MultipleMyelomaHub

Carfilzomib-melphalan-prednisone versus bortezomib-melphalan-prednisone for newly diagnosed multiple myeloma

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Multiple myeloma (MM) is the second most frequent hematologic malignancy. It is found in the spectrum of plasma cell dyscrasias which begins with monoclonal gammopathy of unknown significance to overt plasma cell leukemia and extramedullary myeloma. Transplant eligibility continues to define initial MM treatment.[1] As MM predominantly affects elderly patients, >50% of patients are not candidates for autologous stem cell transplantation, which has typically been offered to patients aged <65 years.[1] As outcomes in transplant-ineligible patients are worse than in transplant-eligible patients, and there remains an unmet need to explore better treatment options for this population.

Previous studies (VISTA, UPFRONT, and ENDEAVOR) have demonstrated improvements in progression-free survival (PFS) and overall survival (OS).[2,3] Based on these results Professor Thierry Facon from the Lille University Hospital, Lille, France, and colleagues, initiated a randomized, open-label, multicenter, phase III study (CLARION; NCT01818752) to compare Carfilzomib-melphalan-prednisone (KMP) with bortezomib-melphalan-prednisone (VMP) in transplant-ineligible NDMM patients. The primary objective of the study was to compare PFS between the two regimens.[4]

Study design

- Patients were recruited from 183 sites in North America, Europe, the Asia-Pacific, and other regions (Mexico, Argentina, Israel)
- Transplant-ineligible patients aged ≥18 years with symptomatic NDMM, measurable disease, and an Eastern Cooperative Oncology Group Performance Status of 0 to 2
- Ultimately, transplant ineligibility was determined by investigators
- Any patient aged <65 years needed to have ≥1 comorbidities, which were reviewed by the medical monitor
- A creatinine clearance of ≥15 mL/min within 21 days prior to randomization was required
- Patients were randomized 1:1 to KMP or VMP for nine 42-day cycles (C)
- Patients received carfilzomib on days (D) 1, 2, 8, 9, 22, 23, 29, 30 (20 mg/m^2: C1D1, C1D2; 36 mg/m^2 thereafter) or bortezomib on D1, 4, 8, 11, 22, 25, 29, 32 (1.3 mg/m^2; D4, 11, 25, 32 omitted for C5-9)
- Melphalan (9 mg/m^2) and prednisone (60 mg/m^2) were administered on D1-4
- The primary endpoint was progression-free survival (PFS)
- N= 955: patients were randomized (intention-to-treat [ITT] population: KMP, n =478; VMP, n =477)

Key findings

- Median PFS was 22.3 months with KMP *vs* 1 months with VMP (hazard ratio [HR], 0.906; 95% confidence interval [CI], 0.746-1.101; P = 0.159)
- Median overall survival was similar and not reached in either group (HR, 1.08; 95% CI, 0.82-1.43)
- Overall response rate was 84.3% for KMP and 78.8% for VMP
- Complete response rate was 25.9% for KMP and 23.1% for VMP
- Minimal residual disease-negative rates were 15.7% (KMP) and 15.5% (VMP)
- Adverse events (AEs) of interest occurring with a ≥5% higher patient incidence in the KMP arm were acute renal failure (13.9% [KMP] *vs*2% [VMP]) and cardiac failure (10.8% *vs* 4.3%)
- Grade ≥3 AE rates were 74.7% (KMP) and 76.2% (VMP)
- Grade ≥2 PN was lower for KMP *vs* VMP (2.5% *vs* 1%)

Conclusion

The study found that there was no statistically significant difference in PFS between the treatment regimens of KMP and VMP in transplant-ineligible NDMM patients. Increased toxicity in the carfilzomib group of CLARION may explain clinical outcomes, and melphalan may not be an ideal drug to combine with carfilzomib in this setting. The study suggested that alternative carfilzomib based regimens merit further evaluation in NDMM patients.

References

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