REDIRECTING NK CELL CYTOTOXICITY BY INNATE CELL ENGAGERS: A DIFFERENTIATED AND INNOVATIVE APPROACH COMPARED TO CAR-NK CELLS

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Background The use of bispecific Innate Cell Engagers (ICE®) has become a successful strategy for immune cell activation and killing of tumor cells through antibody-dependent cellular cytotoxicity (ADCC). Combination of adoptive NK cell therapy with ICE® molecules significantly improved tumor-targeting and has shown unprecedented clinical response rates in heavily pretreated cancer patients. Alternatively, as NK cells alone show short time clinical activity only, genetic modification with chimeric antigen receptors (CAR) has demonstrated improved clinical success in patients with CD19+ hematological disorders. To compare both approaches, we have evaluated the efficacy of NK cells combined with tetravalent bispecific CD16A/CD19-targeting ICE® versus anti-CD19 CAR-NK cells in a preclinical proof-of-concept study using CD19-positive target cells.

Methods NK cells from PBMCs of healthy donors were expanded for three weeks in the presence of IL-2 and IL-15. Anti-CD19 CAR-NK cells were generated by transduction with baboon envelope pseudo-typed gamma-retroviral vectors. NK cell cytotoxic activity was assessed by calcein-release assays, degranulation, cytokine production, and specific CD19 positive target cell killing resolved over time using IncuCyte imaging system after co-culture of non-transduced NK cells plus CD16A/CD19-targeting ICE® or anti-CD19 CAR-NK cells with CD19-positive or negative tumor target cells.

Results Combination of non-transduced NK cells with the CD16A/CD19 ICE® enhanced ADCC activity towards CD19-positive target cells and mediated elevated levels of degranulation when compared to NK cells in the absence of ICE®. In addition, this combination induced target cell dependent TNF-alpha and IFN-gamma secretion by NK cells. CD16A/CD19 ICE-induced NK cell maximal cytotoxicity as well as TNF-alpha and IFN-gamma secretion were comparable to that of a corresponding CD19 CAR NK cells at different effector to target ratios.

Conclusions No major difference in cytotoxicity and TNF-alpha and IFN-gamma release between the two approaches, NK cells in combination with CD16A/CD19 ICE vs. CD19 CAR NK cells, has been observed. Therefore, combination of allogeneic NK cells with bispecific ICE® represent a versatile innovation providing advantages over engineered CAR-NK cells such as more cost-effective manufacturing and potentially reduced safety concerns. Treatment options for ICE® molecules are more flexible since no genetic engineering of NK cells is needed and can be built basically for any target. Moreover, this approach is applicable to a variety of NK cell products of different origins.

REFERENCES


Ethics Approval This work was performed with NK cells from healthy anonymous blood donors approved by the State Chamber of Physicians of Saxony, Germany, under ethical vote number EK-BR-79/21–1.