COMBINATION OF ANTIGEN-SPECIFIC VACCINATION AND TARGETED RADIONUCLIDE THERAPY IMPROVES ANTI-TUMOR EFFICACY IN A MURINE PROSTATE MODEL

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Background While checkpoint blockade has been unsuccessful in prostate cancer trials, the approval of Sipuleucel-T demonstrates the value of antigen-specific vaccination approaches for this disease. 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 likely limited by the immunosuppressive prostate microenvironment. External beam radiotherapy has been shown to sensitize poorly responsive tumors to immunotherapy, but is infeasible for patients with widely metastatic disease. Our group has developed a compound called NM600 that can deliver radiation to all cancer sites simultaneously, similar to other targeted radionuclide therapy (TRT) approaches. In this study, we used TRT in combination with pTVG-AR to improve anti-tumor efficacy in a murine prostate cancer model.

Methods 6-week old male C57BL/6 mice were implanted subcutaneously with TRAMP-C1 cells. pTVG-AR or the empty vector were administered weekly from the day after tumor implantation. An intravenous injection was administered of 50 ("low-dose") or 250 μ Ci ("high dose") of 90Y-NM600, estimated to deliver a dose of 3.1 Gy or 15.5 Gy to 300 mm³ tumors, respectively. In one study, this TRT treatment was repeated once after three weeks. Groups of mice (n=5) were euthanized at several time points for flow cytometry analysis of the tumors. Separate cohorts (n=7) were followed for survival.

Results Low-dose TRT administered once in combination with pTVG-AR (median survival 91 days) significantly improved survival more than low-dose TRT alone (median survival 59 days; p=.049) or pTVG-AR alone (median survival 59 days; p=0.01). Low-dose TRT plus pTVG-AR was also superior to high-dose TRT plus pTVG-AR (median survival 67 days; p=0.05). We next examined the effect of giving high-dose TRT twice in combination pTVG-AR. We found that the combination of fractionated TRT and pTVG-AR greatly slowed tumor growth unlike fractionated TRT alone (p=0.03). High-dose TRT + pTVG-AR caused a two-fold increase in CD86 expression on dendritic cells (p=0.0009) on Day 3 and a 10% increase in effector memory CD8+ T cells (p=0.002) on Day 1 compared to TRT alone. This combination also resulted in T cells with 3-fold lower PD-1 expression (p=4e-7) and 2-fold lower TIGIT expression (p=0.01).

Conclusions These data suggest that the combination of antigen-specific vaccination and TRT can be an effective treatment for cancers that are refractory to immunotherapy. This combination may act through increasing co-stimulation by dendritic cells, leading to a more active cytolytic CD8+ T cell population.

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