

Combination antiretroviral therapy and MCL1 inhibition mitigate HTLV-1 infection *in vivo*

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Background:

BH3 mimetics are small-molecule therapeutics designed to lower the threshold for the induction of intrinsic apoptosis, a form of cell death, by antagonising the function of pro-survival BCL-2 family members. Many blood cancers, including ATL, are recognised to be associated with elevated levels of pro-survival BCL-2 proteins marking them as attractive therapeutic targets for preferential killing. Here, we assessed the efficacy of clinical-stage BH3 mimetics, venetoclax and S63845, in combination with antiretrovirals, for the treatment of HTLV-1 infection in humanised mice.

Methods:

Humanised NOD SCID IL2 $\gamma^{-/-}$ mice were adoptively transferred autologous HTLV-1-infected PBMC before administration of venetoclax or S63845 (BCL-2 or MCL-1 antagonists, respectively) for 3 weeks. Mice were administered antiretrovirals, tenofovir alafenamide and dolutegravir, to mitigate viral spread. HTLV-1c PVL and human cell number were quantified in the periphery at 3-, 5-, and 7-weeks post infection.

Results:

After three weeks of S63845 treatment, HTLV-1c PVL was undetectable in 81% of mice (13 of 16 mice) compared to 20% of control animals (3 of 15 mice) ($p=0.0007$). Provirus was increasingly detectable at later time points, but this was significantly delayed compared to control ((2.33wks (1.05 to 5.21), median survival (95% CI)) ($p=0.0093$). Venetoclax treatment did not significantly impact provirus where 54% of drug-treated mice (7 of 13 mice) had undetectable provirus compared to 42% of control mice (5 of 12 mice) at three weeks post infection ($p=0.6005$). S63845 treatment curtailed HTLV-1c-driven expansion of the CD4⁺ T cell population compared to vehicle treated mice from zero to seven weeks post-infection (5.3-fold and 26.3-fold increase, respectively, $p=0.0024$).

Conclusion:

We provide a rationale for the use of clinical-stage BH3 mimetics, specifically those targeting MCL-1, in combination with antiretrovirals, for the treatment of established HTLV-1 infection. Our data support the initiation of clinical trials to investigate the efficacy of this strategy against HTLV-1.

Disclosure of Interest Statement:

None to declare.

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