More convenient proteasome inhibition for improved outcomes

The development of proteasome inhibitors for the treatment of multiple myeloma has represented a step-change for patients with this incurable plasma cell cancer, bringing increased treatment responses, and improved survival. Gradual familiarisation with toxicity profiles, and optimisation of dosing schedules, have shaped the current use of proteasome inhibitors as key components of several treatment regimens. The first-in-class proteasome inhibitor, bortezomib, was approved in 2003 for relapsed and subsequently also for newly diagnosed multiple myeloma. When used in a twice-weekly intravenous regimen, it was associated with high rates of painful and often debilitating peripheral neuropathy leading, in many patients, to treatment discontinuation. Subcutaneous administration and schedule adaptation to once-weekly use have meanwhile been shown to be both more tolerable and highly efficacious.[1-3]

Carfilzomib is a second-in-class epoxyketone-based, irreversibly binding, proteasome inhibitor, whereas the boronic acid-based compounds, bortezomib and ixazomib, bind reversibly, resulting in some differences in proteasomal subunit inhibition. A consecutive-day, twice weekly dosing schedule was utilised early in the development programme of carfilzomib, which was first approved by the FDA in 2012 as a single agent in relapsed disease at a dose of 27mg/m^2. Recently, carfilzomib was also approved in combination with dexamethasone, or lenalidomide plus dexamethasone, in the US and the European Union, based on positive results from two landmark studies, ENDEAVOR and ASPIRE.[4-6] Carfilzomib dose was 27mg/m^2 in ASPIRE (combination with lenalidomide and dexamethasone) and 56mg/m^2 in ENDEAVOR (combination with dexamethasone only), using a twice-weekly consecutive-day intravenous carfilzomib infusion schedule in both studies. While twice-weekly carfilzomib at these doses is generally well tolerated, with a low rate of peripheral neuropathy, dyspnoea, hypertension and cardiac toxicities stand out as clinically relevant side effects. Moreover, in an age where the long-term prognosis continues to improve for patients with multiple myeloma, the inconvenience of a twice weekly intravenous infusion is a significant burden for both patients and healthcare providers.

In *The Lancet Oncology*, Philippe Moreau and colleagues[7] report the results of a randomised Phase 3 study, A.R.R.O.W., in which patients who had relapsed following two or three prior treatment lines were randomised to receive carfilzomib bi-weekly at 27mg/m^2 or once-weekly at 70mg/m^2, based on a previously established maximum tolerated once-weekly dose.[8] Both arms also contained weekly dexamethasone. The reported pre-planned interim analysis of the 478 patients demonstrates superior progression free survival (hazard ratio 0.69 [95% confidence interval, 0·54-0·83]; p=0·0029), as well as increased overall responses (62.9% versus 40.8%, hazard ratio 2.49 [95% confidence interval, 1·72-3·60]; p<0·0001) and deeper responses (very good partial response or better, 34.2% versus 13.4%) with the once-weekly schedule, without any new safety signals. With the availability of different dose-scheduling regimens, considerations of safety profile are paramount. There were more ≥grade 3 adverse events in the once-weekly arm (67·6% versus 61·7%), including sepsis and lung infections, and more frequent dose reductions, although adverse event-related treatment discontinuations of carfilzomib were similar between the arms. These differences indicate that some spectrum of toxicities may be more prominent in the once-weekly regimen, and it would be important to know if the adverse event profile was different in older patients; however, only a small proportion of patients in the study were older than 75 years.

The study by Moreau and colleagues will lead to the welcome availability of a more convenient once-weekly dosing schedule, and represents an important milestone for future research employing once-weekly carfilzomib in multi-agent protocols, which are becoming the standard of care for treating multiple myeloma. Some questions, however, remain to be answered, such as whether once-weekly carfilzomib is also linked to improved overall survival. Moreover, based on ENDEAVOR, the current standard dose for bi-weekly carfilzomib with dexamethasone is 56mg/m^2, and it remains to be established how this compares with a dose of 70mg/m^2 once-weekly. One might ask if the dose difference actually matters for an irreversibly binding proteasome inhibitor. Area under the plasma concentration-time curve seems to increase with dose from 20mg/m^2 to 56 mg/m^2, with dose-dependent inhibition of proteasome activity, at least in peripheral blood cells.[9] Further studies are therefore still needed to establish standard carfilzomib doses and administration schedules for combinations therapies for relapsed multiple myeloma. Meanwhile, physicians will need to rely on careful scrutiny of adverse event profiles in patient subgroups, as well as reports of real-world experience. Undoubtedly, though, the results of the A.R.R.O.W. study usher in a new era in carfilzomib therapy.

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