TITLE

Antitumor immunity in patients with locally advanced soft tissue sarcoma treated with hafnium oxide nanoparticles and radiation therapy

Authors

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Background

Soft tissue sarcoma (STS) is a large and heterogeneous group of malignant mesenchymal neoplasms characterized by a strong tendency toward local recurrence and metastatic spreading. Consistently, the immune microenvironment in sarcomas is highly variable. A new class of material with high electron density, hafnium oxide, was designed at the nanoscale to efficiently absorb ionizing radiation from within the tumor cells and augment the dose deposited to a tumor. These nanoparticles (HfO_2-NP) administered in a single intratumor injection and activated by fractionated radiotherapy are evaluated in a phase II/III trial in patients with locally advanced STS as neoadjuvant treatment. Besides, beyond the broadly cytotoxic effect of radiation therapy (RT), RT may promote the release of tumor neoantigens during cancer cell death and stimulate local immunological effects. Here, we explore the effects of nanosized hafnium oxide exposed to RT in terms of tumor immune profile changes in patients with STS when compared to RT alone.

Materials and methods

Tumor tissues pre- (biopsy) and post-treatment (resection) are collected from patients with locally advanced STS (NCT02379845), who received either HfO_2-NP activated by RT or RT alone. Immunohistochemistry and Digital Pathology for immune biomarkers and Pan-Immune gene expression profiling are analyzed.

Results

A significant increase of CD8+ T cells and a marked increase of CD3+ and PD-1 T cells and CD103+ immune cell infiltration post- *vs* pre-treatment are observed for HfO_2-NP + RT while not differences are seen for RT alone (more than 10 patients analyzed in each arm). Functional analysis of genes expression up-regulated in HfO_2-NP + RT post- *vs* pre-treatment shows an enrichment of cytokine activity (IL7, IFNA, IL11, IFNG), adaptive immunity (RAG1, TAP1, TAP2, TBX21, IFNG, LTK, CD37, CD22) and T cell receptor signaling pathway (CD28, CTLA4, CD274, BTLA, TIGIT, CD5, ZAP70) when compared to RT.

Conclusions

Promising results are observed in patients who received HfO_2-NP + RT in terms of immune cells infiltration post- vs pre-treatment when compared to RT. Moreover, HfO_2-NP + RT induces a specific adaptive immune pattern. So far, nanosized hafnium oxide exposed to RT bring substantial changes to the tumor immune profile in patients with STS when compared to RT. As such, it may convert immunologically “cold” tumor into “hot” tumor and be effectively combined with immunotherapeutic agents across oncology. More tissue samples are under evaluation to reinforce these findings.