C3 / Padres Pedal the Cause 2018

"Low Dose Chemotherapy for Immuno-activation in Lung Cancer"

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SCIENTIFIC ABSTRACT

While anti-PD1 antibodies have improved outcomes in frontline and second line lung cancer management, response rates to anti-PD1 antibodies rarely exceed 30% in later lines of therapy. The efficacy of checkpoint inhibitors can be increased by the combination of immunogenic cytotoxic therapies that enhance antigen release and presentation. To exert immunogenic activity, chemotherapeutic drugs need to be administered at low, non-myeloablative, doses, but exactly how they work at this dose range is poorly understood. It has been suggested that chemotherapy induces immunogenic cell death, releasing damage associated molecular patterns, which stimulate dendritic cell maturation and antigen uptake and presentation. Curiously, certain chemotherapeutic agents can promote T cell activation at low doses, including oxaliplatin, mitoxanthrone, cyclophosphamide, and anthracyclines. Pre-clinically, we found that the superior immunogenic activity of oxaliplatin correlates with engagement of interferon γ signaling and a stress response, which stimulates processing of tumor associated antigens and enhances their presentation via MHC class I molecules on cancer cells enabling their recognition and killing by primed-cytotoxic T lymphocytes. Low dose oxaliplatin greatly enhances tumor rejection by anti-PD-1 antibodies in lung cancer models. We are conducting a clinical trial in metastatic non-small cell lung cancer patients to assess the clinical efficacy and biomarkers of response for immunogenic chemotherapy. Our experimental plan will involve a statistically controlled clinical trial and specimen evaluation to understand markers of a stress response that leads to enhanced antigen processing and presentation, a hypothesis supported by our pre-clinical and early clinical studies.

LAY ABSTRACT

Immune checkpoint inhibitors are a new class of drugs that have revolutionized lung cancer treatment across various lines of therapy. The most versatile of this group are antibodies that target molecule on immune cells called checkpoints, namely PD-1 or its ligand PD-L1. Although effective in many cancer types, response rates to these drugs rarely exceed 30-40% in later lines of therapy, necessitating the search for agents that may combine to work in synergy with checkpoint blockers to increase effectiveness. Using mouse models of cancer, we found that the conventional chemotherapeutic drug oxaliplatin has the unique ability to greatly enhance the response to immunotherapy. Traditional doses of chemotherapy may not be needed when combined with immunotherapy. We will investigate how low doses of chemotherapy may increase an immune response and minimize side effects

in a clinical trial. Furthermore, we will investigate lung tumor specimens to find markers that will help us to better understand how we can pair appropriate therapies for patients in the future.