Editorial

Stereotactic body radiotherapy in the era of radiotherapy with immunotherapy

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Introduction

The spectrum of clinical use of stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy (SABR) has broaden, which has drawn much attention beyond radiation oncologists (1). Immunology and immunotherapy has been considered to provide curative potential for cancer therapy by key opinion leaders globally in recent years (2). "ISABR", termed by Prof. Chang *et al.* from MD Anderson Cancer Center presented a combination of the two cutting edge approaches for cancer therapies (3). They provided data of preclinical and clinical investigation supporting building immunity with SBRT/SABR. In cope with Prof. Chang, we believe that immunotherapy and SBRT makes a perfect couple. In this editorial, we outline and further explain the mechanisms of tumor microenvironment changes under ISABR and uncover the translation from preclinical research to patient benefits.

Why SBRT?

Efficiency of SBRT by killing cancer cells directly

The advances of radiation physic and medical imaging better define tumor geometry. SBRT enables higher dose to tumor per fraction with minimal damage to normal tissues and organs. The most appropriate alpha/beta ratio in the setting of SBRT gives more damage to tumor than conventional fractionation radiotherapy (4). The clinical efficiency of irradiation attributes to induction of DNA damage, which could result in direct cell death. To reach the most biologically effective dose (BED), the regimen of 6–10 Gy per fractions with a total of 6–10 fractions will be used for efficacy with the linear quadratic (LQ) model (5). In this means, the direct cell killing effect of SBRT is more efficient.

Efficiency of SBRT by triggering body's immune system

Radiotherapy combines opportunities leveraging immunity for the next oncology practice (6). Understanding the pathways responsible for the immune effects of radiotherapy in detail will help to explain why SBRT is the best choice of radiotherapy when combined with immunotherapy. Lee *et al.* observed that single fraction radiation doses higher than 15 Gy and lower than 25 Gy promoted T-cell priming in draining lymph nodes which leads to a CD8+ T-cell-dependent size reductions or elimination of both primary tumors and distant metastases in mouse models (7). However, when use the conventional fractionation, immune responses after irradiation and tumor-killing effects induced by irradiation were abrogated, reflecting the CD8+-depleted condition. In another preclinical study of Lugade *et al.*, giving a dose of 15 Gy one time or fractionated the 15 Gy dose into 5 fractions (3 Gy each fraction) promoted antigen presentation and activation of T cells in draining lymph nodes (8). Both the two fractionations were successful in stimulating the body's immune system. However, it is observed that compared with the regimen using 3 Gy ×5 fractionated dose, tumors were infiltrated with a much greater number of host immune cells after 15 Gy single-dose irradiation. Radiation doses of either 7.5 or 10 Gy is effective in immune stimulation and when higher doses of radiation (such as ≥15 Gy) was used it was found that

Table 1 Ongoing clinical trials

Trail number	Institution	SBRT dose (Gy)/fraction	Target organs	Immunotherapy drug	Treatment order	Phase
NCT01950195	Johns Hopkins University	NS	Brain, spine	Ipilimumab	Immunotherapy, then SABR, then immunotherapy	I
NCT01497808	University of Pennsylvania	NS	NS	Ipilimumab	SABR then immunotherapy	I/II
NCT02239900	MD Anderson Cancer Center	50/4 or 60/10	Liver, lung, adrenal	Ipilimumab	Concurrent; or immunotherapy then SABR	I/II
NCT01862900	Chiles Research Institute	15/1 or 20/1	Lung, liver	Anti-OX40	Concurrent	I/II
NCT01769222	Stanford University	20/2	Any	Ipilimumab	Concurrent	I/II
NCT01401062	New York University	22.5/3	Any	Fresolimumab	Concurrent	I/II
NCT02298946	NIH/NCI	8/1 or 24/3	Liver	PD-1 inhibitor	SABR then immunotherapy	I
NCT01703507	Thomas Jefferson University	24/1 or 21/1 or 18/1 or 15/1	Brain	Ipilimumab	Concurrent	I
NCT02444741	MD Anderson Cancer Center	50/4	Lung, liver	PD-1 inhibitor		

NCI, National Cancer Institute; SBRT, stereotactic body radiotherapy; NS, not specified; PD-1, programmed cell death protein 1.

the fraction of splenic regulatory T (Treg) cells increased and the tumor-specific immunity was suppressed (9). But 5 Gy irradiation showed little stimulation effect. Another experiment showed that expose to a dose of 8 to 10 Gy radiation will activate immune-response-related genes and radiation-induced damage-associated molecular pattern molecules (DAMPs), which result in the secretion of inflammatory cytokines implicated in the modulation of immune response (10). It is suggested that there exists a prescribed limit dose below which immune stimulation might be not desirable and above which immunosuppression blooms. Such findings suggest the theory that SBRT triggers body's immune system efficiently.

Conclusions

With the strong basic and clinical evidence of radiotherapy and immunotherapy and recognized patient benefits, the use of SBRT with immunotherapy is promising but not novel (11). There are ongoing clinical trials but few of them reached the endpoint and provided strong evidence until now (listed in *Table 1*). A lot questions need to be answered before the application (12). The technological breakthroughs have enabled higher dose and SBRT gains its popularity (13). As mentioned by Prof. Joe Y. Chang. The concept of "ISABR" is to provide fundamental instructions to consider regarding the development of future research efforts of SBRT and immunotherapy. And it will evenly beneficial to patients, as what we believe.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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