COMPARISON OF BLINATUMOMAB AND BIOSIMILAR CD19xCD3 BITE RESPONSES IN PBMC-HUMANIZED MICE USED AS A PRECLINICAL LYMPHOMA MOUSE MODEL

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Background The development of new bispecific antibodies such as bispecific T cell engagers (BiTE) is a hot avenue in cancer immunotherapy. BiTE antibodies interact simultaneously with epitopes located on T cells and target cells, so can direct T cells to cancer. Despite significant success, adverse effects are often reported with cancer immunotherapies. In recent years, PBMC-humanized mice have emerged as a valuable preclinical model that recapitulates patient responses observed in clinics. Therefore, such models can be used for personalized screening of a patient’s immune response, and an evaluation of immunotherapy’s efficacy and safety before starting treatment. Here, we used JAX’s established protocol for cancer therapy in PBMC-humanized mice to compare the efficacy and cytokine responses of two BiTE products – Blinatumomab, an FDA-approved drug, and a biosimilar CD3xCD19 BiTE. Blinatumomab, which was approved for treatment of Philadelphia chromosome-negative B-cell acute lymphoblastic leukemia (ALL), is a well-known and heavily studied cause of cytokine release syndrome (CRS). The clinical data showed that up to 15% of patients who received blinatumomab develop CRS, with as many as 5% of those cases reported as severe (CRS score >3).

Methods Raji-Luc lymphoma cells were intravenously injected in PBMC-humanized NSG-MHC I/II double knockout mice. Next, the mice were treated intravenously with blinatumomab or biosimilar BiTE provided at 0.1, 0.01, or 0.001 mg/kg concentrations, which, as previously described, is within the range used in clinics.1 Four hours post-treatment, serum was collected and analyzed for cytokines using Luminex multiplex assay. During the study, we performed daily CRS scoring and in vivo imaging to trace tumor cell clearance for two weeks post-dosing.

Results Strong efficacy and similar cytokine changes for both tested drugs were observed. In addition to IL-2, and consistent with clinical data, we found a dose-dependent increase of multiple CRS-inducing cytokines (IFN-gamma, TNF-alpha, GM-CSF, IL-6, IL-8, IL-10, MCP-1 and MIP-1B). Interestingly, the biosimilar BiTE showed equal or greater efficacy and more robust cytokine production (for some cytokines) than Blinatumomab even at the lowest tested concentrations. This may be due to differences in the expression systems used in their production (HEK and CHO, respectively), or in their formulation.

Conclusions These results confirm previous data from our lab showing that the PBMC-humanized mouse platform could be an important tool in evaluating the anti-tumoral efficacy of immunotherapies. Moreover, the ability of this model to accurately measure biological activity could be used to optimize concentrations of similar products before human use.

Ethics Approval All human samples were obtained from a commercial source.

REFERENCE

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