regimens	Grade 1 with pain or grade 2 peripheral neuropathy	25–50% reduction	Neurological assessment before and during treatment; consider symptomatic treatment with gabapentin, pregabalin, vitamin B complex compounds, amitryptilin, or L-carnitina
		Grade 2 with pain or grade 3 peripheral neuropathy	Dose interruption until peripheral neuropathy resolves to grade 1 or better; restart at 50% dose reduction	
		Grade 4 peripheral neuropathy	Treatment discontinuation	
	Thalidomide-based regimens	Grade 2 peripheral neuropathy	50% dose reduction	
		Grade 3–4 peripheral neuropathy	Treatment discontinuation until peripheral neuropathy resolves to grade 1; restart at 50% dose reduction	
Cutaneous toxicity	Thalidomide and lenalidomide-based regimens	Grade 3–4	Interruption	Steroids and antihistamines
		Grade 2	50% reduction	
Gastrointestinal toxicity	Thalidomide and bortezomib-based regimens	Grade 3–4	Interruption	Appropriate diet, exercise, hydration, antidiarrhetic drugs in case of diarrhea, laxatives in case of constipation
		Grade 2	50% reduction	

Table 2 continued

AE	Anti-myeloma agent	AE grade	Dose reduction	Management
Thrombosis	Thalidomide and lenalidomide-based regimens	All grade	Drug temporary interruption and full anticoagulation, then resume treatment	No or one individual/myeloma thrombotic risk: aspirin 100–325 mg; two or more individuals/myeloma risk factors or patients who receive high-dose dexamethasone or doxorubicin or multiagent chemotherapy: LMWH or full-dose warfarin
Renal toxicity	Lenalidomide	Creatinine clearance: 30–60 ml/min	10 mg/day	Correct precipitant factors (dehydration, hypercalcemia, hyperuricemia, urinary infections, and concomitant use of nephrotoxic drugs)
		Creatinine clearance < 30 ml/min; no dialysis	15 mg every other day	
		Creatinine clearance < 30 ml/min; dialysis	5 mg/day after dialysis	

ANC absolute neutrophilic count, *PLTs* platelets, *G-CSF* granulocyte colony-stimulating factor, *Hgb* hemoglobin, *HVZ* herpes-varicella-zoster, *LMWH* low-molecular-weight heparin

[a] For grade 3–4 only

mainly related to the concomitant use of alkylating agents in combination regimens (with MPT, grade 3–4 thrombocytopenia is reported in 3–14% of patients) [8, 9].

In case of grade 4 thrombocytopenia (platelet count $< 25000/mm^3$) treatment should be stopped and then restart when the toxicity resolves to at least grade 2 (platelet count $\geq 50000/mm^3$) after appropriate dose reduction of the myelotoxic drug.

Extra-hematologic toxicity

Infections

Myeloma patients are at increase risk of infection due to the disease itself and its therapy. The risk is higher during the first 3 months but decreases with disease response to therapy. Chemotherapy-related neutropenia and prolonged treatment with high-dose steroids further increase the risk. In relapsed patients treated with RD, grade 3–4 infections are reported in 10–22% of patients [13, 14]. In newly diagnosed patients, the incidence was similar but significantly drop off with the use of low-dose dexamethasone (Rd regimen) (from 16 to 9%, $P = 0.04$) [4]; in patients treated with MPR severe infections are reported in about 10% of cases [20]. Patients treated with bortezomib, in both the relapse and newly diagnosed settings, presented a similar rate of grade 3–4 infections, ranging from 2 to 13% in different studies, regardless of the concomitant use of steroids or chemotherapy [10–12, 21, 22]. Bortezomib therapy has been correlated to a high risk of HVZ infections [24], as confirmed in the VMP versus MP trial, where patients treated with VMP had a higher incidence of HVZ than patients treated with MP alone (14 vs. 4%); of notice, incidence among patients receiving acyclovir prophylaxis was 3% only [10]. Similar rate of grade 3–4 infections is reported in thalidomide-treated patients (7% of patients receiving TD [3] and 10–14% of patients treated with MPT [8, 9]).

The strategy to prevent and manage infections depends on the clinical situation. Neutropenic patients who developed fever should be thought to seek medical care within 3 h. Fever should be treated with broad-spectrum antibiotics. Intravenous antibiotics are indicated in case of severe systemic infection. Prophylactic trimethoprim-sulphamethoxazole is recommended at least during the first 2 months of chemotherapy or during steroid administration, and acyclovir prophylaxis is indicated for all patients receiving bortezomib-based therapy. Routine antibiotic prophylaxis could be considered for the first 3 months of therapy; it is indicated particularly in patients receiving high-dose dexamethasone, in elderly patients, in patients with comorbidities that increase the risk of infections (i.e., chronic obstructive pulmonary disease, diabetes) and in patients with an increase

infection rate. Nephrotoxic antibiotics (such as aminoglycosides) should be avoided, whenever possible, in myeloma patients with compromised renal function.

Peripheral neuropathy

Peripheral neuropathy is rare at presentation in myeloma patients; when present it is more commonly related to amyloidosis or osteosclerotic myeloma. This AE is frequently reported with bortezomib and thalidomide therapies, and rarely with lenalidomide treatment. Incidence of grade 3–4 neuropathy is similar in thalidomide or bortezomib-based regimen, in both relapsed and newly diagnosed patients (from 3 to 13%) [3, 8–12, 21, 22]. In a randomized trial comparing VMP to VMP plus thalidomide (VMPT), incidence of peripheral neuropathy was higher in patients treated with both thalidomide and bortezomib but, when the standard twice-weekly infusion of bortezomib (1.3 mg/m^2 on days 1, 4, 8, and 11) was reduced to a weekly schedule (1.3 mg/m^2 on days 1, 8, 15, 22), the incidence of grade 3–4 peripheral neuropathy was significantly reduced from 24 to 6% in the VMPT group and from 14 to 2% in the VMP group [22]. Both thalidomide and bortezomib-related neuropathies are cumulative and dose dependent [23, 25]. Prompt dose reduction and discontinuation increase the probability of recovery. Since there are currently no effective medications known to relieve neuropathic symptoms, dose and treatment schedule modifications are the mainstays for the management of peripheral neuropathy. For bortezomib, in case of grade 1 with pain or grade 2, peripheral neuropathy is recommended, a dose reduction to 1.0 mg/m^2; for grade 2 with pain or grade 3, peripheral neuropathy is indicated treatment interruption until peripheral neuropathy resolves to at least grade 1 with re-initiation at 0.7 mg/m^2/week; for grade 4, peripheral neuropathy treatment should be discontinued [25]. Alternatively, if grade 1 with pain occurs the biweekly bortezomib infusion can be reduced to weekly infusion; if grade 2 or higher occurs, interruption is suggested until grade 1 is reached followed by restart on a weekly basis. For thalidomide, patients should be instructed to recognize symptoms of peripheral neuropathy, to promptly reduce the dose or to discontinue the drug when sensory paresthesia is complicated by pain, motor deficiency, or interferes with daily activities. Patients can maintain the assigned dose if neuropathy is grade 1, if neuropathy grade 2 is recommended to decrease the dose by 50%, in case of grade 3 neuropathy thalidomide should be discontinued, and finally resumed at a decreased dose when neuropathy improves to grade 1 [23].

Venous thromboembolism

The incidence of venous thromboembolism (VTE) in MM patients varies from 3 to 10%. The type of drug used to treat the disease is a dominant factor determining the risk of VTE. Thalidomide and lenalidomide alone do not increase the incidence of VTE, whereas the incidence substantially increases when dexamethasone or chemotherapy is added, particularly in newly diagnosed patients, since the risk of VTE at relapse is much lower [26]. In a randomized trial comparing TD versus high-dose dexamethasone alone in newly diagnosed patients, incidence of thrombotic events was 18 vs. 3%, respectively, in the two groups [3], but no specific prophylaxis was mandated. With the MPT combination, VTE incidence varies from 3 to 12% in different studies [8, 9, 27, 28]; in the Italian study, after the introduction of prophylactic enoxaparin, the incidence of VTE was substantially lowered from 20 to 3% [8]. It is still debated which is the best thromboprophylaxis to use in thalidomide-treated patients. The Italian Myeloma Network GIMEMA designed a Phase III trial to investigate the efficacy and safety of low-molecular-weight heparin (LMWH), low-fixed-dose warfarin (1.25 mg/day), or low-dose aspirin as VTE prophylaxis in newly diagnosed patients, who were randomly assigned to receive primary induction with thalidomide-based regimens. The incidence of VTE was 4% with low-fixed-dose warfarin, 5% with LMWH, and 6% with aspirin. No significant relation was found between VTE risk and thromboprophylaxis, induction regimens, or patient age. In patients at standard risk of VTE, LMWH, warfarin, and aspirin are probably all effective thromboprophylaxis [29]. In newly diagnosed patients treated with RD, VTE has been reported in 26% of patients, but incidence significantly decreased with the use of low-dose dexamethasone (Rd) (6%) [4]; in patients treated with MPR and receiving aspirin as prophylaxis, VTEs are reported in about 10% of cases [20]. No increase risk of VTE is related to bortezomib therapy.

Baseline coagulation studies and screening for VTE are not recommended for asymptomatic patients. Thromboprophylaxis in MM patients treated with immunomodulatory agents should be tailored according to the presence of risk factors that may increase the risk of VTE. These include individual risk factors (age, obesity, history of VTE, central-venous catheter, comorbidities such as cardiac disease, chronic renal disease, diabetes, infections, immobilization, surgical procedures, and inherited thrombophilia), myeloma-related risk factors (diagnosis and hyperviscosity), and therapy-related risk factors (high-dose dexamethasone, doxorubicin, or multiagent chemotherapies). Aspirin is indicated for patients without risk factors or with one individual or myeloma-related risk factor. LMWH or full-dose warfarin is preferred for patients with at least two individuals or myeloma-related risk factors and is recommended for all patients receiving high-dose dexamethasone or doxorubicin or multiagent chemotherapy, regardless of the presence of additional risk factors

[26]. It is generally recommended a course of 4–6 months of prophylaxis. Patients who experienced VTE during treatment can continue on treatment or can be retreated after stabilization. Regarding VTE therapy, patients previously on aspirin should received LMWH; patients treated with prophylactic LMWH should be switched to therapeutic doses. Prophylaxis can be restarted after 6 months of therapeutic anticoagulation [30].

Renal failure

Renal impairment is quite frequent in patients with MM. The pathogenesis of renal failure is commonly multifactorial and includes the capacity of the light-chain component of the immunoglobulin to provoke proximal tubular damage, dehydration, hypercalcemia, hyperuricemia, infections, and use of nephrotoxic drugs (such as aminoglycosides and non-steroidal anti-inflammatory agents) [31]. Thalidomide and bortezomib need no dose reduction in patients with renal dysfunction. Lenalidomide can be used with appropriate dose modification and close monitoring of renal and hematological function, particularly in the early cycles. Dose reductions as follows on the basis of creatinine clearance (CLcr) are mandatory: in case of CLcr between 30 and 60 ml/min, the recommended dose is 10 mg/day; if CLcr is less than 30 ml/min and the patient does not require dialysis, the recommended dose is 15 mg every other day, whereas if CLcr is less than 30 ml/min and patient does require dialysis, the dose is 5 mg/day administered after dialysis.

Gastrointestinal toxicity

Gastrointestinal events (nausea, diarrhea, constipation, and vomiting) are quite common with bortezomib, lenalidomide, and thalidomide, but generally mild to moderate. Bortezomib and lenalidomide patients can present both diarrhea and constipation, while constipation is the most common side effects with thalidomide treatment. In relapsed patients, grade 3–4 gastrointestinal events were reported in 6–14% treated with bortezomib alone or plus dexamethasone [11, 12] or plus pegylated-liposomal-doxorubicin [12] (the main frequent AE was diarrhea in all the studies) and in 7–10% of subjects receiving RD (where similar low percentages of diarrhea, nausea, and constipation were reported) [13, 14]. In newly diagnosed patients, incidence of grade 3–4 toxicities (essentially constipation) was 4–11% with the MPT regimen [8, 9, 28], 5–17% of patients treated with VMP (higher rate reported in the VMP versus MP trial, where the main toxicity was diarrhea) [10, 21, 22], and only 2% of patients treated with MPR [20].

Patients suffering from constipation or diarrhea should maintain a high fluid intake; in case of constipation, it is recommended to take a high fiber diet and, if necessary, stool softeners or osmotic laxatives. Antidiarrhetic drugs can be use in case of diarrhea, after exclusion of active infections. In case of severe (grade 3–4) toxicity, a 50% dose reduction of the drug is recommended.

Dermatologic toxicity

Thalidomide and lenalidomide treatments can be related to adverse dermatologic events, including rash, dry skin, and mouth and atrophic lesions. These events are usually mild and easily manageable; rare but serious complications are toxic epidermic necrolysis and Stevens-Johnson syndrome [23]. In patients treated with thalidomide-based regimens, incidence of grade 3–4 dermatological toxicity varies from 1 to 8% [8, 9, 28]: similar rates are reported with lenalidomide [13, 14, 20]. Bortezomib treatment is rarely correlated to dermatological adverse reactions (1–5%, with the higher rate reported with the combination of bortezomib and pegylated-liposomal-doxorubicin, where the toxicity was hand–foot syndrome related to pegylated-liposomal-doxorubicin) [11, 12].

In case of mild toxicity, temporary discontinuation leads to resolution of the rash; antihistamines and steroids can be used. In general, treatment should began with antihistamines; if rash persists, low-dose prednisone (10–20 mg/day for up to 14 days) should be considered [30]. In case of grade 3–4 AEs treatment can be resumed, after complete resolution, with 50% dose reductions.

Bone disease

Bone pain, hypercalcemia, pathological fractures, vertebral compression, or collapse from osteoporosis are the important causes of morbidity and mortality in patients with myeloma. The use of analgesics should be based on established principles of the World Health Organization [32]. The support of expertise from in-hospital pain clinics could be necessary. Non-steroidal anti-inflammatory drugs should be avoided due to the potential for gastric irritation and side effects on renal function. Bisphosphonates are recommended in MM patients suffering from lytic bone disease or osteoporosis: intravenous administration (pamidronate or zoledronic acid) should be preferred, but oral administration (clodronate) can be an option for patients unable to attend hospital visits. It is recommended to monitor CLcr, electrolytes, and albuminuria in patients with renal impairment. Osteonecrosis of the jaw is an uncommon but potentially serious complication of intravenous bisphosphonates. All patients should receive a complete dental examination and should be educated regarding optimal dental hygiene prior to bisphosphonate therapy. Temporary bisphosphonates interruption is

recommended in case of invasive dental procedures. It is generally recommended to continue bisphosphonate therapy for 2 years, but the period could be extended at physician's discretion in patients with persistent active bone disease; treatment should be resumed in case of disease progression or relapse [33].

Other measures for bone pain control include local radiotherapy and vertebroplasty. Local radiotherapy is effective for pain relief and the recommended dose for pain control is 8 Gγ single fraction [34]. The use of radiotherapy should be however limited as the long-term use of radiation can affect hematopoietic reserve and bone healing. Vertebroplasty provides local pain relief and bone strengthening and can be an option in patients with vertebral collapse, but does not restore vertebral height [35].

Conclusions

New drugs have substantially improved survival of myeloma patients. Different, highly efficacious, treatment options are now available for both young and elderly patients. Physicians should now choose the best treatment regimen for each patient balancing efficacy with toxicity, taking into account patient characteristics (age and comorbidities). Patients with high risk of VTE can be safely treated with bortezomib-based regimens, without increasing their risk of thrombosis; in patients with renal impairment both thalidomide and bortezomib are safe and well tolerated and do not require dose modification, whereas lenalidomide can be used with appropriate dose reduction; in patients with pre-existing neuropathy lenalidomide should be preferred. Patients with significant comorbidities (lung, heart, liver, or kidney dysfunction) and elderly patients (in particular patients over 75 years old) can be safely treated after appropriate dose modification. Prompt management and dose reduction in case of AEs can further improve treatment efficacy by reducing discontinuation rate and can assure the best therapeutic care.

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