Review

Optimal Management of Histone Deacetylase Inhibitor-Related Adverse Events in Patients With Multiple Myeloma: A Focus on Panobinostat

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Abstract

Recent advances in treatment have extended the survival of patients with multiple myeloma. This improvement in itself poses challenges because of the length of time that patients live with myeloma, its physical complications, and toxicities of treatment. Thus, improvements in maintaining quality of life are essential, and part of this challenge involves learning how to optimally use new therapeutic agents. Panobinostat is the first histone deacetylase inhibitor approved for the treatment of multiple myeloma. It is approved for use in combination with bortezomib and dexamethasone for the treatment of patients with relapsed or relapsed and refractory multiple myeloma who have received $\geq$ 2 previous regimens, including bortezomib and an immunomodulatory drug. In this review multiple myeloma-related symptoms and adverse events resulting from treatments for multiple myeloma are discussed, with a focus on adverse events related to histone deacetylase inhibitors and histone deacetylase inhibitor combinations. The contribution of myeloma to these adverse events is discussed as well as how these AEs can best be managed.

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Introduction

Multiple myeloma (MM) is a neoplasm characterized by uncontrolled proliferation of abnormal plasma cells in the bone marrow and, typically, the overproduction of monoclonal proteins.[1] It accounts for approximately 2% of all new cancer cases and 18% of new cases of hematologic malignancies.[2] Although MM is incurable, recent advances in the treatment of MM have extended survival such that, for substantial periods of time, it can be a manageable chronic disease in many.[3] Thus, patients live with the burden of the disease and any cumulative toxicities of treatment. Improvements in quality of life are needed to match improvements in survival. A number of new treatments have been approved for MM; however, for a time, new agents will inevitably be unfamiliar to clinicians, who will need to gain experience and understand how to use them optimally within the challenges of a real-world setting.

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Multiple myeloma-related complications and adverse events (AEs) due to treatments are typically managed with dose reductions/interruptions, anti-infectives, transfusion, anticoagulation, growth factors, bisphosphonates, and pain control. However, if patients experience lack of response or intolerable AEs, involvement is required from other specialists, such as those in palliative medicine, pain management, radiotherapy, orthopedics, and psychology. A multidisciplinary approach is vital to the overall management of patients with MM because of the multisystem nature of the disease and the wide range of treatment-related toxicities that can occur.

In this review the difference between AEs resulting from treatment for MM and symptoms that are a result of the disease itself is discussed. Histone deacetylase inhibitor (HDACi) treatment-related AEs, the contribution of the disease to these symptoms, and strategies for their management are also discussed. Certain regimens for dose reduction/interruption and supportive care are suggested; however, these regimens should be taken as guidelines and might not be appropriate for all patients and individual circumstances.

Disease-Related Symptoms Versus Treatment-Related AEs

Multiple myeloma might be associated with hypercalcemia, renal impairment, anemia, bone disease, and/or infection.[4-6] Treatment aims are to control the disease burden, prolong survival, and maintain or improve quality of life. Classes of drugs currently approved for the treatment of MM include proteasome

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inhibitors (PIs; bortezomib, carfilzomib, and ixazomib), immunomodulatory drugs (IMiDs; thalidomide, lenalidomide, and pomalidomide), HDACi drugs (panobinostat), and monoclonal antibodies (daratumumab and elotuzumab). Treatment-related AEs vary according to drug class and can include myelosuppression, infection, fatigue, gastrointestinal toxicity, peripheral neuropathy, thrombosis, renal impairment, and cardiac toxicity, many of which might be symptoms of MM itself (Table 1).[7] Disease symptoms and treatment-related AEs can be managed with supportive care; AEs can also be managed with dose reduction/interruption to allow for recovery.

Panobinostat is the first HDACi approved by the US Food and Drug Administration, the European Commission, and the Japanese Pharmaceuticals and Medical Devices Agency for the treatment of MM. It is a pan-HDACi approved in the United States (US Food and Drug Administration), Europe (European Commission), and Japan (Pharmaceutical and Medical Devices Agency) for use in combination with bortezomib and dexamethasone for the treatment of patients with relapsed or relapsed and refractory MM who have received $\geq$ 2 previous regimens, including bortezomib and an IMiD.[8] Gastrointestinal toxicity, myelosuppression, fatigue, and potential cardiac abnormalities are key toxicities associated with panobinostat.[9] AEs during panobinostat treatment can be managed with dose interruption/delay or supportive care. In the event of clinically relevant toxicity, we recommend that the dose of panobinostat be reduced in increments of 5 mg and discontinued if the dose needs to be reduced to < 10 mg 3 times a week (TIW).[9]

Although the regimen of PAN-BTZ-Dex (panobinostat with bortezomib and dexamethasone) might be associated with issues regarding tolerability, drug-related toxicities can be managed effectively, allowing patients to continue treatment and obtain maximal benefit. Herein, we outline some strategies for managing PAN-BTZ-Dex–associated toxicities.

Myelosuppression

Myelosuppression is a common feature of MM. Bone marrow infiltration by MM cells leads to a reduction in the number of erythroid precursors,[10] and MM-associated renal impairment also leads to anemia.[11] In addition, certain antimyeloma therapies, including chemotherapy and HDACi therapy, cause cytopenia.[11]

Thrombocytopenia. Thrombocytopenia is a class effect of HDACi therapy,[12-15] and in the case of panobinostat, results from decreased platelet release from megakaryocytes.[12-14] However, panobinostat-induced thrombocytopenia typically resolves rapidly after treatment interruption or discontinuation.[9,15]

In the phase III PANORAMA 1 trial (NCT01023308: N = 758; panobinostat arm, n = 381; placebo arm, n = 377), thrombocytopenia was observed in 98% (371/380) of patients treated with PAN-BTZ-Dex versus 84% (314/376) of those treated with Pbo-BTZ-Dex (placebo with bortezomib and dexamethasone).[9] Grade 3/4 thrombocytopenia occurred in 67% (256/380) of patients in the panobinostat arm versus 31% (118/376) in the placebo arm. Within the study, thrombocytopenia was generally manageable, with median platelet counts recovering to baseline at the end of each cycle. Thrombocytopenia led to treatment interruption or dose modification in 31% of patients in the panobinostat arm and 11% in the placebo arm, and platelet transfusions were required in 33% of patients in the panobinostat arm and 10% in the placebo arm.[8] The rate of Grade 3/4 hemorrhages was 4% (16/381) in the panobinostat arm and 2% (9/377) in the placebo arm.[9]

Managing Thrombocytopenia in Patients Treated With PAN-BTZ-Dex. For patients with Grade 3 thrombocytopenia (platelet count $< 50 \times 10^9$/L), platelet counts should be monitored at least weekly,[8] and interruption of panobinostat and bortezomib initiated for patients with Grade 3 thrombocytopenia with bleeding or Grade 4 thrombocytopenia (platelet count $< 25 \times 10^9$/L). When thrombocytopenia recovers to Grade $\leq$ 2 (platelet count $\geq 50 \times 10^9$/L), panobinostat should be restarted at a reduced dose, with bortezomib restarted as soon as thrombocytopenia recovers to Grade $\leq$ 2 (platelet count $\geq 50 \times 10^9$/L)[16] or, ideally, Grade $\leq$ 1 (platelet count $\geq 75 \times 10^9$/L). If only 1 dose was omitted before correction to these levels, bortezomib should be restarted at the same dose. If $\geq$ 2 doses were omitted consecutively or within the same cycle, bortezomib should be restarted at a reduced dose.

Platelet transfusions should be considered for patients who experience severe thrombocytopenia. If the condition is clearly related to treatment, panobinostat might need to be discontinued if severe thrombocytopenia does not improve and/or the patient requires repeated platelet transfusions.

Table 1 Multiple Myeloma-Related Symptoms Versus Treatment-Related AEs

Symptom	Disease-Related	DACi-Related	PI-Related	IMiD-Related	mAb-Related
Myelosuppression	X	X	X	X	X
Infection	X		(BTZ)	(Len)	
Pain	X				
Fatigue	X	X	X	X	(Elo)
Skeletal Complications	X				
GI Toxicity	X	X	X	X	(Elo)
Peripheral Neuropathy			(BTZ)	(Thal)	
Thrombosis	X			X	
Cardiac Events		(PAN)	X	(Thal)	
Renal Impairment	X		(CFZ)	(Thal)	

X indicates a class effect. An abbreviated drug name in parentheses indicates that the symptom is limited to that drug within the class.
Abbreviations: AE = adverse event; BTZ = bortezomib; CFZ = carfilzomib; DACi = deacetylase inhibitor; Elo = elotuzumab; GI = gastrointestinal; IMiD = immunomodulatory drug; Len = lenalidomide; mAb = monoclonal antibody; PAN = panobinostat; PI = proteasome inhibitor; Thal = thalidomide.