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FLT3L-Primed *in situ* vaccine for patients with low-grade lymphoma: Tumor regression at untreated sites (NCT01976585)

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Objectives: Though low-grade lymphoma is generally incurable, T-cell based therapy such as allogeneic transplant can induce prolonged remissions, possibly cures, even for chemo-resistant disease. If anti-tumor T cell immunity could be mobilized without the morbidity of transplant, it could change the paradigm of lymphoma therapy. Previously, we completed three trials of an 'in situ vaccine' combining low-dose XRT with intratumoral administration of a TLR agonist demonstrating partial and complete remissions of patients' non-irradiated sites of disease, lasting as long as 4+ years. One obstacle to the induction of potent anti-tumor immunity with the in situ vaccine approach is the paucity of professional antigen presenting cells, e.g. dendritic cells (DC) at the tumor site.

Methods: To address this problem, we have adopted the approach by adding a priming step of intratumoral administration of the predominant DC differentiation factor - Flt3L. The aim of the adopted approach is to use:

- intratumoral Flt3L administration to recruit DC to the tumor,
- low-dose XRT to induce immunogenic cell death and release tumor-associated antigens, and
- intratumoral poly-ICLC administration to activate tumor antigen-loaded DC, inducing anti-tumor T cells and anti-tumor immunity.

Results: Preliminary immune correlative data for the first two patients receiving the in situ vaccine demonstrate a significant (up to 200-fold) increase in the proportion of intratumoral DC subsets (BDCA-1 and BDCA-3) at the treated tumor site. We also observe a marked increase in the intratumoral proportion of CD80 (high) PD-L1 (low) activated DCs after XRT and poly-ICLC administration. This latter finding is in contrast to the activation status of DC in the peripheral blood.

Conclusions: Flt3L-primed in situ vaccination demonstrates immunologic and clinical proof-of-principle and warrants continued investigation. We will present additional immunologic and clinical results as well as ongoing studies to quantify anti-tumor T cells and to determine potential tumor-associated antigens.

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Manipulation of lymphocytes by sphingolipid analogue for therapeutic purposes

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Immune cells have been revealed to be beneficial for immune therapy in various pathological conditions. However, the inability to control the cells once administrated is still a major obstacle to the development of immunotherapeutic treatments. Recent studies demonstrate that sphingolipid analogues influence some crucial processes during immune response. In immune cells, sphingolipid metabolism is involved in a common signaling pathway which controls the main stages of immune cell development and function. The use of sphingolipid analogues, such as FTY-720, is currently under investigation as a therapy for different immune disorders. We have synthesized a group of sphingolipid analogues. The effects of the analogue AD-2900, on human lymphocytes activation was investigated and compared with sphingosine-1-phosphate (S1P) and the commercial sphingolipid analogues FTY-720 and SEW-2871. We found out AD-2900 can activate sphingosine-1-phosphate S1P receptor 1 and may be also work through other S1P receptors. AD2900 affects different signal transduction pathways comparing to the other sphingolipid analogues tested and induces different extracellular signal-regulated kinase ERK phosphorylation pattern. In addition, AD-2900 also inhibits T cell proliferation, inflammatory cytokine secretion and induces apoptosis dose-dependently, but in a compromised way comparing with FTY-720, a commercialized sphingolipid analogue. To further illustrate the mechanism of AD-2900, the effect of AD-2900 on different immune cells such as dendritic cells and macrophages will be tested. Hopefully, sphingolipid analogue, AD-2900 may play a key role as immunomodulator for immunotherapy and other therapeutic purposes in the future.

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