ELSEVIER

Blood 142 (2023) 417–418

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

605.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: LYMPHOID NEOPLASMS

Phenotypic Drug Response Profiling Identifies Asparaginase-Based Synergistic Combinations for Very High Risk Acute Lymphoblastic Leukaemia

Jasmeet Sidhu, MD[1,2,3], *Fabio D. Steffen, PhD*[4], *Iria Anne Jimenez*[3], *Yun Huang*[3], *Kerstin K. Rauwolf*[3], *Arijit Chakraborty*[5], *Shekhar Krishnan*[2,1,6], *Vaskar Saha, PhD FRCP, FRCPath*[6,2,1], *Beat Bornhauser, PhD*[4], *Jean-Pierre Bourquin, MD PhD*[7]

[1] Tata Translational Cancer Research Center, Tata Medical Center, Kolkata, India
[2] Department of Paediatric Haematology and Oncology, Tata Medical Center, Kolkata, India
[3] University Children's Hospital, Zurich, Switzerland
[4] Department of Oncology, University Children's Hospital Zurich, Zurich, Switzerland
[5] Tata Translational Cancer Research Center, Kolkata, India
[6] Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom
[7] Department of Oncology and Children's Research Center, University Children's Hospital Zurich, Zurich, Switzerland

In acute lymphoblastic leukaemia (ALL), empirical multi-drug chemotherapy combinations lead to >85% cure rates in children. But 10-15% of patients show suboptimal response and as drugs are dosed to tolerance, further intensification is not possible. An exception is the key antileukaemic drug, asparaginase (ASNase), which is not associated with dose-related toxicity. We evaluated the use of *ex-vivo* co-culture based drug response profiling (DRP) to identify novel synergistic and effective drug combinations with ASNase for patients with suboptimal responses to standard chemotherapy in ALL.

Patient-derived xenograft (PDX) ALL cells from 5 patients with high-risk B-ALL (3 B-other, 2 *IKZF*^{plus}) were treated with 120 drugs in 5-point serial dilutions in combination with or without an IC_{50} dose of ASNase, in co-cultures with hTERT-immortalized primary bone marrow stromal cells. Eight clinically relevant agents with promising sensitizing activity as identified by decreased area-under-the-curve with addition of ASNase were identified (SEL, selinexor; ELTA, eltanexor; VEN, venetoclax; BZM, bortezomib; navitoclax; carfilzomib; mitoxantrone, birinapant).

We validated combinations of ASNase with the 8 selected drugs plus 4 drugs used in induction therapy (prednisolone, dexamethasone, vincristine and daunorubicin) using a 4x4 drug matrix in 15 high-risk ALL PDX samples. Synergy scores were calculated using the zero-interaction potency (ZIP) model. Synergy (ZIP score ≥10) or additivity (ZIP score >0 and <10) with ASNase was identified for exportin-1 inhibitors (XPO1i; selinexor, eltanexor), venetoclax and proteosomal inhibitors (bortezomib, carfilzomib) in 100% (15/15), 86.6% (13/15) and 80-86.6% (12/15 and 13/15) samples respectively. Antagonism (ZIP score <0) was noted in more than one-third (6/15) of samples with ASNase in combination with steroids or vincristine. Three-drug combinations were evaluated *ex-vivo* in these 15 PDX samples. Synergy was identified with addition of low doses of BZM or VEN to the ASNase-SEL combination (ASNase-SEL-BZM and ASNase-SEL-VEN).

Next, 4-6 mice per treatment arm were transplanted intravenously with 1 million ALL cells from 4 high-risk B-ALL patients. Randomized cohorts were treated with vehicle, ASNase-BZM-ELTA (ABE) and ASNase-dexamethasone-vincristine (ADV). Leukemic burden was assessed weekly using flowcytometry. The mice tolerated both treatment arms well. Platelet counts recovered within one week after an initial drop in the ABE arm. Both treatment groups had significant improvement in event free survival (EFS) as compared to the control group (ABE p-value 0.0082; ADV p-value 0.0325) though no significant differences were noted between the 2 treatment arms (p-value 0.8971).

Three patients with high-risk medullary relapsed/refractory BCP-ALL, 2 not in morphological remission and 1 at time of very early relapse, received a combination of ASNase-BZM-VEN-SEL (ABVS) after consent. One patient for whom DRP suggested sensitivity to both SEL and VEN achieved molecular remission (molecular minimal residual disease $< 10^{-5}$) after one course of therapy remaining in complete remission 11 months later. Two patients with sensitivity to SEL but not to VEN as assessed by DRP, had progressive disease. ABVS was well tolerated in these patients with no grade 3-4 adverse events.

Our results identify XPO1 inhibitors as a new class of drugs with promising anti-leukaemic activity in BCP-ALL. Co-culture based DRP shows promise in identifying alternative novel sensitive synergistic combinations *ex-vivo* with decreased toxicity for patients who have an inadequate response to standard therapy.

Disclosures No relevant conflicts of interest to declare.

OffLabel Disclosure: Exportin-1 inhibitors block the muclear export of over 1000 proteins in humans. They are used for treatment in multiple myeloma and various clinical trials have reported their use in acute myeloid leukemia.

https://doi.org/10.1182/blood-2023-172885