



Florida
CHAPTER



Proteasome Inhibitors | Patricia Guerrero, MD

CANCER BACKGROUND

Bortezomib and Carfilzomib are two clinically available Proteasome Inhibitors (PIs) that are used for the management of multiple myeloma (MM) and mantle cell lymphoma. Bortezomib (approved in 2003) is a first-in-class PI and acts as a reversible inhibitor. Carfilzomib (approved in 2012) is more potent and irreversibly binds to the active sites of the targeted proteasomes. Carfilzomib is often reserved for patients that have failed bortezomib. A third and more recently approved PI for relapsed and refractory MM is the oral Ixazomib. Patients with MM often are older, with multiple comorbidities and trials conducted in this population had an elevated baseline rate of adverse events attributed to cardiovascular etiology.

ADVERSE EFFECTS

Proteasomes are protein complexes responsible for degrading dysfunctional or unnecessary proteins. PIs lead to intracellular accumulation of aggregate waste proteins which can prove fatal for hyper-metabolic cancer cells. Proteasomes also play an important maintenance role in the normal cardiac ventricular myocyte and are up-regulated in various cardiac disease states. Inhibition of proteasomes may lead to impairment of the ventricular myocyte particularly in situations of

myocardial stress, left ventricular hypertrophy and heart failure (HF). PIs are associated with cardiovascular adverse effects (CVAEs) of HF, hypertension and less commonly, cardiac arrhythmias. The incidence of HF with Bortezomib is reportedly 4% and with the more potent agent Carfilzomib, up to 25%. HF is usually reversible.

Bortezomib is also associated with bradycardia, supraventricular tachycardia and ventricular tachycardia/fibrillation. Carfilzomib is associated with vascular toxicity, including ischemic heart disease, ventricular tachycardia and fibrillation. Most CVAEs occur relatively early (2-3 months) in the course of treatment and are more common in patients with cardiovascular comorbidities or prior exposure to cardiotoxic agents.

RECOMMENDATIONS

Currently, there are no validated protocols to determine patients at high risk of CVAE during therapy, nor is there management guidance for patients who experience CVAE. Routine assessment of left ventricular ejection fraction (LVEF) is not recommended before or during treatment with PIs. It would appear that a reasonable strategy should include CV risk stratification at baseline and medical optimization of preexisting cardiovascular comor-

bidities, including hypertension, ischemia or HF. The recent PROTECT study (Cornell, et al) identified elevated baseline BNP (>100 pg/ml) or NTproBNP (>125 pg/ml) was predictive of increased incidence of CVAEs of which HF was the most common. PROTECT study patients with CVAEs presented within the first 3 months of initiation of the PI, had an inferior progression-free survival and an inferior overall survival, usually due to progression of the MM. Carfilzomib was associated with a CVAEs rate of 50.7% while with Bortezomib it occurred in 16.7% of the patients. PI administration was safely continued or resumed with modification in most patients in the PROTECT study.

DATA TO SUPPORT

Grandin, EW, Ky B, Cornell RF, Carver J, Lenihan DJ. Patterns of cardiac toxicity associated with irreversible proteasome inhibition in the treatment of multiple myeloma J Card Fail. 2015;21:138-44.



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Koulaouzidis, G. and Lyon, A.R. Proteasome inhibitors as a potential cause of heart failure. *Heart Fail Clin.* 2017;13:289-95. Elsevier Inc
Cornell Robert F; Ky, Bonnie et al. Prospective Study of Cardiac Events During Proteasome Inhibitor Therapy for Relapsed Multiple Myeloma. <https://doi.org/10.1200/JCO.19.00231>

INDICATIONS

PIs are used for the treatment of multiple myeloma and mantle cell lymphoma. These patients are often older and with multiple comorbidities. PIs are also a part of the treatment of patients with heart failure due to light chain cardiac amyloidosis, a small proportion (10-15%) of whom overlap with multiple myeloma. PIs are often combined with other immunomodulators such as lenalidomide which is independently associated with venous and arterial thrombosis.

ONCOLOGY COMMENTS

Reduced myocardial function associated with the use of these agents is often reversible if identified and treated promptly. Consider a baseline BNP level in high risk patients with repeated BNP surveillance early in the course of therapy. An echocardiogram should be obtained if there is elevated BNP or symptoms of heart failure. In many cases, the proteasome inhibitor may be continued or resumed after initiating HF therapy.