Nature Reviews Clinical Oncology | Published online 17 Jan 2017; doi:10.1038/nrclinonc.2017.5

HAEMATOLOGICAL CANCER

Landmark survival achieved in MM

In 2007, the SWOG S0777 trial was initiated to compare two of the most active regimens available at that time for the treatment of newly diagnosed multiple myeloma (MM): VRd, comprising the proteosome inhibitor bortezomib, the immunomodulatory drug lenalidomide, and dexamethasone; and Rd, consisting of lenalidomide and dexamethasone. Now, almost 10 years on, the final results have been published and exemplify how the availability of a number of highly active drugs for testing in combination regimens is greatly improving the outlook for patients with MM.

As lead author Brian Durie explains, "it was known that each regimen had good activity, the key question was: how important is it to start treatment with the slightly more aggressive triplet versus the doublet?" The investigators wanted to focus on assessment of the efficacy of the combination regimens alone; thus, autologous stem-cell transplantation (ASCT) was delayed, when possible. In fact, only 46 of the 471 patients evaluated underwent ASCT after leaving the study.

The findings of the trial are striking. In comparison with Rd treatment, the use of VRd led to substantially improved objective response and complete remission rates, and survival outcomes; median overall survival, in particular, was prolonged by 11 months, to an unprecedented 75 months. As Durie emphasizes, "the 75-month figure for overall survival really is a landmark, moving the average survival for a patient with MM, which in 2007 had been in the 4-year range, to beyond 6 years"

> "...the 75-month figure for overall survival really is a landmark..."

Importantly, the benefits of VRd treatment extended to all age groups, including those aged >75 years, and remained when patients who underwent ASCT were excluded from the analysis. Moreover, additional toxicity of VRd over the Rd regimen was mainly limited to more frequent and severe polyneuropathy, which might be ameliorated by switching from intravenous to subcutaneous administration of bortezomib.

"As triplet therapy is more cumbersome, expensive, and potentially more toxic, documenting the true added value to the patient in a reliable fashion is important; the S0777 data clearly demonstrate this value and support the VRd regimen as the new standard of care," Durie opines. MM therapy is evolving rapidly, however, and the S0777 results might not necessarily capture the outcomes that can be expected with novel triplet regimens; combinations including the alternative proteosome inhibitor carfilzomib or the anti-CD38 antibody daratumumab could soon supplant VRd.

As Durie concludes: "The S0777 study has brought into focus the need for earlier end-point evaluation — waiting 10 years for results is no longer acceptable. The added benefit of VRd treatment was reflected in deeper responses, which can be assessed in the 1–3-year timeframe. Thus, the way forward is to provide early testing for minimal residual disease, in order to select better therapies in a more expeditious fashion."

David Killock

ORIGINAL ARTICLE Durie, B. G. *et al.* Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet* http://dx.doi.org/10.1016/S0140-6736(16)31594-X (2016)