Carfilzomib, lenalidomide, and low-dose dexamethasone in elderly patients with newly diagnosed multiple myeloma

A number of combination regimens with immunomodulatory agents or proteasome inhibitors have been developed for use in elderly patients with newly diagnosed multiple myeloma (NDMM). Regimens including bortezomib, melphalan, and prednisone (VMP), and including melphalan, prednisone, and thalidomide (MPT), have demonstrated improved disease control and survival, with manageable toxicity compared with the prior standard of melphalan and prednisone (MP).[1,2] Because elderly patients are often frail, early studies with these multidrug regimens generally limited treatment to 9-12 cycles.[1,2] However, results from subsequent studies in transplant-ineligible patients suggested that more extended treatment might provide the added benefit of longer progression-free survival (PFS).[3-5]

Recently, the benefit of extended treatment was clearly demonstrated in the phase III FIRST (Frontline Investigation Of Lenalidomide + Dexamethasone Versus Standard Thalidomide) study where transplant-ineligible patients who received continuous lenalidomide and low-dose dexamethasone (Rd) achieved superior survival outcomes compared with those who received 18 cycles of Rd (Rd18) or MPT.[6] Median PFS was significantly longer for continuous Rd (25.5 months) compared with Rd18 (20.7 months; P=0.00006) or MPT (21.2 months; P=0.00001), with no significant difference between the latter two treatment arms. Given these findings, extended treatment with Rd represents a promising option in this patient population. Nonetheless, median PFS in this study was still relatively short compared with studies of 3- or 4-drug regimens.[4,5] Also, based on subset analysis of FIRST, patients with high-risk cytogenetics will likely require the addition of proteasome inhibition.[6] Bortezomib has been shown to overcome, at least in part, the negative impact of cytogenetic factors, whereas results with lenalidomide have been more mixed;[7] however, extended use of bortezomib may be limited by peripheral neuropathy.[8]

Carfilzomib, a selective proteasome inhibitor, has demonstrated single-agent activity in relapsed and/or refractory myeloma with a low rate of peripheral neuropathy and no evidence of cumulative toxicity after extended treatment.[9,10] A number of studies are exploring carfilzomib in triplet combinations for transplant-ineligible NDMM, with encouraging preliminary results.[11-13] We previously reported results from a phase I/II study of carfilzomib with lenalidomide and low-dose dexamethasone (CRd) in 53 transplant-eligible and -ineligible patients with NDMM, a study designed to allow for prolonged CRd treatment *(http://www.clinicaltrials.gov; National Clinical Trial number: 01029054)*.[13] After a median of 12 cycles (range 1–25) and 13 months of follow up (range 4–25 months), CRd provided a high rate of deep and durable responses with a safety/tolerability profile that supported extended treatment. In this brief report, we present outcomes with updated follow up in the subset of 23 elderly patients (age ≥65 years).

Details of study methods have been reported previously.[13] Briefly, transplant-eligible and -ineligible patients with NDMM, an Eastern Cooperative Oncology Group performance status of 0-2, and adequate liver, kidney, and bone marrow function were eligible. During dose escalation, carfilzomib was administered at 20 mg/m^2 for cycle 1 on Days 1, 2, 8, 9, 15, and 16 of 28 days, and then at 20, 27, or 36 mg/m^2 for 7 cycles. For maintenance CRd (cycles 9-24), carfilzomib was administered on Days 1, 2, 15, and 16. Lenalidomide 25 mg was administered daily on Days 1–21. Low-dose dexamethasone was administered on Days 1, 8, 15, and 22 at 40 mg for cycles 1-4, and at 20 mg thereafter. The maximum tolerated dose was not established, but based on efficacy and safety, we proceeded to phase II using carfilzomib 36 mg/m^2.[13] After 24 cycles, patients continued single-agent maintenance lenalidomide off protocol.

Patients were followed for response (International Myeloma Working Group (IMWG) criteria plus near complete response (nCR) and minimal response), survival, and safety. Immunophenotypic complete response (iCR) was assessed using a 10-color multiparameter flow cytometry assay to evaluate minimal residual disease (MRD). The primary end point was rate of nCR or better after 4 cycles. The study protocol was approved by the institutional review boards of the participating centers and conducted in accordance with the Declaration of Helsinki. Patients pro-

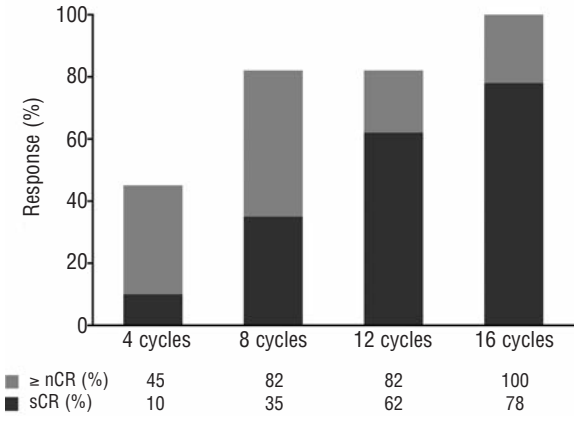

Figure 1. Response over the course of treatment with carfilzomib, lenalidomide, and low-dose dexamethasone (n=23). nCR: near complete response; sCR: stringent complete response.

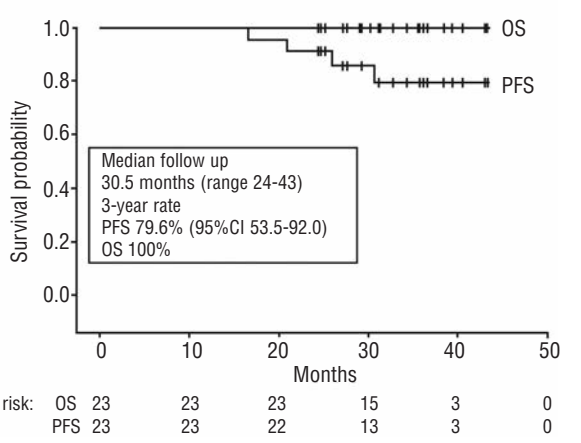

Figure 2. Overall survival (OS) and progression-free survival (PFS) by the Kaplan–Meier method (n=23). CI: confidence interval.

vided written informed consent. For this exploratory subgroup analysis, we provide results after extended follow up (data cut off May 31, 2013). Median age in the elderly subgroup was 72 years (range 65-81); 13 patients (57%) were male, 16 (70%) had International Staging System stage II/III disease, and 7 (30%) had high-risk cytogenetics according to IMWG criteria.[14] Patients received a median of 24 CRd cycles (range 1-24), 2 at a carfilzomib dose level of 20 mg/m^2, 4 at 27 mg/m^2, and 17 at 36 mg/m^2.

CRd provided deep and durable responses. All patients (100%) achieved at least a partial response (PR), 91% at least a very good PR (VGPR), 87% at least an nCR, 79% at least a CR, and 65% a stringent CR (sCR). Depth of response improved with duration of treatment; sCR increased from 10% after 4 cycles to 78% after 16 cycles (Figure 1) with median time to PR of 1 cycle (range 1-3) and to sCR of 9 cycles (range 3-15). Of 14 patients tested for MRD (13 sCR, 1 nCR), 12 (86%) were MRD negative for an estimated iCR of 60%. Within a median follow up of 30.5 months (range 24-43), 4 patients had progressed and none had died for a 3-year PFS rate of 79.6% (95%CI: 53.5-92.0) and 100% for overall survival (OS) (Figure 2).

Treatment was well maintained throughout induction and maintenance, with only 4 patients discontinuing before completion of 24 cycles (one pulmonary edema during induction, one patient preference, 2 opted for autologous stem cell transplantation), although dose modifications were needed to manage adverse events (AEs). During induction (cycles 1-8), grade 3/4 AEs were generally hematologic and included thrombocytopenia (39%), lymphopenia (35%), neutropenia (30%), and anemia (26%); non-hematologic grade 3/4 AEs (>10%) included hyperglycemia (39%), hypophosphatemia (22%), and thromboembolic events (13%). During maintenance (cycles 9-24), the majority of AEs were grade 1/2 and manageable. Grade 3/4 AEs were generally hematologic but less frequent: neutropenia (26%), lymphopenia (26%), and thrombocytopenia (16%). Non-hematologic grade 3/4 AEs (>10%) included infection (16%), hypophosphatemia (16%), and hyperglycemia (16%). Grade 1/2 peripheral neuropathy attributed to CRd occurred in 22% of patients during induction (grade 2, 9%) and 37% during maintenance (grade 2, 21%); there were no grade 3/4 events. Dose modification of carfilzomib, lenalidomide, and dexamethasone was required by 74%, 83%, and 70% of patients during induction and by 52%, 57%, and 61%, respectively, during maintenance. There were no second primary malignancies or treatment-related deaths.

Overall, this subgroup analysis demonstrated that extended treatment with CRd was feasible in elderly patients. The efficacy of the CRd regimen compares favorably with that of other non-transplant combinations,[1,2,4,6,11,12] with recognition of the limitations of cross-trial comparisons. In the FIRST trial, at least VGPR rates were 43.5% for continuous Rd, 42.7% for Rd18, and 28.1% for MPT (18 cycles). Three-year PFS was 42% for continuous Rd (42%) compared with 23% for Rd18 (P=0.00006) and 23% for MPT (P=0.00001), and 4-year OS was 59.4%, 55.7%, and 51.4%, respectively, with a statistically significant difference between continuous Rd *versus* MPT (P=0.0168).[6] Given the current findings and growing evidence of an association between depth of response and survival outcomes in elderly patients,[15] one can reason that outcomes with continuous Rd in this population might be improved further by adding selected agents, such as carfilzomib, that do not significantly affect tolerability. Our data show that use of the CRd regimen for an extended period of time can result in a high rate of deep responses that is associated with very encouraging time to events. These results support further research in this direction to ultimately improve survival in elderly patients with NDMM. This will require confirmation in a randomized trial. Considering that transplant-ineligible studies will likely use extended Rd as a control, this subset analysis should inform the design of a CRd arm.

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