Cyclophosphamide, Bortezomib and Dexamethasone (CYBORD) Treatment for Relapsed/Refractory Multiple Myeloma

Jorge Monge, MD; K. Martin Kortüm, MD; A. Keith Stewart, MB, ChB; P. Leif Bergsagel, MD;
Joseph Mikhael, MD; Craig B. Reeder, MD; Angela A. Mayo, PA-C; Rafael Fonseca, MD
Division of Hematology and Oncology – Mayo Clinic – Scottsdale, Arizona – USA

Abstract

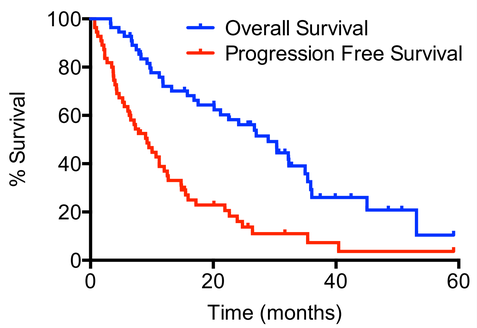
Background: Patients with multiple myeloma have experienced an increase in survival due to rescue options provided by novel agents used alone and in combination. There is a paucity of data for combinatorial regimens in this population. CYBORD has been validated as an upfront strategy with excellent long-term outcomes, but its use in relapsed disease has not been fully reported.[1,2] We report a series of 55 patients with relapsed/refractory MM and their response to CYBORD.

Methods: 55 patients with relapsed/refractory MM were treated with CYBORD on a 28 day cycle. Dosing was cyclophosphamide 300 mg/m^2 PO once weekly; bortezomib 1 (2%), 1.3 (22%) or 1.5 mg/m^2 (76%), IV (89%) or SQ (11%), once (87%) or twice weekly (13%); and dexamethasone 40 mg PO once weekly. We report response using the IMWG criteria[3], and new onset neuropathy based on NCI CTCAE[4].

Results: Mean age was 65.6 years and 56% were male. Of the 55 patients, 64% had progressed while on therapy and 56% had a previous ASCT. Mean number of previous treatment lines was 3.3, and 36% and 82% were proteasome inhibitor (PI) and CYBORD naïve. Median follow up time was 24.1 months and mean number of cycles was 5 (±4.4). ORR was 71%, 26% had ≥VGPR, and 13% CR. PI naïve patients had an ORR of 95% while patients who had previously received a PI had an ORR of 57%. Median PFS and OS were 9.2 and 29 months, respectively. After a mean of 6 cycles, 22% of patients underwent subsequent ASCT. New onset grade 1 neuropathy was present in 16% of patients, while only 2% had grade 2 and none had grade 3 or greater neuropathy. We found an increase in PFS in PI naïve patients (14.8 v 5.2 months, HR 0.4, 95%CI 0.2-0.7), patients that underwent a subsequent ASCT (19.7 v 6.3 months, HR 0.3, 95%CI 0.2-0.7) and patients that had ≤3 prior treatment lines (12 v 6.1 months, HR 0.5, 95%CI 0.2-0.8); no difference was found by mSMART[5] risk or prior ASCT. An increase in OS was found only in PI naïve patients (35.4 v 21.2 months, HR 0.5, 95%CI: 0.3-0.98) and patients that underwent a subsequent ASCT (53.1 v 26.7 months, HR 0.3, 95%CI 0.2-0.8); no difference was found by number of previous treatment lines, mSMART risk or prior ASCT.

Conclusions: CYBORD is an effective treatment regimen without significant increase in side effect profile for patients with relapsed/refractory MM, achieving better outcomes in PI naïve patients and those who undergo a subsequent ASCT, regardless of mSMART risk.

All Patient Survival

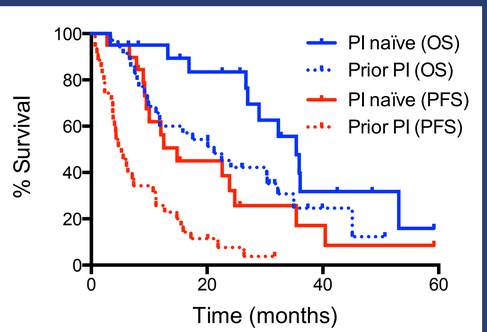


Median OS and PFS were 29 and 9.2 mos., respectively, with a 71% ORR.

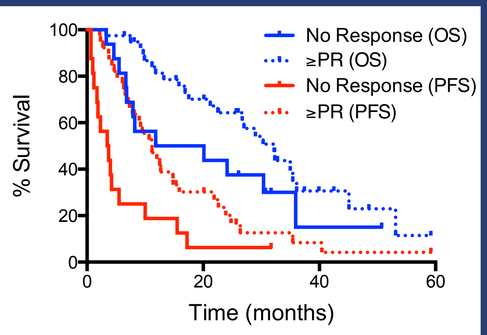
Subgroup Survival Analysis

	PI naïve v. Prior PI Therapy	No Prior ASCT v. Prior ASCT	Progressed Off v. On Therapy	No Response v. ≥PR	No ASCT v. Subsequent ASCT	Standard v. High Risk by mSMART	≤3 v. >3 Previous Treatments
ORR (%, p-value)	**95 v. 57 (0.004)**	79 v. 65 (0.37)	80 v. 66 (0.36)	N/A	70 v. 75 (0.51)	73 v. 64 (0.73)	78 v. 61 (0.23)
Median PFS (months, p-value)	**14.8 v. 5.2 (0.002)**	10.7 v. 6.6 (0.15)	15.9 v. 6.6 (0.08)	**3.6 v. 11.2 (<0.0001)**	**6.3 v. 19.7 (0.003)**	6.6 v. 8.9 (0.76)	**12.0 v. 6.1 (0.01)**
Hazard Ratio (95%CI)	**0.4 (0.22 – 0.68)**	0.66 (0.37 – 1.16)	0.59 (0.34 – 1.04)	**2.35 (1.45 – 6.74)**	**3.12 (1.38 – 4.53)**	1.11 (0.58 – 2.12)	**0.49 (0.24 – 0.81)**
Median OS (months, p-value)	**35.4 v. 21.2 (0.049)**	30.4 v. 24.1 (0.38)	45.1 v. 26.7 (0.11)	16.0 v. 32.2 (0.08)	**26.7 v. 53.1 (0.014)**	26.7 v. 19.4 (0.56)	32.3 v. 24.1 (0.14)
Hazard Ratio (95%CI)	**0.51 (0.26 – 0.98)**	0.75 (0.38 – 1.42)	0.56 (0.3 – 1.14)	1.83 (0.92 – 4.52)	**3.24 (1.25 – 5.27)**	0.81 (0.37 – 1.7)	0.62 (0.31 – 1.17)

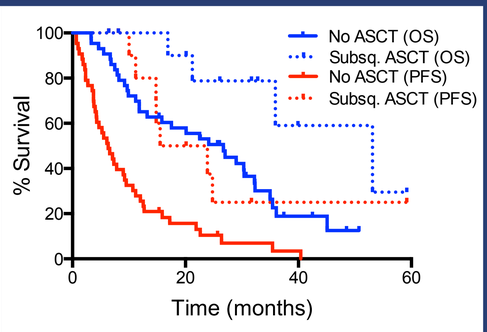
PI naïve v. Prior PI Therapy



No Response v. ≥PR



No ASCT v. Subsequent ASCT



References

1. Reeder CB, Reece DE, Kukreti V, Chen C, Trudel S, Hentz J, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. Leukemia. 2009;23(7):1337-41.
2. Khan ML, Reeder CB, Kumar SK, Lacy MQ, Reece DE, Dispenzieri A, et al. A comparison of lenalidomide/dexamethasone versus cyclophosphamide/lenalidomide/dexamethasone versus cyclophosphamide/bortezomib/dexamethasone in newly diagnosed multiple myeloma. British journal of haematology. 2012;156(3):326-33.
3. Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20(9):1467-73.
4. Common Terminology Criteria for Adverse Events v4.0. National Cancer Institute. NCI, NIH, DHHS. May 29, 2009. NIH publication # 09-7473
5. Mikhael JR, Dingli D, Roy V, Reeder CB, Buadi FK, Hayman SR, et al. Management of Newly Diagnosed Symptomatic Multiple Myeloma: Updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines 2013. Mayo Clin Proc. 2013;88(4):360-76.