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Abstract 2952 Anti-Myeloma Effects of Carfilzomib with Cyclophosphamide (CY) or Bendamustine (Ben)

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Introduction: Carfilzomib (Onyx Pharmaceuticals, South San Francisco, CA, USA) is an irreversible proteasome inhibitor (PI) that has shown preclinical and clinical efficacy against multiple myeloma (MM). It has shown clinical benefit as a single agent and with steroids in early clinical trials, even among patients resistant to prior bortezomib treatment. We determined the anti-MM effects of carfilzomib in combination with cyclophosphamide (CY) or bendamustine (Ben) *in vivo* using our xenograft model of human MM, LAGk-1A. *Methods:* Each SCID mouse received a 20 – 40 mm^3 MM tumor piece surgically implanted into the hind limb. Seven days post-implantation mice were bled, human IgG levels were measured by ELISA and mice randomized into groups. Carfilzomib stock solution (2 mg/ml) was diluted to 3 mg/kg using 10% capsitol and administered twice weekly via intravenous (i.v.) injection. Cyclophosphamide (Baxter, Deerfield, IL, USA) stock solution (20 mg/ml) was diluted in sodium chloride and administered via oral gavage once weekly at 10 mg/kg. Bendamustine (Teva Pharmaceuticals, North Wales, PA, USA) stock solution (5 mg/ml) was diluted to 5 mg/kg in sterile water and administered via intraperitoneal (i.p.) once weekly. Mice (n = 8) were bled to determine hIgG levels and the tumors were measured using standard calipers. Data was analyzed as the mean ± SEM. *Results:* LAGk-1A-bearing mice treated with single agent carfilzomib or CY did not show a reduction in tumor growth compared to vehicle-treated mice. In contrast, the combination of carfilzomib plus CY resulted in a statistically significant decrease in tumor size and IgG levels when compared to vehicle-treated mice on days 35, 42, 49, and 56 (tumor volume; $P = 0.0007$, $P = 0.0003$, $P = 0.0008$ and $P = 0.0001$: IgG levels; $P = 0.0023$, $P = 0.0327$, $P = 0.0219$ and $P = 0.0190$, respectively). Toxicity was minimal as seven of eight mice survived this combination regimen. Furthermore, tumor growth delay (TGD) to a volume of 1,125 mm^3 was delayed by 53.6% (22 days, day 41 for control compared to day 63 for the carfilzomib + CY group) among animals receiving this combination treatment regimen when compared to vehicle-treated animals. In contrast, shorter TGDs were obtained when mice were dosed with single agents. When mice were dosed with carfilzomib alone, a TGD of 12.1% (5 days, day 41 for

control compared to day 46 for the carfilzomib group) was obtained. When mice were dosed with CY alone, a TGD of 26.8% (11 days, day 41 for control compared to day 52 for the CY group) was obtained. Percentage inhibition of tumor growth (*T/C*) is represented as the median tumor volume of the test drug group over the median tumor volume of the vehicle group. A *T/C* ratio of ≤42% is indicative of drug efficacy. At day 56 post tumor implantation, mice receiving single agent treatment with carfilzomib or CY had T/C's of 88% and 67%, respectively. In contrast, at the same time point, mice receiving the cafilzomib plus CY regimen resulted in a lower percentage *T/C* of 29%. We also evaluated the combination of carfilzomib plus Ben in LAGk-1A-bearing mice. Animals treated with single agents did not result in a reduction in tumor volume compared to vehicle-treated mice. In contrast, the combination of carflzomib and Ben resulted in a decrease in tumor size compared to vehicle-treated mice on days 35, 42, 49, and 56 ($P = 0.0184$, $P < 0.0001$, $P = 0.0035$, and $P = 0.0026$, respectively). Additionally, this combination resulted in a reduction in IgG levels compared to vehicle-treated mice on days 42, 49 and 56 ($P = 0.0426$, $P = 0.0257$ and $P = 0.0204$, respectively). Furthermore, six of eight mice survived this treatment regimen. Compared to vehicle-treated mice, animals treated with the combination treatment showed a TGD to 1,250 mm^3 of 38% (16 days, day 42 for control compared to day 58 for the carfilzomib + Ben). When compared to vehicle-treated mice, carfilzomib-treated animals showed a TGD of only 14.3% (6 days, day 42 for control compared to day 48 for the carfilzomib), and there was no TGD for mice treated with Ben alone. *Conclusions:* We have shown that the combination of carfilzomib plus CY or Ben shows marked anti-MM effects using our xenograft MM model LAGk-1A. The results from these preclinical studies provide the basis for clinical trials evaluating the combination of carfilzomib with CY or Ben for patients with MM.

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