Graft-versus-Host Disease (GvHD) Concerns in Preclinical Evaluation of Chimeric Antigen Receptor T-Cell (CAR-T) Therapy in Immunodeficient Mice

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INTRODUCTION

The rapid development of CAR-T (chimeric antigen receptor T-cell) therapies offers great promise in cancer treatment. Efficacy and safety assessments in immune-deficient mice are critical components for successful therapeutic development. However, the occurrence of Graftversus- Host Disease (GvHD) presents challenges in assessing preclinical toxicity of novel CAR-T therapies.

Despite a number of studies that have analyzed the development of GvHD in mouse models, and the available standards for GvHD assessment in humans, safety evaluation remains difficult due to similar responses of tumor-bearing mice and mice with GvHD.

This study aims to identify specific parameters and standards for GvHD recognition in preclinical toxicity studies of CAR-T therapies.

METHODS

To identify useful parameters that define GvHD in tumor bearing mice dosed with CAR-T cell therapies, 25 preclinical toxicity studies with different CAR-T products were analyzed.

Clinical observations after treatment including body weight changes and other GvHD manifestations defined in previously set diagnostic standards as well as comprehensive histopathology evaluations were analyzed from 1659 mice. The data were categorized as tumor-bearing control group (n = 397), control T-cell group (n = 318), low dose CAR-T cell group (n = 433) and high dose CAR-T cell group (n = 511).

Table 1. Information of Study Distribution

Cell Therapy Studies Total	**75**
CAR-T	42
Species Used in CAR-T	
NOG Mice	25
NOD Mice	2
NPG Mice	6
NCG Mice	5
ICR Mice	1
B-NDG Mice	3

RESULTS

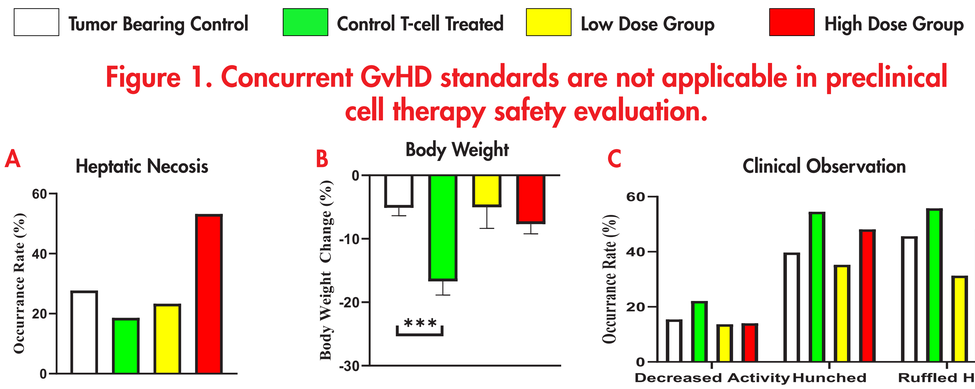


Figure 1. Concurrent GvHD standards are not applicable in preclinical cell therapy safety evaluation.

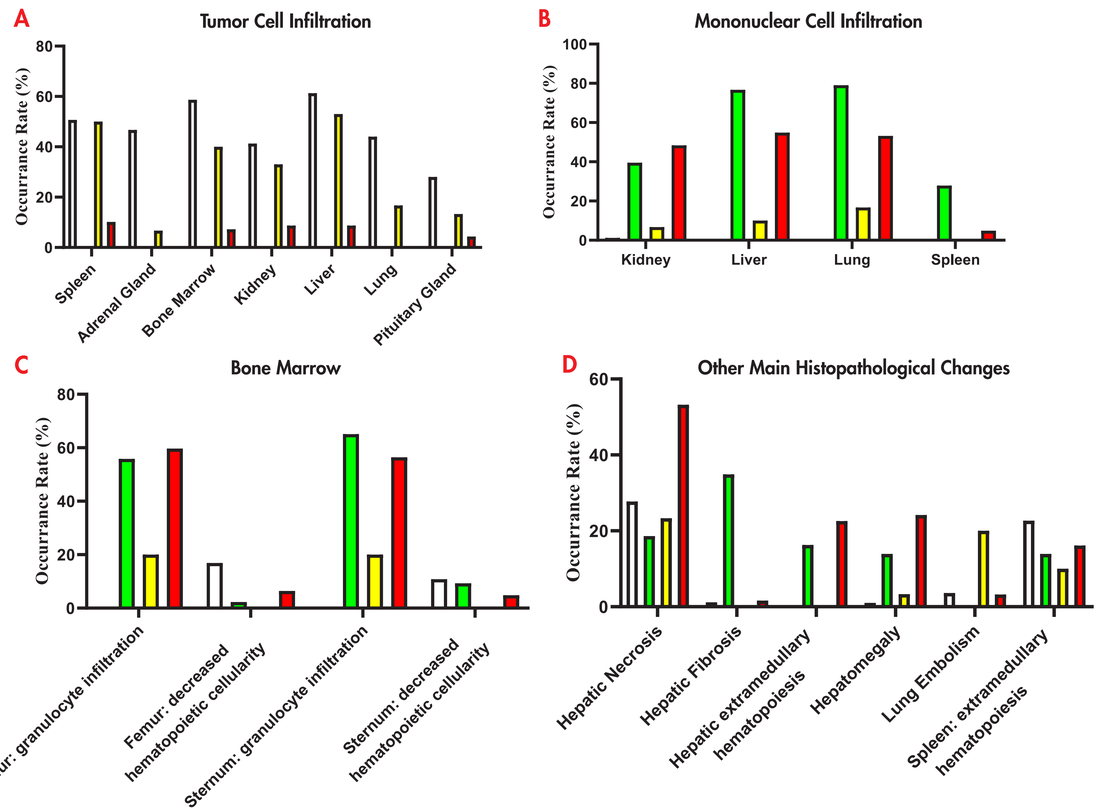


Figure 2. Main Histopathology Changes in Animals Found Dead

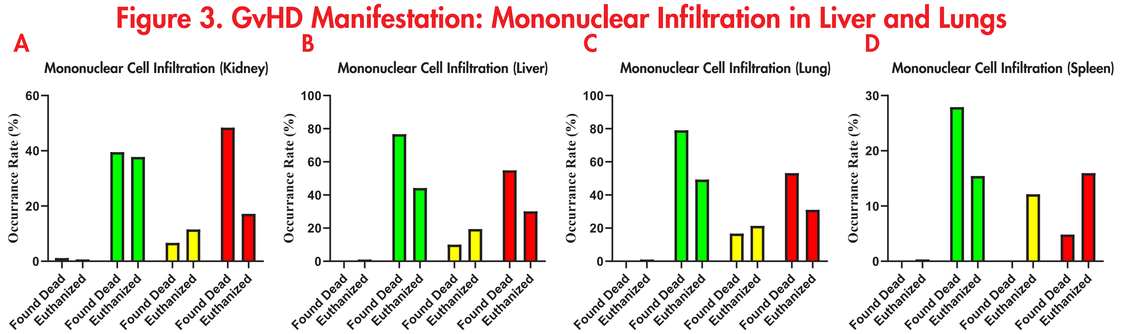


Figure 3. GvHD Manifestation: Mononuclear Infiltration in Liver and Lungs

Figure 4. GvHD Manifestations: Hepatic fibrosis, Extramedullary Hematopoiesis and Hepatomegaly

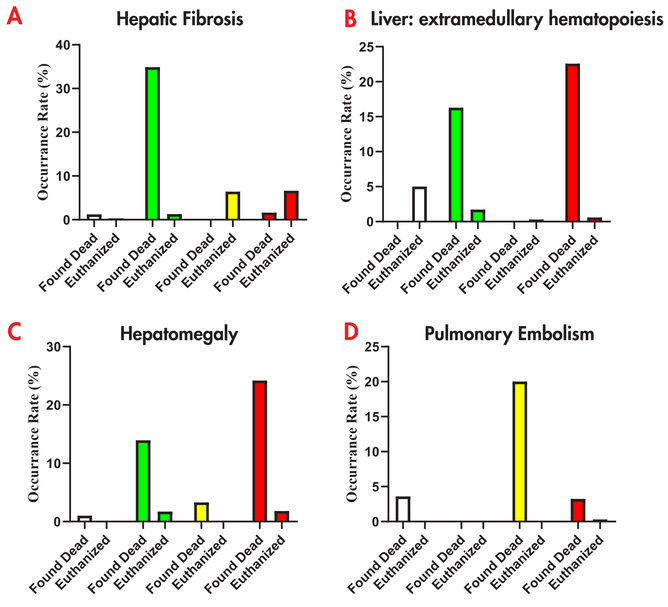
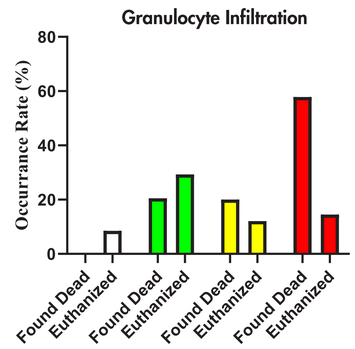


Figure 5. GvHD Manifestation: Granulocyte Infiltration



CONCLUSION

Specific parameters including hepatic fibrosis, hepatic extramedullary hematopoiesis, hepatomegaly, granulocyte infiltration in bone marrow and mononuclear cell infiltration in liver and lungs in immunodeficient mice were identified in this study as key markers of GvHD. This study established a reliable standard to differentiate effects of GvHD versus toxicity in CAR-T cell safety assessment studies. This study paves the way for improving evaluation of toxicity for preclinical safety assessment of CAR-T and/or cell therapies.

ACKNOWLEDGEMENTS

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