DEVELOPING HUMAN PLACENTAL CD34-DERIVED NATURAL KILLER CELLS WITH HIGH AFFINITY AND CLEAVAGE RESISTANT CD16 AND SECRETED IL-15 (CYNK-201) FOR CANCER IMMUNOTHERAPY

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Background Natural killer (NK) cells can display antibody dependent cellular cytotoxicity (ADCC) activity against tumor cells via the CD16 Fc receptor in combination with tumor specific antibodies. IL-15 is important for NK cell survival, proliferation and function. Celularity is developing human placental CD34+-derived, cryopreserved, off-the-shelf, allogenic NK cells (CYNK-201) with high IgG binding affinity, protease cleavage resistant CD16 and secreted IL-15 for cancer treatment. Here we report the preclinical efficacy results of CYNK-201 against tumor cells.

Methods CYNK-201 cells were generated by transduction of human placental CD34 cells with lentivirus vector expressing CD16 and IL-15, followed by culture expansion in the presence of cytokines. Transgene expression and phenotype of CYNK-201 cells were characterized by flow cytometry. The concentration of secreted IL-15 by CYNK-201 was measured by a human IL-15 ELISA kit. ADCC activity of CYNK-201 against HER2+ gastric cancer cell line NCI-N87 and CD20+ Burkitts lymphoma cell line Daudi was assessed in combination with trastuzumab and rituximab, respectively.

Results CYNK-201 was generated from multiple placental CD34+ donors (n=5) with 91.8±1.1% CD56+CD3-, 78.9±9.77% CD16 expression, 3274±1605 fold expansion and the average of 203±1.1 pg/mL secreted IL-15. While 2h PMAi treatment resulted in 61.6±11.3% CD16 cleavage on non-transduced (NT)-CYNK cells, no cleavage was observed from CYNK-201 demonstrating CD16 shedding resistance. CYNK-201 showed increased expression of activation markers including CD11a, NKGD2, CD226 and Nkp30 as compared to the NT-CYNK cells. CYNK-201 displayed enhanced in vitro ADCC against NCI-N87 and Daudi compared to that of NT-CYNK cells. At an E:T ratio of 1:1, CYNK-201 elicited increased ADCC against NCI-N87 with trastuzumab compared to that of NT-CYNK cells, with 65.6±15.1% vs. 52.0±9.1% at 4 hours. At an E:T ratio of 2:1, CYNK-201 showed higher cytotoxicity against Daudi in combination with rituximab compared to that of NT-CYNK with 49.0±18.8% vs. 31.8±9.9%. Post 14 days of infusion, CYNK-201 cells were detectable in NGS mice, with significantly higher abundance than that of NT-CYNK cells plus recombinant IL-15. This enhanced persistence of CYNK-201 led to significant tumor reduction in NCI-N87 tumor model in combination with trastuzumab.

Conclusions Our results demonstrated enhanced in vitro ADCC, in vivo persistence and anti-tumor activity of CYNK-201. Further development of CYNK-201 is warranted.

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