ELSEVIER

Blood 142 (2023) 1454

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

605.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: LYMPHOID NEOPLASMS

New Suitable Eμ-Tcl1 Mouse Model for Research on BH3-Mimetics Therapy Response In Vivo

Ismini Halmer, MD[1,2,3], *Laura Beckmann, MD*[1,2,3], *Gero Knittel, PhD*[4,1,3], *Hamid Kashkar, PhD*[5], *Hans Christian Reinhardt, MD*[6,1,3], *Michael Hallek, MD*[1,2,3], *Alexandra Da Palma Guerreiro, PhD*[1,2,3], *Lukas Peter Frenzel, MD*[1,2,3]

[1] Faculty of Medicine and Cologne University Hospital, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, University of Cologne, Cologne, Germany, Cologne, Germany
[2] CECAD, Center of Excellence on Cellular Stress Responses in Aging-Associated Diseases, Center for Molecular Medicine Cologne, Cologne, Germany, Cologne, Germany
[3] Center of Integrated Oncology Aachen Bonn Cologne Duesseldorf (ABCD), University Hospital Cologne, Cologne, Germany, Cologne, Germany
[4] Department of Hematology and Stem Cell Transplantation, University Hospital Essen, Essen, Germany
[5] Med. Microbiol. and Immunol. University of Cologne, Cologne, Germany
[6] Department of Hematology and Stem Cell Transplantation, University Hospital Essen, Essen, Germany

Introduction: Generation of appropriate mouse models to study clinically active compounds is inevitable. Currently, the commonly used mouse model for CLL is the TCL1 transgenic model, which shows an expression of the human TCL1 oncogene in B cells. While this model resembles many features of human CLL, it is resistant to venetoclax, a BCL2 inhibitor which represents an important treatment option for CLL and other hematological malignancies. The lack of therapeutic response to venetoclax is an important limitation of the TCL1 mouse model. As a result, the effectiveness, the mechanisms, and the development of venetoclax resistance and other BH3 mimetics cannot be investigated in the TCL1 transgenic setting.
Methods and results: To overcome the stated limitations, a novel mouse model was generated expressing human BCL2 in B cells under the control of the TCL1 promoter. We established a new mouse model (TBC) by crossbreeding Eμ-Tcl1 $^{tg/wt}$ mice with mice containing a B cell specific conditional Bcl-2 $^{Rosa26/wt}$; Cd19Cre $^{Cre/wt}$ overexpression (control group Eμ-Tcl1 $^{tg/wt}$; Cd19Cre $^{Cre/wt}$: TC). Initial data show a strong leukocytosis ($p<0,0001$) and splenomegaly in TBC mice leading to a significantly shortened overall survival compared to TC mice (log-rank: $p=0,0028$). Immunophenotyping revealed a population of class-switched IgM $^{-}$ B cells within TBC mice and only a small population of Cd19 $^{+}$/Cd5 ^{dim} cells. Transcriptomics followed by gene enrichment analysis showed a development of GCB-type DLBCL in TBC mice compared to TC mice.
Apoptosis assays revealed high sensitivity towards BH3 mimetics, especially BCL2 inhibitor venetoclax. *In vitro* experiments demonstrated that B cells from TBC mice are 10 times more sensitive towards venetoclax treatment. Based on this fact, we treated 5 TBC mice for 4 weeks with venetoclax. Even in this short treatment time frame, there was a strong loss of leukocytes in peripheral blood of about 60%, leading to normal ranges of leukocytes in TBC mice after even 14 days of treatment with venetoclax. Interestingly, we observed a massive change of Cd4 $^{+}$/Cd8 $^{+}$ ratio towards Cd4 $^{+}$ cells due to venetoclax treatment, indicating that our novel model resembles human settings.
Conclusions: We were able to show a strong therapy response towards treatment with venetoclax *in vivo* in TBC mice leading to a loss of leukocytes, a gain of CLL typical Cd19 $^{+}$/Cd5 ^{dim} cells and a strong effect on tumormicroenvironment with a significantly changed Cd4 $^{+}$/Cd8 $^{+}$ ratio. This makes the new mouse model very suitable for testing and observing venetoclax therapy response, its side effects and outcome *in vivo*, to provide our patients with the best possible therapy.

Disclosures Hallek: *Gilead:* Consultancy, Honoraria, Research Funding; *Janssen:* Consultancy, Honoraria, Research Funding; *Abbvie:* Consultancy, Honoraria, Research Funding; *BeiGene:* Consultancy, Honoraria, Research Funding; *AstraZeneca:* Consultancy, Honoraria, Research Funding; *Roche:* Consultancy, Honoraria, Research Funding.

https://doi.org/10.1182/blood-2023-186330