Natural Killer cell-based immunotherapeutic approaches for soft-tissue sarcoma: combining ex-vivo NK cell expansion and Anti-GD2 antibody-mediated ADCC

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Background: Patients with advanced soft-tissue sarcoma (STS) have a poor prognosis with high relapse rates. Immunotherapeutic strategies tailored to reverse a tumor-associated Natural Killer (NK) cell dysfunction aim to eradicate quiescent malignant cells as origin of relapse. Restoring NK cytotoxicity by ex vivo expansion and redirecting NK cells by tumor antigen-specific antibodies might be synergistic strategies to convey anti-tumor immunity.

Methods: We compared the NK cytotoxicity of STS patients and healthy donors (HD) in a 51Cr release assay against K562 cells. NK cell expansion and augmentation of cytotoxicity was evaluated after long-term culture in an Interleukin 2-containing bioreactor, and expression of NK cell antigens was analyzed by flow cytometry. Additionally, effects of ch14.18, an antibody directed against GD2 (an antigen frequently expressed on STS) on NK cytotoxicity were tested against sarcoma cell lines with diverging GD2 expression (TC-71, SW872, SKUT-1).

Results: Patient NK cells showed impaired cytotoxicity against K562, whereas lytic activity against STS cell lines was minimal for both patient and HD NK cells. Expansion of NK cells of patients (n=4) and HD (n=3) resulted in cell counts of up to 90-fold of baseline, and led to a significant increase in cytotoxicity against K562 and STS cell lines. Patient NK cells showed altered expression of NK cell receptors (e.g. NKp46, CX3CR1) compared to HD NK cells. Expression of activating receptors (e.g. NKG2D) was upregulated after expansion. Addition of ch14.18 increased cytotoxicity of unstimulated NK cells of healthy donors and patients against GD2-expressing STS cells of up to 7-fold. For expanded NK cells of healthy donors, no additional effect of ch14.18 was seen.

Conclusions: Reconstitution of NK cytotoxicity might be a promising immunotherapeutic strategy for STS patients. Bioreactor-based long-term cell expansion and use of anti-GD2 antibodies are complementary approaches to stimulate anti-STS cytotoxicity in vitro and warrant further evaluation.

Session: NK cells and cancer