COMBINED ALLOGENEIC NK CELL AND HERZUMA® IS EFFECTIVE IN HER2-LOW BREAST CANCER PRECLINICAL MODEL BY ENHANCING ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY

Yong Moon*, Mithun Gosh, Hee-Jung An, Tae Hoen Kim, Sa Deok Hong, Nar Bahadur Katuwal, Minsil Kang. CHA Bundang Medical Center, Seongnam, Republic of Korea; The Graduate School, CHA University, Seongnam, Republic of Korea

Background Trastuzumab has shown significant improvements in the overall survival in patients with HER2-positive breast cancer. However, HER2 is expressed at varying levels in breast cancer patients, therefore, only a fraction with robust HER2 overexpression is beneficia from trastuzumab therapy. Moreover, the efficacy of trastuzumab in HER2-low expressing breast cancer, which is defined as immunohistochemistry 1+ or 2+ and lack of HER2 amplification by in situ hybridization, is not reported yet. Therefore, to enhance the effects of trastuzumab in HER2-low expressing breast cancers, we investigated a novel combination of Herzuma® (a trastuzumab biosimilar), paclitaxel and allogeneic Natural Killer (NK) cells in the HER2-low breast cancer preclinical models.

Methods Two breast cancer cell lines, BT-474 (HER2-low, by western blot) and SKBR3 (HER2-high, by western blot) were used for in-vitro study. Cytotoxicity was analyzed by flow cytometry (CFSE, 7AAD) after co-culture, where cancer cells were used as target (T) cell and allogeneic NK cells as effector (E) cell at various E:T ratio in the presence or absence of Herzuma®. Antibody-dependent cellular cytotoxicity (ADCC) activity was analyzed by evaluating interaction of Herzuma® and FCϒIII (CD16) of NK cells. Lastly, HER2-low breast cancer patients-derived tumor xenograft (PDTX) model was used for in vivo efficacy test. When tumor size reached to 100mm³, mice were randomly divided in 4 groups (control, Herzuma® + paclitaxel, NK, Herzuma® + paclitaxel + NK) and treated.

Results Cytotoxicity assay demonstrated that dead target cells were only increased in the combined Herzuma® and NK therapy as compared to NK monotherapy in both cell lines (BT474, SKBR3) at various E:T ratio. To confirm the above-mentioned cytotoxic effect of the combination therapy is an ADCC effect, we conducted co-culture using HER2-low BT474 cells after blocking the CD16 of NK cells. Dead target cells were not increased in the combined Herzuma® and NK therapy group after CD16 blocking, whereas similar cytotoxic effects were observed in NK monotherapy and combination therapy respectively, suggesting the above-mentioned cytotoxic effect resulted from ADCC. Finally, the in-vivo study using HER2-low breast cancer PDTX model showed that the NK therapy in combination with Herzuma® and paclitaxel group significantly inhibited the tumor growth as compared to combined Herzuma® and paclitaxel group or control (p=0.003, vs control; p=0.01, vs Herzuma® + paclitaxel).

Conclusions The combination of allogeneic NK therapy, Herzuma® and paclitaxel showed synergistic anticancer activity in HER2-low breast cancer preclinical model. This combination merits further clinical investigation in HER2-low breast cancer patients.

Acknowledgements The study was funded by CELLTRION PHARM, Inc. (Chungcheongbuk-do, Republic of Korea)

Ethics Approval IACUC190139