Chemotherapy Can Enhance the Therapeutic Potential of Vaccine-Mediated Immunotherapy

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Abstract

Purpose: Many advanced cell lung cancer (NSCLC) patients undergo surgery followed by a period of non-advanced chemotherapy, which includes cisplatin in combination with docetaxel. In view of these data, the median survival of patients with metastatic disease is less than 10 months. Previous studies have shown that chemotherapy given prior to vaccine can enhance vaccine-mediated outcomes. Since chemotherapy is standard of care in many cancer types, the feasibility that chemotherapy can be used concomitantly with vaccine was explored. Since chemotherapy regimens induce immune perturbations, which are followed by a recovery phase, we hypothesized that administering vaccine during the T-cell recovery phase would enhance the effectiveness of the vaccine. Experimental Design: We examined the effects of chemotherapy on the growth of tumor and vaccine responses, and T-cell-mediated cytotoxicity against cancer cells. We then tested the potential for vaccine cross-reactivity through antibody and T-cell responses to enhanced vaccine in a model of NSCLC. We evaluated the effects of chemotherapy on immune surveillance and functions of regulatory T-Cells.

Results: These studies demonstrate that (1) the combination of cisplatin plus docetaxel increases MHC class I and II expression, as well as regulatory T-cell (Treg) expansion in healthy mice and (2) cisplatin plus docetaxel treatment leads to local inflammation at the tumor site, which increases vaccine mediated antigen specific IgG and CD4 T-cell responses. These findings suggest that chemotherapy enhances the cell surface expression of co-stimulatory molecules and improves antigen-specific CD8 T-cells, thereby circumventing the effects of chemotherapy on immune surveillance and functions of regulatory cell subsets.

Rationale

Non-Small Cell Lung Cancer (NSCLC)
- Accounts for over 80% of all lung cancer cases
- Half of all new cases present locally advanced or metastatic disease
- Stage dependent
- Lung adenocarcinoma, NSCLC
- Metastatic
- Surgery plus adjuvant chemotherapy (platinum-based), e.g., cisplatin + docetaxel

Can we combine chemotherapy with current CEA vaccine?

Future Plans

Phase 1 Trials
- NSCLC Vaccine/Cisplatin-Based CEA Vaccine in Patients with Stage IIIB NSCLC, following
- Non-Small Cell Lung Cancer (NSCLC), Advanced, multi-drug treatment failure
- Combination therapy with chemotherapy and vaccine
- Cisplatin/docetaxel + CEA vaccine
- Safety and feasibility of combined CEA vaccine and chemotherapy

Figures:
- Figure 1: Effects of chemotherapy and Cisplatin/docetaxel on NSCLC growth.
- Figure 2: Cisplatin/docetaxel enhances antigen-specific CD8 T-cell responses.
- Figure 3: Effects of chemotherapy on immune surveillance and functions of regulatory T-cells.