MYELOID DERIVED SUPPRESSIVE CELLS ATTENUATE THE ANTI-TUMOR EFFICACY OF ANDROGEN DEPRIVATION THERAPY AND TARGETED RADIONUCLIDE THERAPY IN A MURINE PROSTATE CANCER MODEL

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Background Androgen deprivation therapy (ADT) is the cornerstone treatment for recurrent prostate cancer. ADT is also routinely used in combination with external beam radiation therapy (EBRT) for localized prostate cancer, and the combination results in a high rate of cure for low-risk disease. However, for metastatic castration-resistant prostate cancer (mCRPC), EBRT is typically only used in the palliative setting, because of the inability to radiate all sites of disease. We have developed an alkyl phosphocholine compound, NM600, that is selectively retained by multiple tumor types following systemic delivery. ⁹⁰Y-NM600 is being explored as a means of targeted radionuclide therapy (TRT) to irradiate all sites of metastases specifically and simultaneously in different tumor models, and a treatment that might modulate the tumor immune microenvironment. We hypothesized that ADT with TRT should be effective in the treatment of metastatic prostate cancer and tested this approach in a relevant murine tumor model.

Methods 6-week-old male FVB mice were implanted subcutaneously with MycCaP tumor cells. Mice were given a single intravenous injection 250 μCi of ⁹⁰Y-NM600, estimated to deliver 16 Gy to 0.2 cm³ tumors, in combination with ADT (degarelix). The sequence of administration was evaluated for effect on tumor growth, and groups of mice were euthanized at different time points to characterize the tumor-infiltrating immune populations by flow cytometry.

Results ADT delivered prior to TRT resulted in a significantly greater anti-tumor response and overall survival than if delivered after TRT. Similar studies performed in immunodeficient NRG mice demonstrated no difference with respect to the treatment sequence, suggesting this difference was immunologically mediated. Flow cytometry analysis revealed that CD4+ and CD8+ T cells persisted in the ADT prior to TRT group while they were significantly reduced in the other sequence. CD11b+Gr-1+ myeloid derived suppressor cells (MDSCs) were significantly increased in tumors following TRT prior to ADT treatment and retained immune suppressive function. Depletion of MDSC led to greater anti-tumor response following either treatment sequence.

Conclusions The combination of ADT and TRT significantly delayed tumor growth and improved anti-tumor responses in a murine model of prostate cancer, however this was dependent on the order of administration. This was found to be due to one treatment sequence leading to an increase in infiltrating MDSC. Current studies are investigating the mechanism of these findings.