Plinabulin ameliorates chemotherapy-induced neutropenia: Mechanistic insights

Amlan K. Ghosh1, Yanfang P. Zhu1, Zhichao Fan1, Jacqueline F. Miller1, George K. Lloyd2, Catherine C. Hedrick1, Ramon Mohanlal2, Huang Lan2, and Klaus Ley1,3.

1La Jolla Institute 2BeyondSpring Pharmaceuticals 3University of California San Diego

Introduction

− Chemotherapy-induced neutropenia (CIN) is a major side effect of cancer chemotherapy associated with life-threatening infections, hospitalization, chemotherapy dose reduction and/or delay
− CIN is currently treated with recombinant human G-CSF but it has significant limitations such as bone pain and inconvenient administration regimen for patients receiving chemotherapy

− Plinabulin (NP1-2358) was discovered from marine and terrestrial Aspergillus sp.

− Plinabulin is a microtubule de-polymerizing agent (MDA) which binds to the β tubulin of the tubulin monomer near the colchicine binding site and prevents cell cycle progression of tumor cells
− Plinabulin is currently in Phase 3 clinical trial for NSCLC in patients undergoing docetaxel chemotherapy
− Plinabulin modulates tumor microenvironment by activating DCs and priming anti-tumor T cells
− It inhibits angiogenesis, disrupts existing tumor vasculature and induces cancer cell apoptosis
− Plinabulin also reduces CIN in cancer patients by mechanisms which remain unaddressed and is the focus of this study

Tubulin network in neutrophil under arrest

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Fig. 1. TIRF imaging with 10x oil objective of human neutrophils isolated from blood of healthy donors, labeled with 3uM Sir-Tubulin dye at the 2x10⁶/ml cell concentration at 37°C for 30 min before imaging. The cells were incubated with mAb24-AF488 and KIM127-DL550, 5ug/ml each, at RT and 3% of live CD45+ 3% of live CD45+ 3% of live CD45+ 3% of live CD45+ 3% of live CD45+ 3% of live CD45+ 3% of live CD45+ 3% of live CD45+ 3% of live CD45+

Results

Plinabulin partially rescues blood neutropenia

Plinabulin is currently in Phase 3 clinical trial for NSCLC in patients undergoing docetaxel chemotherapy

Plinabulin caused neutropenia in mice

− Docetaxel causes neutropenia in mice

Plinabulin effect on severe neutropenia in mice

− Docetaxel 25 mg/kg causes severe (grade 4) neutropenia in most mice defined as below mean - 50% (outside 95% confidence interval of normal). Plinabulin 15 or 20 mg/kg significantly reduces severe neutropenia caused by docetaxel on day 4 and almost eliminates severe neutropenia on day 5.

Mechanism: Flow cytometry of bone marrow

Plinabulin partially restores bone marrow neutrophils

Plinabulin has no effect on monocyte lineage

Conclusions

− Plinabulin effectively blunts docetaxel-induced neutropenia in mice
− One mechanism could be by relieving the docetaxel-induced accumulation LSK cells in the bone marrow
− Plinabulin specifically affects neutrophil production and has little effect on the monocye lineage
− Convenient administration regimen of G-CSF shows promise for treatment of CIN