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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*

Prasanth Ganesan

Department of Medical Oncology, JIPMER, Puducherry, India

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 (COMMPASS 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/m^2 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/m^2.[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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Address for correspondence:
Dr. Prasanth Ganesan, Department of Medical Oncology, JIPMER, Puducherry - 605 006, India.
E-mail: p.ganesan@jipmer.edu.in

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Table 1: Important/landmark trials

Trial (references)	Setting	Design	Result and remarks
ASPIRE[2]	RRMM, *n*=792	KRd versus Rd for PFS	PFS superior with KRd. Led to approval of carfilzomib
ARROW[6]	RRMM, *n*=578	Compared 27 mg/m^2 twice a week with 70 mg/m^2 once a week for PFS along with weekly dexamethasone	PFS was superior with the weekly dosing regimen with comparable toxicity
COMPASS[5]	NDMM, *n*=609	KRd versus VRd	Better EFS and responses with KRd. Only abstract available

RRMM – Relapsed/refractory myeloma; NDMM – Newly diagnosed myeloma; PFS – Progression-free survival

20 mg/m^2 to assess tolerability. From D8 of cycle, 170 mg/m^2 is administered once a week (D1, D8, and D15 of a 28-day cycle – dexamethasone on D1, D8, D15, and D22). Thus, three doses are administered in each cycle.[6]

Administration Instructions

Antiviral prophylaxis for herpes zoster is recommended which is similar to bortezomib. Premedication with dexamethasone (only if given as monotherapy – otherwise recommended weekly dose of dexamethasone can be used as IV/PO at least 30 min before carfilzomib). Hydration is required before and after carfilzomib to reduce the risk of tumor lysis, especially before each dose in cycle 1. The vial is reconstituted with sterile water and diluted in 100 ml 5% dextrose and infused over 30 min. IV line to be flushed after administration. Vials should be stored in a refrigerator at 2°C–8°C, and the reconstituted solution can be stored for up to 24 h at 2°C–8°C.

Common/Important Toxicity

The most common adverse events are anemia, neutropenia, and thrombocytopenia, when carfilzomib was used with lenalidomide and dexamethasone in RRMM in the ASPIRE trial.[2] However, all these were equal between KRd and Rd arms, meaning that there was no excess hematological toxicity with the addition of carfilzomib. However, the following nonhematological toxicities were more with KRd: hypokalemia (9% vs. 4%), cough (28% vs. 17%), Grade 3–4 hypertension (4.3% vs. 1.8%), Grade 3–4 cardiac failure (3.8% vs. 1.8%), and dyspnea (2.8% vs. 1.8%). Specific side effects to watch out for are cardiac failure and tumor lysis (especially during the first cycle). In the first-line trial comparing KRd and VRd (COMMPASS), the treatment discontinuation rates were similar in both arms (3.8%).

Comments

Relapsed refractory myeloma

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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Conflicts of interest

There are no conflicts of interest.

References

1. Kortuem KM, Stewart AK. Carfilzomib. Blood 2013;121:893-7.
2. Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Špička I, Oriol A, *et al.* Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 2015;372:142-52.
3. Dimopoulos MA, Goldschmidt H, Niesvizky R, Joshua D, Chng WJ, Oriol A, *et al.* Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): An interim overall survival analysis of an open-label, randomised, phase 3 trial. Lancet Oncol 2017;18:1327-37.
4. Carfilzomib: highlights of Prescribing Information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202714lbl.pdf. [Last accessed on 2019 Mar 04].
5. Landgren O, editor. Carfilzomib-Lenalidomide-Dexamethasone Versus Bortezomib-Lenalidomide-Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma: Results from the Prospective, Longitudinal, Observational Commpass Study. 60th Annual Meeting and Exposition. ASH; 1-4 December, 2018.
6. Moreau P, Mateos MV, Berenson JR, Weisel K, Lazzaro A, Song K, *et al.* Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): Interim analysis results of a randomised, phase 3 study. Lancet Oncol 2018;19:953-64.