A PHASE I STUDY OF AUTOLOGOUS ACTIVATED NK CELLS ± RHIL15 IN CHILDREN AND YOUNG ADULTS WITH REFRACTORY SOLID TUMORS

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Background Patients with high-risk pediatric solid tumors experience poor outcomes and require improved treatments. NK cell immunotherapies hold promise for potential anti-tumor activity; however, clinical translation faces challenges of NK expansion, persistence, and inhibition. Interleukin-15 (IL-15) fosters NK cell development, homeostasis, lytic capacity, and survival. Preclinical data demonstrate that NK cells expanded ex vivo by IL15 and 4–1BBL are largely resistant to inhibitory signals and mediate potent tumor killing in vitro, suggesting efficacy against solid tumors.

Methods and Study Design In this single-institution Phase I trial (NCT01875601), we enrolled children and young adults with refractory solid tumors, including brain tumors, to evaluate the feasibility of manufacturing and safety of infusing activated NK cells. Using a 3+3 design for dose escalation, NK cells were administered after lymphodepleting cyclophosphamide. Artificial antigen-presenting cells (aAPC) expressing human 4–1BBL and human IL-15Ra were used to stimulate and expand autologous NK cells ex vivo. Three dose levels (DL) (1x10^6 cells/kg, 1x10^7 cells/kg, 1x10^8 cells/kg) of NK cells were explored for Cohort A. Cohort B evaluated administration of 1x10^7 NK cells/kg followed by a ten-day rhIL-15 infusion with 4 DLs planned (0.25 mcg/kg/day, 0.5 mcg/kg/day, 1 mcg/kg/day, 2 mcg/kg/day).

Results Sixteen patients enrolled, with median age of 16.1 years. The average ex vivo NK cell expansion was 19.4 fold, readily supporting DLs up to 1x10^7 cells/kg. Expansion was insufficient to achieve the top DL of 1x10^8 cells/kg. Following administration, partial responses per RECIST criteria were observed in 3 patients with refractory osteosarcoma, Ewing sarcoma, and medulloblastoma, two in DL1 of Cohort A, and one in DL1 of Cohort B. The remaining 13 patients had stable disease.

The most common adverse events were hematologic toxicities, likely chemotherapy-related. Symptoms of cytokine release syndrome occurred in 2/12 patients in Cohort A, one being a dose limiting toxicity. Four patients received rhIL-15 at the 0.25 mcg/kg/day DL with one dose limiting toxicity related to pericardial tamponade and capillary leak syndrome, prior to pause of enrollment for supply issues.

Conclusions Harvesting, expanding, and administering 1x10^7 cells/kg of aAPC-activated autologous NK cells is feasible and safely tolerated. The addition of rhIL-15 shows potential promise although further exploration is necessary to identify if higher dose levels would be beneficial. Anti-tumor activity was observed following administration of aAPC-activated autologous NK cells with three partial responses in heavily pre-treated patients. Correlative studies are underway to better understand the immunological impact of NK cells and explore differences between responders and non-responders.

Trial Registration ClinicalTrials.gov Identifier: NCT01875601

Ethics Approval The study was approved by the National Institutes of Health Intramural Institutional Review Board, approval number was NCT01875601. Written informed consent was obtained from the patient or guardian before taking part in the trial.

Consent Written informed consent was obtained from the patient or guardian for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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