**Drug Review: Carfilzomib**

**Abstract**
Carfilzomib is a second generation proteasome inhibitor approved for use in relapsed/ refractory multiple myeloma. The mechanism of action, usage, toxicity and key trials involving this agent are briefly reviewed here.

**Keywords:** Carfilzomib, proteasome inhibitor, multiple myeloma

**Mechanism of Action**
Carfilzomib is an irreversible proteasome inhibitor. It selectively blocks the chymotrypsin-like activity of the 20S proteasome. With this, the degradation of unwanted proteins in the cell is blocked, leading to the buildup of polyubiquitinated proteins. This causes cell cycle arrest, apoptosis, and cell death, which is more in myeloma cells, as the protein production is enhanced in this cancer.[1]

It differs from bortezomib in the following aspects: (1) its binding is more selective than bortezomib; (2) it is irreversible; and (3) because of 1 and 2, it is less prone to the development of resistance.[1]

**Uses**

**Approved uses**
Multiple myeloma is the only condition where carfilzomib is used in clinical practice.

The approved use of this agent as per the U.S. Food and Drug Administration is in relapsed refractory myeloma (RRMM) in combination with lenalidomide and dexamethasone (based on the ASPIRE study[2]) and also with dexamethasone (based on the ENDEAVOR study[3]) or as a single agent (based on single-arm Phase I trial called Study PX-171-007).[4]

**Other uses where there is no Food and Drug Administration label**
Carfilzomib has been used in multiple Phase I and II studies in combination with other antimyeloma agents with proven safety and efficacy. These include daratumumab, elotuzumab, cyclophosphamide, thalidomide, pomalidomide, and selinexor to name a few. Thus, carfilzomib can be safely combined with most of the existing antimyeloma therapies.

**Carfilzomib use in newly diagnosed myeloma**
Various Phase II studies showed high efficacy of carfilzomib (K)-based triplet combinations in newly diagnosed myeloma (e.g., KCyD, KRd, KMP, and KTD). Based on this, a Phase III trial compared carfilzomib–lenalidomide–dexamethasone (KRd) with standard VRd (COMPASS study) and showed improvement in event-free survival (EFS), higher responses, and complete responses at 12 months [Table 1].[5]

**Drug controller general of India (DCGI) approval status**
Carfilzomib is approved by the DCGI for used in relapsed myeloma. DCGI has mandated that a Phase IV trial with this agent be conducted by the parent company.

**Dosage**
The dosage (in combination with lenalidomide and dexamethasone as per the ASPIRE trial) initially approved was 27 mg/m² twice a week (D1,2- D8,9- D15,16) – three times in a 28-day cycle – with the first two doses alone given at 20 mg/m².[2]

However, this dosing was inconvenient, and subsequent studies showed that a weekly dosing regimen was safe, effective, and more convenient. The weekly dosing schedule of carfilzomib is as follows (based on the ARROW study): In cycle 1, D1 is administered at...

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Carfilzomib is an important option for therapy of patients who have been previously exposed to refractory to bortezomib and also for patients who cannot tolerate bortezomib due to neuropathy. Although it can be used as a single agent or in combination with steroids, response rates are better with triplet combinations and these are preferred whenever feasible. Because most patients in the current era may have already used lenalidomide in the first-line setting, triplets involving daratumumab, cyclophosphamide, or pomalidomide may be preferred.

**Newly diagnosed myeloma**

At present, there is no approval for the front-line use of carfilzomib. However, data from some Phase II trials have suggested that responses are high with KRd, especially in the high-risk subsets. It could thus be considered in selected high-risk patients or in those with preexisting neuropathy where bortezomib may be contraindicated.

**Precautions**

All infusion precautions must be followed as detailed above. Start with lower dose in cycle 1 to prevent tumor lysis. Cardiac failure with carfilzomib usually occurs within the first 2–3 months of use. Although screening ECHO is not actually recommended, it may be considered, especially in older individuals and those with coronary risk factors. Heightened awareness is very important to recognize and preempt cardiac toxicity.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**