Nature Reviews Clinical Oncology **12**, 65 (2015); published online 23 December 2014; doi:10.1038/nrclinonc.2014.228

HAEMATOLOGICAL CANCER

ASPIRE for unprecedented benefit with carfilzomib in MM

Many advances in the treatment of multiple myeloma (MM) have been made in recent years. In particular, the efficacy of lenalidomide plus dexamethasone therapy until disease progression has been recognized, and this regimen has become a reference treatment for this disease. Nevertheless, relapse remains a considerable challenge. Carfilzomib, a proteasome inhibitor, has shown promise in this setting, both as a monotherapy and combined with lenalidomide–dexamethasone. Now, the phase III ASPIRE trial has further demonstrated the efficacy of the triple drug regimen in relapsed MM.

The ASPIRE trial randomly assigned 792 patients with relapsed MM to receive either carfilzomib (initially 20 mg/m^2; target dose 27 mg/m^2), lenalidomide (25 mg) and weekly dexamethasone (40 mg), or lenalidomide–dexamethasone. All patients had received 1–3 previous treatments; >65% of patients in each group had been treated with bortezomib, another proteasome inhibitor. At the prespecified interim analysis, with a median follow-up duration of ~32 months, the primary end point of significantly improved progression-free survival (PFS) was met. In fact, median PFS was 26.3 months in carfilzomib arm—a remarkable and unprecedented duration—and 17.6 months in the lenalidomide–dexamethasone control group (HR 0.69; $P = 0.0001$); without transplantation, PFS in patients with MM has not been prolonged to this extent by any other regimen.

> “...PFS in patients with MM has not been prolonged to this extent by any other regimen”

In addition, the rate of complete response or better, the objective response rate, and the mean time to and duration of response were all markedly improved by adding carfilzomib to therapy. Although median overall survival was not reached in either treatment arm, 24-month overall survival was 73.3% and 65.0% in the triple therapy and control cohorts, respectively, with a trend towards improved survival for the carfilzomib regimen (HR 0.79; $P = 0.04$).

The adverse effects rates were similar between the groups, despite a substantially longer median treatment duration in the carfilzomib cohort. A slightly increased rate of cardiovascular events associated with carfilzomib demands caution. Importantly, however, health-related quality of life was better in the triple therapy arm compared with the control group ($P < 0.001$).

These findings—particularly a possible overall survival benefit—and the ideal carfilzomib dosing schedule require confirmation in other studies. Nevertheless, “the impressive clinical benefit and reassuring adverse effects profile, in my opinion, makes this combination a new standard of care in relapsed MM,” states Keith Stewart, who led the trial.

David Killock

Original article Stewart, A. K. *et al*. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N. Engl. J. Med*. doi:10.1056/NEJMoa1411321