2024 MCC CCSG Pilot Project Award

Understanding Immune regulation of advanced cervical cancer during radiation therapy

Jyoti Mayadev, MD
Sunil Advani, MD
Ramez Eskander, MD
Pandurung Vijayanand, MD, PhD

Scientific Abstract:

Cisplatin based chemo-radiotherapy remains the standard of care for women with locally advanced cervical cancer. We propose a precision oncology trimodal chemo-radio-immunotherapy paradigm with antibody drug conjugates (ADCs) targeting delivery of potent cytotoxic radiosensitizers to irradiated tumors that potentiate immunotherapy. ADCs consist of a tumor targeting antibody coupled to cytotoxic drug. The cervical cancer approved tissue factor directed ADC tisotumab-vedotin (TV) has a monomethyl auristatin E (MMAE) drug payload. Our lab was the first to show MMAE radiosensitizes tumors, stimulating anti-tumor immunity resulting in durable tumor control. To translate these findings for cervical cancer, we propose parallel studies in irradiated patient biopsies and preclinical models. We hypothesize radiotherapy modulates TF, and immune infiltration can then be exploited to advance a precision chemo-radio-immunotherapy strategy by using TV instead of cisplatin as a radiation sensitizer in cervical cancer. Using tumor biopsies collected longitudinally from cervical cancer patients before, during and after radiotherapy we will test if radiation alters tissue factor expression and determine the temporal changes in the irradiated tumor immune microenvironment by immunostaining and flow cytometry. Using a panel of irradiated cell culture and murine cervical cancer xenograft models treated with TV, free MMAE, tisotumab or cisplatin we propose to test if TV selectively radiosensitizes TF expressing cervical cancer cells, if irradiation alters tissue factor expression, the anti-tumor efficacy and specificity of tumor targeted TV with radiotherapy in cervical cancer xenografts compared to non-targeted cisplatin based radiosensitization. To facilitate clinical translation, Pfizer Oncology has agreed to provide clinical grade TV (Tivdak).

Lay Abstract:

The standard of care treatment for locally advanced cervical cancer remains combined radiotherapy with cisplatin. Although patients have improved outcomes with chemo-radiotherapy, tumor recurrence remains a problem. Moreover, combining chemotherapy with radiotherapy increases treatment related side effects. While breakthroughs in radiotherapy and immunotherapy have resulted in precision cancer care, chemotherapies given with radiotherapy remain non-targeted drugs. Also, due to medical contraindications, some patients are unable to receive the standard of care chemoradiation and there are no viable alternative treatment options. We propose a precision oncology strategy, replacing classical chemotherapies with a targeted antibody drug conjugate, tisotumab-vedotin. In this proposal,

we will perform key translational studies necessary for clinical trial testing of tisotumab-vedotin with radiotherapy and immunotherapy for women with cervical cancer.