First-in-human experience with hypomethylating agents and Venetoclax in Relapsed/Refractory North American Adult T-Cell Leukemia and Lymphoma patients (NA ATLL).

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Background/Purpose:

North American ATLL (NA ATLL) is a highly aggressive malignancy with a dismal prognosis at relapse. Epigenetic mutations have been proposed to be one of the main drivers of the chemotherapy refractory nature and aggressivity of this malignancy. We have shown previously in vitro activity of hypomethylating agents.

Approach:

Four patients heavily pre-treated, refractory and without other therapeutic options were treated with hypomethylating agents (Decitabine or Azacytidine) and/or Venetoclax depending on clinical context. Three patients had distinct epigenetic driver mutations.

Outcomes/Impact:
A 53 y/o man with lymphomatous ATLL who relapsed after conventional chemotherapy (cc), radiation therapy and Mogamulizumab was treated with Venetoclax and Decitabine and achieved a partial response. The second case was a 56 y/o woman with acute ATLL who relapsed rapidly after multiple lines of cc. Her mutations included BRCA2, TBL1XR1, CARD11, MALT1, POT1 and TET2 genes. She was treated with Azacytidine and Venetoclax and had 83% decrease in circulating ATLL cells. The third case was a 69 y/o man with acute ATLL relapsing cc. He had mutations in NTRK1, PBMR1 and TP53. He was treated with Decitabine and Venetoclax which resulted in decreased pleural and pericardial effusions. His circulating ATLL cells decreased 85%. Our fourth case was a 61 y/o lady with Acute ATLL with fulminant relapse immediately after cc. Her genomic profile revealed mutations in ARID2, KLF2, TP53 and CD274. She received ICE and Venetoclax with stabilization of calcium and LDH as well as decitabine resulting in an 80% decrease in circulating leukemia cells.

**Innovation and Significance:**

This is the first report of hypomethylating agents and venetoclax to treat chemotherapy refractory NA ATLL patients with both lymphomatous and acute forms showing objective responses. Earlier use of these agents may circumvent chemotherapy resistance and should be considered in prospective clinical trials.

**Disclosure of Interest Statement :**

*No pharmaceutical grants were received in the development of this study.*