HIGH-DOSE RADIATION IS REQUIRED FOR EFFECTIVE COMBINATION WITH TUMOR-SPECIFIC VACCINATION IN A PROSTATE CANCER MODEL

Hemanth Potluri*, Carolina Ferreira, Joseph Grudzinski, Christopher Massey, Reinier Hernandez, Jamey Weichert, Douglas McNeel. UW-Madison, Madison, WI, United States

Background The approval of Sipuleucel-T demonstrates the value of antigen-specific vaccination approaches for prostate cancer. We have studied a DNA vaccine specific for the ligand-binding domain of the androgen receptor (pTVG-AR) as a more scalable vaccination approach, though its efficacy is limited by the immunosuppressive prostate microenvironment. Radiation has been shown to sensitize poorly responsive tumors to immunotherapy. Our group has developed a compound, NM600, that is selectively retained by tumors following intravascular delivery, and is therefore capable of delivering radiation systemically to metastases (targeted radio-nuclide therapy, TRT). In this study, we evaluated whether TRT or external beam radiation therapy (EBRT) in combination with pTVG-AR could improve anti-tumor efficacy by increasing antigen-specific CD8+ T cell tumor infiltration in a murine prostate cancer model.

Methods 6-week old male C57Bl/6 mice were implanted subcutaneously with TRAMP-C1 cells. pTVG-AR or empty vector were administered weekly from the day after tumor implantation. Mice were then given an intravenous injection of 50 (“low-dose”) or 250 μCi (“high dose”) 90Y-NM600, estimated to deliver a dose of 1-2 Gy or 5-6 Gy to 300 mm3 tumors, respectively. EBRT was delivered to flank tumors in a single fraction of 6-12 Gy. Groups of mice (n=5) were euthanized at several timepoints for flow cytometry analysis of the tumors. Separate cohorts (n=7) were followed for tumor growth.

Results Single-dose TRT did not have greater anti-tumor efficacy when used in combination with vaccine, regardless of TRT dose or the schedule of the vaccine. Combination treatment did not increase CD8+ T cell infiltration. However, TRT administered twice three weeks apart, in combination with pTVG-AR, significantly slowed tumor growth, unlike fractionated TRT alone (p=0.01). Combination-treated mice did not have greater infiltration of memory CD8+ T cells or T cells more responsive to antigen-specific stimulation. Moreover, PD-1 expression was lower on infiltrating CD8+ T cells or PD-L1 expression was lower on dendritic cells (p=0.004). We then used EBRT to evaluate whether these differences might be dose-dependent. We found that vaccination combined with 12 Gy of EBRT, but not 6 Gy or 8 Gy, elicited a significantly improved anti-tumor response compared with EBRT alone (p<0.001).

Conclusions These data suggest that doses of RT in excess of 8 Gy, higher than what can be delivered by single treatment with 90Y-NM600, may be necessary to optimally combine with antigen-specific vaccines in this model. Further work will explore the mechanism of this potential dose threshold.

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