869 NBTXR3-ENHANCED PROTON BEAM IMMUNORADIOTHERAPY RESHAPES TUMOR IMMUNE MICROENVIRONMENT AND IMPROVES ABSCOPAL EFFECT IN AN ANTI-PD1-RESISTANT LUNG CANCER

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Background Proton beam therapy (PBT) has frequently yielded superior results to conventional X-ray therapy. However, combination of PBT with checkpoint inhibitors is rarely reported for treating metastatic cancers. NBTXR3 is a radioenhancer with immunomodulatory capacities able to restore efficacy of anti-PD1 (aPD1) in a model resistant to this treatment with conventional X-ray therapy. Therefore, we hypothesized that addition of NBTXR3 to localized PBT combined with aPD1 could enhance the systemic antitumor immune response in aPD1-resistant lung cancer in mice.

Methods Five groups of 8 mice each were inoculated with $5x10^4$ aPD1-resistant 344SQR murine lung cancer cells in each hind leg, 4 days apart, to establish 'primary' (right, to-be-irradiated) and 'secondary' (left, not-to-be-irradiated) tumors. aPD1 (200 μg) was intraperitoneally administered on days 7, 10, 14, 21, 28, 35, and 42. Primary tumors were intratumorally injected with NBTXR3 on day 7, followed by 12 Gy PBT on days of 8 and 9 (24 Gy total). The immune microenvironment of both irradiated and unirradiated tumors was analyzed through NanoString and single cell sequencing. On day 76, the right flank of the survivor mice treated with NBTXR3+PBT+aPD1 was rechallenged with $5x10^4$ 344SQR cells.

Results The therapies of PBT, PBT+aPD1, NBTXR3+PBT, and NBTXR3+PBT+aPD1 each resulted in significantly delayed growth in both primary and secondary tumors relative to control. In addition, adding NBTXR3 to both PBT and PBT+aPD1 significantly retarded the progress of the two tumors. Remarkably, the combination therapy of NBTXR3 +PBT+aPD1 achieved 37.5% survival rate and the lowest number of lung metastases. Moreover, the survivor mice maintained potent antitumor immunological memory, effectively rejecting tumor re-challenge. NanoString analysis of immune-related genes revealed that the triple therapy (NBTXR3+PBT +aPD1) significantly upregulated the activities of a wide range of antitumor immune pathways in the two tumors. Single cell analysis demonstrated that both PBT+aPD1 and NBTXR3 +PBT+aPD1 increased tumor infiltration by NKT cells, innate lymphoid cells, and $CD8^+$ T cells, $CD4^+$ T cells, and gamma delta T cells, as well as promoted cytotoxic lymphocyte activation. Lastly, PBT-mediated immunoradiotherapy enriched specific TCR repertories that may target tumor antigens.

Conclusions PBT combined with aPD1 was able to potently activate systemic antitumor immunity and effectively control both irradiated and unirradiated tumors. In this context, the addition of NBTXR3 to PBT+aPD1 significantly improved treatment efficacy through modulating the tumor immune microenvironment.

Ethics Approval All mouse studies were approved by the Institutional Animal Care and Use Committee of MD Anderson Cancer Center.

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