Phase I clinical trial of adoptive cellular immunotherapy with APN401 in patients with solid tumors

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From 30th Annual Meeting and Associated Programs of the Society for Immunotherapy of Cancer (SITC 2015)
National Harbor, MD, USA. 4-8 November 2015

Background
Casitas-B-lineage lymphoma protein-b (Cbl-b), an E3 ubiquitin ligase, has been identified as a key intracellular checkpoint limiting lymphocyte activation. Inhibiting Cbl-b has been shown to enhance T cell and natural killer cell mediated antitumor activity in mouse tumor models. APN401 is a suspension of autologous peripheral blood mononuclear cells (PBMCs) transfected with a siRNA that knocks down Cbl-b. A Phase I clinical trial has been initiated to establish feasibility and to determine toxicity of the intravenous infusion of APN401.

Methods
Patients with metastatic solid tumors no longer responding to standard therapies have been enrolled into one of three successive dosing cohorts in which they received a single intravenous infusion of 5, 10, or 50 x10⁵/kg transfected PBMCs. Eligibility criteria included at least 4 weeks since prior therapy, ECOG performance status 0-1, and adequate hematologic and organ function. Patients with active autoimmune disease or a requirement for immune suppressive drugs were excluded. PBMCs were collected by leukapheresis. The following day PBMCs were transfected with Cbl-b siRNA ex vivo by electroporation and then infused over 30 minutes.

Results
Three patients have been treated in each of the three dosing cohorts. PBMCs were successfully collected and transfected with Cbl-b siRNA in all patients, which included 6 with pancreatic, 2 with colon, and 1 with kidney cancers. Among PBMCs, CD56 cells were most efficiently transfected (55%), followed by CD3 (46%), CD19 (45%), and CD14 (23%) cells. Cbl-b-siRNA-transfected PBMCs produced 4-fold more interferon gamma and 2-fold more interleukin-2 in response to stimulation with anti-CD3/CD28 antibody in vitro. APN401 infusions were well tolerated. One patient in the first, three in the second, and two in the third cohort developed grade 2 chills at the completion of the infusion. These responded to meperidine. Grade 3 or 4 toxicities were not observed. No immediate hypersensitivity was noted. There was no evidence of autoimmune adverse effects. Patients are being followed for systemic immune effects.

Conclusion
A single intravenous infusion of 50 x10⁵/kg of APN401, autologous Cbl-b silenced PBMCs, into patients with refractory solid tumors is feasible and safe. The results support Phase II clinical trials of multiple infusions of APN401.