Background

Immunotherapy is an important tool that can be used to stimulate a patient's own immune system against cancer. One of these immunotherapy targets is 4–1BB, a costimulatory molecule designed to activate anti-tumor activity. Two 4–1BB agonists, urelumab and utomilumab, investigated in clinical trials showed different safety profiles. Urelumab was found to induce liver toxicity while utomilumab was well tolerated. We recently evaluated urelumab and utomilumab in our PBMC humanized mouse model with two PBMC donors and showed similar results to the clinical trials. Urelumab treated mice showed liver toxicity, while utomilumab treated animals did not. Following the FDAs recommendations for evaluating safety profiles from multiple PBMC donors, we here evaluated urelumab induced toxicities in five new PBMC donors.

Methods

For this study, NSG-DKO mice were engrafted with PBMC from one of five human PBMC donors and then dosed with 3 mg/kg of urelumab or PBS. Mice were evaluated daily for bodyweight loss and clinical evaluation scores. Mice were euthanized six days after treatment. Livers and terminal serum were collected for histology and serum clinical chemistry.

Results

Of the five donors, two donors showed significant bodyweight loss compared to the PBS treated mice. Three of the five donors demonstrated elevated serum AST and ALT, as well as elevated IFNγ, IL-8, TNFα, IP-10, MIG, MCP-1, MIP-1α and MIP-1β. Likewise, these same three donors also displayed higher necrosis, mononuclear cell infiltrate, and apoptosis scoring on liver histology. One PBMC donor showed no significant differences in any of the tissues we analyzed while the other donor, not included among the three donors with severe toxicity, showed moderate signs of toxicity including liver necrosis, liver apoptosis, and marked mononuclear infiltrates.

Conclusions

The results of urelumab treated PBMC humanized mice mimicked findings from the clinical trial suggesting that our model could identify the clinically relevant toxicity profile induced by 4–1BB agonists. Furthermore, the differing toxicity profiles from the five PBMC donors illustrate the value of using PBMC humanized mouse models for preclinical safety assessments. Data from multiple PBMC donors can be used as a tool to evaluate how therapeutics will be tolerated in the greater population as well as used as a tool to assess individual patient responses.

Ethics Approval

This study was approved by The Jackson Laboratory IACUC# 16000–1 and by The Jackson Laboratory IBC #2016–0014. All human derived cells were obtained from commercially available sources.

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