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Abstract

Allogeneic hematopoietic stem cell transfer (HSCT) can act as a powerful immunotherapy and is a cornerstone treatment for many malignant hematologic diseases. However, development of graft versus host disease (GVHD) remains as a major complication after HSCT, and affects numerous organs. Furthermore, chronic GVHD is emerging as a predominant cause of morbidity. Chronic GVHD has a distinctive pathology and pathogenesis and can develop in the form of scleroderma manifested with cutaneous sclerosis, loss of hair follicles, epidermal atrophy and replacement of peri-accinar fat. We and others have previously demonstrated that bortezomib, a proteasome inhibitor, can prevent acute GVHD if given immediately after HSCT but that continuous treatment of mice resulted in accelerated GVHD-induced gut pathology in the colon and CD4+ T-cells. We therefore wanted to assess the effects of bortezomib on chronic GVHD or in particular acute GVHD models where CD4+ T-cells were responsible for the disease.

Materials and Methods

Chronic GVHD model

Different strains of mice were used for the experiments. All mice were housed under pathogen-free conditions and were maintained in a 12-hour light/dark cycle. Mice were fed standard chow and water ad libitum. Treatment with bortezomib (1.0 mg/kg) or vehicle, 5 days per week, was started before transplantation in the chronic GVHD model. A total of 10 mice were treated with bortezomib and 10 mice were treated with vehicle. Treatment was continued for 4 weeks after transplantation. The mice were examined weekly for skin lesions, weight gain, and other signs of disease.

Fig. 1. Increase of bortezomib on cutaneous lesions.

Fig. 2. Gene expression of bortezomib with chronic GVHD treatments.

Fig. 3. Decrease of B cells post-acute GVHD with bortezomib treatment.

Results

Conclusions

We have shown the organ-specific protection of low-dose bortezomib in both acute and chronic MHC-mismatch allogeneic immunotherapy models.

References

1. Chen-Chun Pai1, Erik Ames, PhD, Minjiye Chen, MD, PhD, Lam Khue1, Anna-Mirsoian, Abedi, Annie E Zamora1, Arta Mongeza1, MD, PhD, Julian Perks, PhD, Shubh Jumaa2, Methidad Abebi, MD and William J Murphy1

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Fig. 4. Treatment of chronic GVHD with bortezomib in a clinical GVHD patient.

A single institution pilot study of bortezomib was initiated in patients with clinical-dependent, steroid-refractory, or -intolerant chronic GVHD. Patients received oral bortezomib at a dose of 1.5 mg/m2 daily for 5 days a week. GVHD was assessed using the NIH chronic GVHD Clinical Activity Index. The results were collected through the institution. Total number of sampled blood (0.25-0.50ml) from 5 patients were analyzed by flow cytometry and bioluminescence. In addition to the follow-up, dose escalation (0.25-0.50ml) were also analyzed. The differences were compared to the total number of served samples and analyzed by ANOVA and Tukey's test to compare between individual groups. P<0.05 (**), P<0.01 (***) and P<0.001 (****) were considered as significant.

Fig. 5. The bortezomib ameliorates chronic GVHD lesions while maintaining GvHD effects. Chronic GVHD mice were treated with bortezomib on day 21. 30 days after transplantation, the mice were sacrificed and the skin was harvested for histology. The skin samples were collected at day 5, 10 and 15 PTH was performed to detect BMF gene expression levels. All of the data are shown in average ± SEM and analyzed by Tukey’s test or by ANOVA (**). P<0.05 (**), P<0.01 (***) and P<0.001 (****) were considered as significant.

Fig. 6. Bortezomib ameliorates chronic GVHD lesions while maintaining GvHD effects. Chronic GVHD mice were treated with bortezomib on day 21. 30 days after transplantation, the mice were sacrificed and the skin was harvested for histology. The skin samples were collected at day 5, 10 and 15 PTH was performed to detect BMF gene expression levels. All of the data are shown in average ± SEM and analyzed by Tukey’s test or by ANOVA (**). P<0.05 (**), P<0.01 (***) and P<0.001 (****) were considered as significant.