

A Trial of Belinostat as Consolidation Therapy with Zidovudine for Adult T-Cell Leukemia-Lymphoma: Interim Results

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Background:

Adult T-cell leukemia-lymphoma (ATLL) is a generally fatal malignancy caused by the human T-cell leukemia virus (HTLV-1) frequently encountered in endemic regions of Japan, the Caribbean, and South America. Clinical trials using standard modern therapies have only yielded modest results. ZDV plus interferon (IFN α) can be efficacious in patients with leukemic ATLL forms, but response rates are still suboptimal as patients usually relapse and succumb to their disease. Belinostat is a pan-histone deacetylase (HDAC) that demonstrated apoptotic effects augmented by ZDV, induced Tax expression, and blocked HBZ in our ATLL preclinical models. Based this, we hypothesized that belinostat would reactivate HTLV-1 provirus in ATLL cells in subjects treated with ZDV (+/-IFN α), thus augmenting anti-tumor immune responses to help to eradicate residual disease.

Methods:

This phase 2 trial evaluates belinostat with ZDV-based therapy with optional standard or pegylated IFN α consolidation in patients with persistent ATLL after prior treatments. The regimen consists of eight 21-day cycles of intravenous belinostat 1,000 mg/m² (Days 1-5), oral ZDV 300mg three times daily with optional continuation of IFN α , followed by maintenance until at least month 12. The primary objectives are to evaluate safety and the complete molecular response rate. Secondary outcomes include clinical response rates, and molecular correlates measuring disruption of HTLV-1 latency in vivo, cytotoxic T-cell responses, and proviral load.

Results:

Clinical activity has been observed in 5 of 6 patients so far. Belinostat was discontinued in 2 patients who experiencing recurrent hematologic toxicities. Two patents have had major hematologic and molecular responses with no monoclonal evidence of blood-circulating ATLL cells by multiplex PCR lasting up to 16 months.

Conclusions:

The breakthrough clinical data so far demonstrated in 2 patients supports our main hypothesis that HDAC inhibitors may help eradicate ATLL cells in vivo, possibly by inducing HTLV-1 and provoking an immune response.

Disclosure of Interest Statement:

Nothing to disclose.