Towards an Implantable Replenishable Delivery Device for Natural Killer Cell and Tri-Specific Killer Engager Antibodies to the Intraperitoneal Space to Treat Ovarian Cancer

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Background: Ovarian cancer (OC) global 5-year survival rate is <30% for advanced-stage disease. Natural killer (NK) cell immunotherapy and Tri-specific Killer Engager (TriKE) antibodies have shown promising pre-clinical results. As OC is primarily a disease that remains intraperitoneal (IP), repeated delivery of these novel therapies IP is clinically of interest. IP delivery is, however, plagued by malfunctioning ports and catheter blockage. This ongoing study investigates the delivery of primary NK cells (pNK), and B7H3-TriKE or IL-15, through a novel implantable refillable delivery device developed by our group in vitro and in vivo.

Methods: pNKc OR TriKE were delivered via our device and compared to a syringe delivery with a 22G needle. pNKc Viability/Number post-delivery: 25μL of cell suspension was delivered to Celica MX Nexcelom cell counter. Protein content post-delivery: 2μL of TriKE was delivered to A280 machine, and absorbance was measured at 280nm. Cytotoxicity: 20,000 OVCAR-8 cells were plated in xCELLigence 96 well-plate for 24-hours. After 48-hours 2:1 pNKc alone, with 12nM IL-15 or 0.3nM TriKE were delivered to OVCAR-8 cells via device or syringe. N=3 devices/group in triplicate. For ongoing in vivo studies, NOD-scid-gamma mice were implanted with delivery devices and OVCAR-8 cells. Repeated delivery of pNK (3x), alone or with IL-15 or B7H3-TriKE (3x/week for study duration), will be tested over an 8-week period.

Results: Post-delivery through our device there was no significant difference in viability (96.11±0.8% vs 96.11±0.57%) (figure 1A), pNKc number (0.29±0.04x10⁶ vs 0.27±0.03x10⁶) (figure 1B), or TriKE concentration (0.064±0.002mg/mL vs 0.062±0.010mg/mL) (figure 1C) compared with delivery through a syringe with 22G needle. There was no significant difference in treatment (Area under curve (AUC)) at 48 hours for NK cell alone (140.05±0.8 vs 121.1±1.3 AUC) (figure 1D), or with IL-15 (117.2±1.4 vs 118.8±0.4 AUC) (figure 1D), or with 0.3nM TriKE (134.5±0.2 vs 128.1±0.8 AUC) (figure 1D) post-delivery through device vs a 22G needle syringe. There was no significant difference in treatment (Area under curve (AUC)) at 48 hours for NK cell alone (140.05±0.8 vs 121.1±1.3 AUC) (figure 1D), or with IL-15 (117.2±1.4 vs 118.8±0.4 AUC) (figure 1D), or with 0.3nM TriKE (134.5±0.2 vs 128.1±0.8 AUC) (figure 1D) post-delivery through device vs a 22G needle syringe. There was no significant difference in treatment (Area under curve (AUC)) at 48 hours for NK cell alone (140.05±0.8 vs 121.1±1.3 AUC) (figure 1D), or with IL-15 (117.2±1.4 vs 118.8±0.4 AUC) (figure 1D), or with 0.3nM TriKE (134.5±0.2 vs 128.1±0.8 AUC) (figure 1D) post-delivery through device vs a 22G needle syringe. After 48-hours, treatment pNKc combined with 0.3nM TriKE (2.07±0.332 Cell-Index (CI),p<0.05, figure 1E) provided superior cytotoxicity to pNKc alone (2.86±0.304CI (figure 1E)) or with IL-15 (2.22±0.147CI (p<0.05, figure 1E)) compared to control (3.05±0.135CI). Our animal model is ongoing.

Conclusions: Prospective studies have found that chemotherapy delivered IP after optimal surgical debulking can significantly reduce the risk of death, but up to 40% of women discontinued IP chemotherapy due to catheter placement issues, blockages, and other complications. Specifically designed IP delivery devices, as we are testing here, could improve future clinical outcomes and patient experience.

Ethics Approval: IACUC Protocol 2207–40255A

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