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Abstract

A phase 1 trial of PT-100 in patients receiving myelosuppressive chemotherapy

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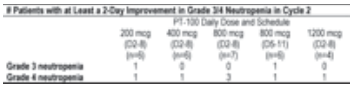
Background: PT-100 is a small molecule which competitively inhibits dipeptidyl peptidase activity of fibroblast activation protein (FAP) and dipeptidyl peptidase IV (DPP-IV). It rapidly increases cytokine (G-CSF, IL-8) production, accelerates neutrophil and erythrocyte regeneration, and causes tumor regression in mice via inhibition of FAP and DPP-IV. This dose-escalation study was conducted to evaluate the safety of PT-100 in patients receiving myelosuppressive chemotherapy (a doxorubicin or taxane based regimen) and to assess its effects on neutrophil recovery. **Methods:** Patients received 2 cycles of chemotherapy: the first cycle (C1) served as each patient's individual control. PT-100 was administered orally for 7 days in cycle 2 (C2) as a 200, 400, 800, and 1200mcg total daily dose (divided twice daily) to 6, 6, 13, and 4 patients, respectively. Most patients received PT-100 on Days 2–8 of chemotherapy in C2, except at 800mcg where one cohort was treated on a Day 5 –11 schedule. Patients had to have Grade 3/4 neutropenia in C1 to receive PT-100 in C2. **Results:** Five of 13 patients receiving PT-100 800mcg experienced a ≥ 2-day improvement in ≥ Grade 3 neutropenia, and a 62% improvement in median AUC in C2 vs. C1 was observed in patients treated on the Day 2–8 schedule. A corresponding upregulation in G-CSF, IL-6, and IL-8 was observed in most patients. Overall, PT-100 was well-tolerated. Edema/peripheral swelling, hypotension, and hypovolemia were the most common non-hematologic AEs considered related to PT-100. Two Grade 3 AEs were considered related to PT-100: syncope (1200mcg) and orthostatic hypotension (800mcg). An MTD was not reached. **Conclusions:** Given the accelerated neutrophil recovery, strong preclinical evidence of antitumor activity, and tolerable toxicities of PT-100, studies using a longer PT-100 dosing schedule are warranted to investigate its antitumor and neutrostatic effects.



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Author Disclosure

Employment or Leadership	Consultant or Advisory	Stock Ownership	Honoraria	Research Funding	Expert Testimony	Other Remuneration
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