Natural Killer T cell-based immunotherapy for cancer

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1. Introduction

Cancer is one of the most threatening diseases nowadays and immunotherapy is a successful field of research. Therefore, oncology immunotherapy has become a potential source of investigation, and its main results are related to cell therapy and monoclonal antibodies

My work is based on cell therapy, specifically, on Natural Killer T cells

Objectives
- To describe NKT functions and roles in tumor immunity
- To take a deep look into current NKT cell-based therapies
- To analyze relevant clinical trials and future directions

2. Natural Killer T cells

Characteristics
- Antigen-CD1d complexes recognition
- They express TCR and NK receptors
- They develop and mature in the thymus

Features	Type I (iNKT)	Type II (vNKT)
TCR α chain	Vα24Jα18	Diverse
TCR β chain	Vβ11 (and others)	Diverse
Subsets (coreceptors)	$CD4^-$ $CD8^-$ (DN) $CD4^+$ $CD8^+$	$CD4^-$ $CD8^-$ (DN) $CD4^+$ γδ T cells
Antigens	Glycolipid (α-GalCer)	Sulfatide moieties
Main role in cancer	Enhance immune response	Suppress immune response

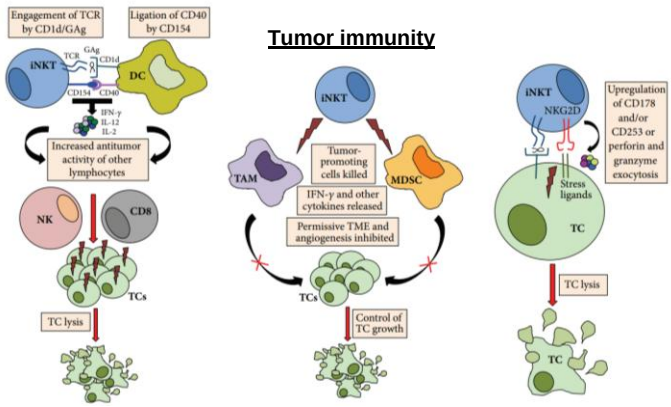


Figure 1: Altman J. et al. Journal of Immunology Research. 2015.

3. NKT cell-based immunotherapy of cancer

Therapy objectives
- Elimination of MHC +/- cells in order to avoid tumor relapse
- Use of adjuvants as tumor cells are low immunogenic
- To induce DC maturation to promote efficient responses

- Free α-GalCer injection

It activates antitumor immune responses directed by iNKT cells, but it shows conflicting effects as it induces Th-0-like cell responses (cytokine mix)

α-GalCer analogs
- ↑Hydrophobic → pro-inflammatory, Th-1 cytokines
- ↑Solubility → anti-inflammatory, Th-2 cytokines

Trial outcomes
- Toleration, safety and transient increase of NKT cells have been observed but it also has shown inefficient immune responses with a long period of anergy

- Autologous DCs loaded *ex vivo* with α-GalCer

It increases iNKT cell expansion and its INF-γ production. Moreover, it is tolerated and less likely to generate anergy of iNKT cells than a plain α-GalCer injection. Finally, various routes of administration have been successful

Trial outcomes
- Tumor size and necrosis reduction have been observed
- It has shown disease stabilzation in some cases

- Tumor cells loaded with α-GalCer

It has high specificity, yet it needs adjuvants so as to be effective

Cancer	Immunotherapy
CD1d +	αGC-loaded tumor cells
CD1d –	αGC + cross-presentation

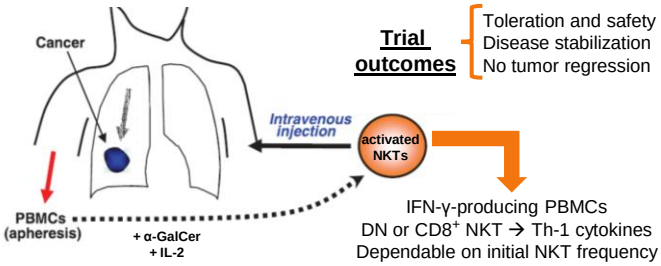
Trial outcomes
- IFN-γ route enhancement: activation of iNKT, NK and CTL

Novel: Immune memory after its combination with anti-4-1BB Ab reported

- Other α-GalCer immunotherapies

Anti-PDL1 Ab: it promotes iNKT Th-1 cytokine production and NK activation
Anti-ganglioside GD2 Ab: it shows iNKT-NK interaction and enhancement
Antibody + CD1d/αGC complexes: they induce tumor-specific CTL activation
Live bacteria as αGC vector: it activates tumor-specific CTL

- *Ex vivo* expansion of autologous iNKT cells



Trial outcomes
- Toleration and safety
- Disease stabilization
- No tumor regression

Figure 2: Motohashi S. et al. Cancer Science. 2008.

- Combination immunotherapy

Ex vivo expanded autologous iNKTs and α-GalCer-pulsed DCs

Trial outcomes
- Toleration and no severe side effects reported
- It shows moderated responses in NKT and NK cell activities
- It induces partial response, stable disease and tumor regression

4. Conclusions

- Immunosupressive TME eradicates antitumor responses
- Small NKT population, which is even lower in cancer patients, is associtaed with worse prognosis
- All studies are small scale trials without long monitoring
- Differences between mouse and human in CD1d and iNKT frequencies
- **Novel**: reserach in humanized mouse models, αGC analogs, delivery vectors
- Trials with mature DCs or PBMCs have shown better results than DCs
- Combination immunotherapy is not as good as expected theorically
- Irradiated tumor approaches are the best candidate for vaccination
- **Novel**
  - iPS: reinfusion of larger numbers of NKT promotes CTL activation
  - CARs: NKT transduced with CAR.GD2 induces persistent activity

5. Bibliography

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