Pre-clinical Activity of Tipifarnib in Cutaneous T-cell Lymphoma

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Introduction
Cutaneous T-cell lymphoma (CTCL) is a rare form of non-Hodgkin lymphoma characterized by malignant infiltration of skin-homing CD4+ T-cells, manifesting clinically as patches and plaques on the skin. The disease will often progress from an indolent skin-limited form, Mycosis Fungoides (MF), to an aggressive leukemic variant, Sezary Syndrome (SS). As there are few effective therapies available for advanced-stage CTCL, we sought to explore potential novel therapeutic modalities. Farnesyl transferase inhibitors (FTIs) are a relatively new class of anticancer drugs, the exact mechanism of which is unknown. Tipifarnib is one such FTI, which has demonstrated clinical activity as a single agent in patients with relapsed and refractory lymphomas. Despite encouraging clinical and preclinical data, the precise molecular mechanisms of tipifarnib’s activity in lymphoma remain to be fully elucidated.

Methods and Results
We utilized CTCL patient-derived cell lines to evaluate the potential efficacy of tipifarnib in vitro. Our data on patient-derived cell lines show that half maximal effective concentration (EC50) ranged from 7.5nM for HuT78 to 50nM for SeaX (Figure 1A). This cytotoxicity was correlated to increases in apoptosis in these lines (Figure 1B). Importantly, there was no cytotoxic effect on normal donor CD4+ T-cells in vitro (data not shown). Based on these promising findings, we evaluated tipifarnib in vivo using a recently described interleukin-15 (IL-15) transgenic mouse model of CTCL (Mishra A, et al. Can Discov 2016). Following 2 weeks of dosing in 5 week old mice, we found a significant decrease in gross lesion severity in tipifarnib-treated mice (0.5±1.22 out of a possible score of 5) compared to vehicle-treated mice (3.3±2.57, p=0.0076) (Figure 2A, 2B). Histologically, IL-15 transgenic mice develop characteristic malignant CD4+ T-cell infiltrates in the dermis and epidermis (Figure 3A). Tipifarnib-treated mice, however, have minimal lesions in the skin (Figure 3B, 3C). These dramatic changes are reflected in a significantly decreased histologic severity score in tipifarnib-treated mice (3.8±0.75 out of a possible score of 7 (compared to vehicle-treated mice (7±0, p=0.0002) (Figure 3B).

Results
Figure 1. Tipifarnib, a farnesyl transferase inhibitor, decreases cell viability and increases apoptosis in CTCL lines in vitro

Figure 2. Tipifarnib treatment in vivo decreases CTCL disease severity in IL-15 transgenic mice

Figure 3. Tipifarnib treatment in vivo decreases histologic lesion severity in IL-15 transgenic mice

Conclusions
Our findings demonstrate that tipifarnib may prove beneficial for the treatment of CTCL as shown in efficacy observed in patient derived cell lines and mouse models of cutaneous T-cell lymphoma. Further studies to elucidate the mechanism of antitumor activity of farnesyl transferase inhibition in malignant T-cells are in progress.

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References