The challenge of cross-trial comparisons using limited data

The manuscript by Dr David Siegel and colleagues,[1] "Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase 2 clinical studies", provides a comprehensive assessment of the available safety data associated with the new proteasome inhibitor carfilzomib, which was granted accelerated approval by the US FDA in 2012.[2] The report provides important information on the use of this promising agent in relapsed and refractory multiple myeloma (RR MM), which will assist the MM community as we seek to advance drug treatments for the benefit of patients. In evaluating these findings in the context of data for other therapies, the authors make extensive use of cross-study comparisons in their discussion of the safety data for carfilzomib. We wish to highlight the potential difficulties associated with making such comparisons and to urge caution regarding this approach.

We agree with the authors when they state that, "…it is difficult to make cross-trial comparisons…".[1] By design, single-arm phase II clinical trials such as those described in the paper by Siegel *et al*. do not enable comparisons with other agents utilized for the same indication, and thus direct cross-study comparisons using such data may potentially suggest misleading similarities or differences. The present paper does not report a comparative statistical analysis between carfilzomib and other agents approved for the treatment of RR MM, and the cross-study comparisons in the Discussion are not made in a systematic manner with respect to clinical trials referenced, particular adverse events (AEs), grade of these AEs, and drug comparators. Furthermore, the comparisons may be confounded by various factors.

For example, a comparison is made between the rates of "cardiac failure" with carfilzomib and bortezomib, which are both associated with cardiac toxicity and include cardiac adverse reactions under 'Warnings and Precautions' in their respective US labels.[2,3] The authors state that "it is important to note that the rate of cardiac failure AEs observed in these studies (7.2%) was similar to the 5% reported for bortezomib in the APEX trial."[1] However, in the absence of statistical tests, it appears difficult and premature to conclude non-inferiority on the basis of these data alone.

Additionally, it is important to note that there are a number of differences between the studies of carfilzomib and APEX in terms of factors that may affect cardiac risk, and these may confound the interpretation of the rates of cardiac events. A key difference is that in APEX, a large, international, phase III study comparing high-dose dexamethasone to bortezomib monotherapy,[4] all patients were initiated at the FDA-approved dose of bortezomib, whereas in the phase II carfilzomib trials only 52.9% of patients initiated treatment at the approved dose, with the rest receiving lower doses.[1,5-9] Other differences between the trials included differences in patient age, median number of prior therapies, sequencing and types of therapies, and number of patients previously exposed to anthracyclines, thus rendering meaningful comparisons of cardiac toxicity difficult. Indeed, as a general issue, caution should be exercised when attempting to interpret or extrapolate data from the relapsed/refractory setting in the context of earlier in the disease course or even the upfront setting. Furthermore, there may also be factors that are as-yet not understood that may affect the risk of cardiac toxicity.

Although comparative studies are underway to generate randomized data of carfilzomib *versus* other agents, including bortezomib, far fewer patients have been treated with carfilzomib to date. Bortezomib has been investigated in several large, randomized, controlled phase III trials[4,10-13] and has been administered to more than 450,000 patients worldwide. Data from bortezomib studies thus provide an appropriate benchmark for the risk of cardiovascular toxicity with proteasome inhibition. In large, randomized, controlled trials, the rates of grade of 3 or higher congestive heart failure (CHF) with bortezomib + melphalan-prednisone (MP) *versus* MP alone were 4.7% *versus* 3.9%, respectively, in the VISTA trial,[12] and 2.1% in both arms of the APEX trial.[4] In aggregate, these data would suggest that bortezomib-induced high grade CHF is an uncommon event.[14] For carfilzomib, it is important to recognize that the much lower overall exposure compared to bortezomib means that the point estimates of safety events, especially serious AEs with single-digit incidences overall such as CHF, fall in wider confidence intervals. Therefore, a more accurate relationship of cardiac toxicity to carfilzomib remains to be established.

We agree with the authors' statement that "Results from the ongoing phase 3 ENDEAVOR (*clinicaltrials.gov identifier: 01568866*) and CLARION (*clinicaltrials.gov identifier: 01818752*) trials, in which patients are being treated with either carfilzomib or bortezomib, will provide more information on the cardiotoxicity of the two proteasome inhibitors", as will results from the phase III ASPIRE trial (*clinicaltrials.gov identifier:01080391*). Until the results of these studies and others are available, we suggest avoiding comparisons that could lead to premature and erroneous conclusions.

We also agree that as a complication CHF clearly warrants further study and careful evaluation, much in the same way that peripheral neuropathy has been examined for bortezomib. Furthermore, it is also important to note that not all 'cardiotoxicity' is the same across novel cancer therapies; additional research is needed to clarify the nature of the cardiotoxicities associated with carfilzomib and bortezomib, including the rate of acute severe cardiotoxicities, and strategies to prevent and treat them. Similarly, there is a need to incorporate more sensitive diagnostic assessments of cardiotoxicity, such as echocardiography and evaluation of brain natriuretic peptide (BNP) as well as troponin, moving forward, informed by our experience to date, and by more sophisticated pre-clinical studies to guide comprehensive assessment of cardiac function.[15] This in turn should enable better characterization and monitoring of cardiotoxicity with proteasome inhibitors and other agents in the future.

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