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

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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 radioisotope 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. However, PD-1 expression was lower on infiltrating CD8+ T cells (p=0.047) and 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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