

BRIEF OPINION

Does Heavy Ion Therapy Work Through the Immune System?

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Combination of local therapies with immunotherapy, to convert the individual tumor into an in situ vaccine, is currently considered one of the most promising strategies to defeat cancer. The application of local radiation therapy as an adjuvant to immunotherapy is under active investigation both preclinically and clinically. The recent work of Gameiro et al published in the Red Journal in May this year as part of the Particle Therapy Special Issue (1) shows that protons can induce immunogenic modulation of the irradiated tissue, as already described with photons.

Radiation induces both immune-stimulating and immune-suppressive pathways (2, 3). Photon radiation induces immunogenic cell death in a dose-dependent manner, by calreticulin translocation, High mobility group box 1, and adenosine triphosphate release (4). The complex balance between immunosuppressive and stimulatory effects can be shifted using a combination of immunotherapy. Sporadic observations of the abscopal effects in patients show that, if some of these immune suppressive pathways are counteracted, a systemic antitumor response can occur (2).

Densely ionizing particle radiation may lead to a broader immunogenic response (5). Enhanced effectiveness in inducing nontargeted effects has been shown for high linear energy transfer radiation in 2-dimensional and 3-dimensional cell cultures (6). The experiments of

Gameiro et al in different tumor cell lines shows that protons mediated calreticulin translocation to the cell surface, thus increasing cross-priming and sensitivity to cytotoxic T-lymphocytes (1). The effect can be enhanced using densely ionizing heavy ions such as carbon, which induce DNA lesions qualitatively different from sparsely ionizing radiation or cytotoxic drugs. The clustered DNA lesions trigger distinct DNA damage-response pathways, as demonstrated by different gene expression signatures after exposure to light and heavy ions (7). Heavy ions can effectively kill tumor cells independently of TP53 or Bcl2 status (7), a promising clue for enhanced cell death and potential enhancement of release of neoantigens or overexpression of immunogenic epitopes. Results observed in the few preclinical studies in Japan in murine models on the induction of abscopal response using carbon ions in combination with immunotherapy (8) complement the in vitro results. The occurrence of occasional abscopal responses in metastatic cancer patients treated with heavy ions (Fig. 1) and the substantial increase in survival when compared with the best results of photon-based radiation therapy in a series of patients with locally advanced pancreatic cancer treated with carbon ions at National Institute of Radiological Sciences in Chiba, Japan (9) may reflect an enhanced immune response to carbon ion therapy.

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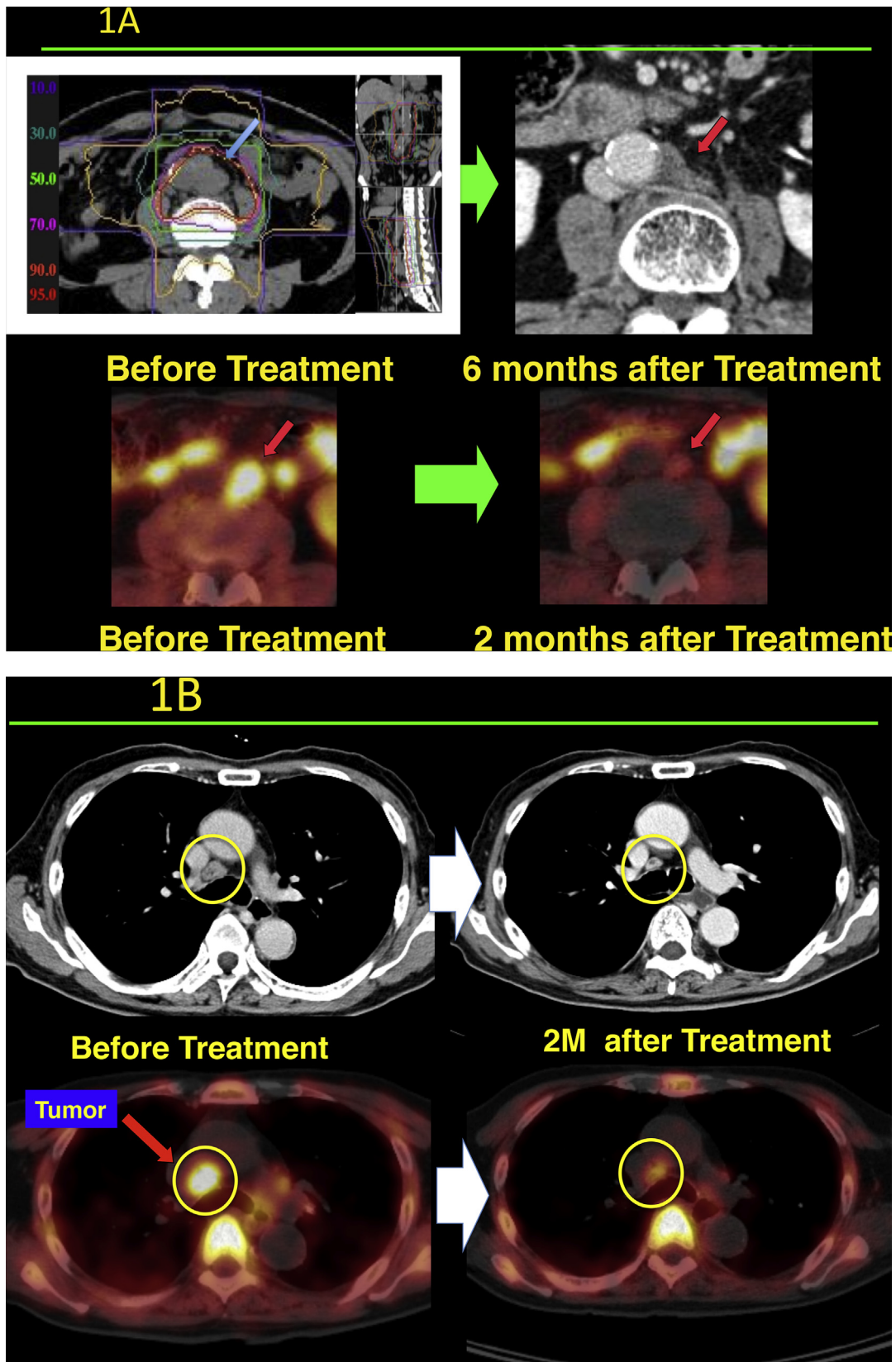


Fig. 1. An 85-year-old patient received 50.4 GyE in 12 fractions for an ascending colon carcinoma at National Institute of Radiological Sciences, Chiba, Japan (A). At the time of treatment the patient had mediastinal lymph node metastasis, at computed tomography and methionine positron emission tomography imaging (B). Six months after treatment, resolution of both the irradiated lesion (A) and the metastasis occurred (B). Courtesy of Dr Shigeru Yamada.

The physics of charged particle therapy also contributes to their biological advantage. An effective immune response requires a sufficient number of active effector and memory T cells. Classic protracted regimens of fractionated radiation therapy notoriously induce some degree of lasting lymphopenia, by exposure of circulating blood during treatment and inclusion of active hematopoietic organs within relevant dose volumes. Mathematical models suggest that a single fraction of 2 Gy to a field of approximately 8 cm³ can deliver approximately 0.5 Gy to 5% of circulating lymphocytes (10). The more favorable integral dose of particle therapy (6) likely reduces this effect. For instance, despite the fact that carbon ions are more effective than X rays in the induction of chromosomal aberrations per unit dose, lower levels of aberrations were observed in the peripheral blood of patients treated with carbon ions when compared with photons. In addition, when similar irradiated volumes were compared for different solid tumors (11, 12), recipients of carbon ion therapy were less lymphopenic than patients treated with intensity modulated radiation therapy. The favorable normal tissue sparing associated with the dose distribution of charged particles extends to circulating immune mediators, potentially enabling a better systemic antitumor immune response, while the tumor is rendered an in situ vaccine, during and after radiation therapy.

In conclusion, the work of Gameiro et al (1), along with the experience in Japan (8), suggest that charged particles may be more immunogenic than photons. We hypothesize that charged particles, and especially heavy ions, may distinctly affect cell death pathways, leading to increased immunogenicity, and that their reduced integral dose likely spares more naïve T lymphocytes and memory T cells, essential to direct and sustain a tumor-specific immune response. If indeed particles are more effective than X rays at inducing clinical abscopal effects, their utilization could revolutionize radiation therapy. Research in preclinical models on the effects of ions on the immune system and

their combination with immunotherapy is a high priority for particle therapy.

References

1. Gameiro SR, Malamas AS, Bernstein MB, et al. Tumor cells surviving exposure to proton or photon radiation share a common immunogenic modulation signature, rendering them more sensitive to T cell-mediated killing. *Int J Radiat Oncol Biol Phys* 2016;95:120-130.
2. Demaria S, Golden EB, Formenti SC. Role of local radiation therapy in cancer immunotherapy. *JAMA Oncol* 2015;1:1325-1332.
3. Crittenden M, Kohrt H, Levy R, et al. Current clinical trials testing combinations of immunotherapy and radiation. *Semin Radiat Oncol* 2015;25:54-64.
4. Golden EB, Formenti S. Is tumor (R)ejection by the immune system the “5th R” of radiobiology? *Oncimmunology* 2014;3:e28133.
5. Durante M, Reppingen N, Held KD. Immunologically augmented cancer treatment using modern radiotherapy. *Trends Mol Med* 2013;19:565-582.
6. Belyakov OV, Mitchell SA, Parikh D, et al. Biological effects in unirradiated human tissue induced by radiation damage up to 1 mm away. *Proc Natl Acad Sci U S A* 2005;102:14203-14208.
7. Loeffler JS, Durante M. Charged particle therapy—optimization, challenges and future directions. *Nat Rev Clin Oncol* 2013;10:411-424.
8. Shimokawa T, Ma L, Ando K, et al. The future of combining carbon-ion radiotherapy with immunotherapy: Evidence and progress in mouse models. *Int J Particle Ther* 2016; <http://dx.doi.org/10.14338/IJPT-15-00023.1>.
9. Kamada T, Tsujii H, Blakely EA, et al. Carbon ion radiotherapy in Japan: An assessment of 20 years of clinical experience. *Lancet Oncol* 2015;16:e93-e100.
10. Yovino S, Kleinberg L, Grossman SA, et al. The etiology of treatment-related lymphopenia in patients with malignant gliomas: Modeling radiation dose to circulating lymphocytes explains clinical observations and suggests methods of modifying the impact of radiation on immune cells. *Cancer Invest* 2013;31:140-144.
11. Durante M, Yamada S, Ando K, et al. X-rays vs. carbon-ion tumor therapy: Cytogenetic damage in lymphocytes. *Int J Radiat Oncol Biol Phys* 2000;47:793-798.
12. Pignalosa D, Lee R, Hartel C, et al. Chromosome inversions in lymphocytes of prostate cancer patients treated with X-rays and carbon ions. *Radiother Oncol* 2013;109:256-261.