2017 Immunotherapy Workshop (June 15-16, 2017) Bethesda, MD

Hafnium oxide nanoparticle, a potent radiation enhancer for in-situ cancer vaccine

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Abstract Text:

Purpose

Radiotherapy (RT) has proven its ability to function like an in-situ vaccine, showing potential for successful combination with immunotherapeutic agents. Hafnium oxide nanoparticle (HfO_2-NP), undergoing clinical trials for enhancing RT, was designed as high electron density material at the nanoscale. HfO_2-NPs are taken up by cancer cells and, when exposed to RT, locally increase the radiation dose deposit, triggering more cancer cells death when compared to RT. We hypothesized that HfO_2-NP+RT could trigger an enhanced immune response when compared to RT, both in preclinical and clinical settings.

Methods

CT26 cells were subcutaneously injected into both flanks of BALB/c mice. Once tumors reached volume of 50-120 mm^3, the right flank tumors only received HfO_2-NP+RT (3x4Gy) or RT. Mice were sacrificed when one tumor reached 800 mm^3. Alternatively, tumors were collected 7 days after the last RT fraction and analyzed for Tumor Infiltrating Lympocytes (TILs) by immunohistochemistry.

Tumor tissues pre- (biopsy) and/or post-treatment (resection) were collected from patients with locally advanced Soft Tissue Sarcoma (STS), who received either HfO_2-NP as intratumor injection and RT (14 pts) or RT (12 pts), as preoperative treatment (NCT02379845). Immunohistochemistry and Digital Pathology for immune biomarkers were analyzed. Gene expression profiling and pre-optimized immune-gene signatures called Immunosign were also used.

Results

In mice bearing CT26 tumors, an abscopal effect was observed with HfO_2-NP+RT and not with RT. HfO_2-NP+RT resulted in control on the untreated tumor and significant increase of overall survival. These results correlated with an increase of TILs in both treated and untreated tumors when compared to RT.

In STS patients, a significant increase of T cells (CD3+, CD8+) and a marked increase of CD103+ immune cell infiltration post- *vs* pre-treatment were observed for HfO_2-NP+RT ($P<0.01$), while no differences were seen for RT. Consistently, the up-regulation of adaptive

immunity genes expression between pre- and post-treatment, was pronounced for HfO_2-NP+RT when compared to RT. Functional analysis of genes up-regulated in HfO_2-NP+RT showed an enrichment of cytokine activity (IL7, IFNA, IL16, IL11, IFNG), adaptive immunity (RAG1, GZMA, TAP1, TAP2, TBX21, STAT4, IFNG, LCK, LTK, CD37, CD22) and T cell receptor signaling pathway (CD28, CTLA4, CD274, BTLA, TIGIT, CD40LG, CD5, CD3E, ZAP70).

Conclusions

In CT26 tumor bearing mice, HfO_2-NP+RT demonstrated marked enhancement of the immune response compared to RT. In STS patients, promising preliminary data showed that HfO_2-NP+RT induces a specific adaptive immune pattern. As such, it may act as effective in-situ cancer vaccine and be combined with immunotherapeutic agents across oncology.