REVIEW

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ABSCOPAL EFFECT OF RADIOTHERAPY: AN OLD CONCEPT IN A NEW ERA

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Summary

The abscopal effect is a phenomenon that describes the systemic antitumor response that can occur as a result of a localized radiotherapy. Although sporadic cases of abscopal effect have been reported since 1960's, the number of reported cases are significantly increasing in the immunotherapy era. Immunotherapy seems to enhance the immunogenic effects of radiotherapy, thus increasing systemic antitumor response. Although combination of radiotherapy and immunotherapy is a promising strategy in the treatment of metastatic cancers, many questions regarding the optimal treatment remain unanswered. Increasing number of ongoing studies will hopefully provide answers to these questions, enabling the utilization of this strategy in systemic anticancer treatment.

KEY WORDS: *abscopal effect, radiotherapy, immunotherapy*

INTRODUCTION

Ever since it was first introduced into the treatment of cancer, radiotherapy has been utilized predominantly in the local treatment of cancer. Its effects can be seen mainly within the irradiated volume, with seemingly no effect on the cells and tissues outside of the treated area. Because of this, radiotherapy has found its place in the primary, neoadjuvant and adjuvant treatment of many sites of localized cancers, as well as palliative treatment of cancer metastases.

Lately, based on a series of case reports and further prompted by promising results of preclinical and clinical studies, a new question has risen: can radiotherapy be used not only for locoregional treatment, but as an active treatment of metastatic disease?

In 1953. Mole was first to use the word *abscopal*. He defined it as *at a distance from the irradiated volume, but within the same organism* (1). The word itself is derived from the Latin prefix *ab*, which means *away from*, and Greek word *scopus*, which means *target*. Essentially, the term *abscopal effect* refers to an effect of certain treatment occurring outside of the treatment field. Over the course of the last sixty years, number of case reports described regression and even disappearance of distant metastases following radiation treatments of a single site. While cases varied in patient age, gender and tumor biology, it was clear that abscopal effect occurred mainly in immunogenic tumors, such as melanoma, renal cell carcinoma, lung adenocarcinoma, lymphomas and leukemias (2). All of these tumors are known to have high T-cell infiltration scores.

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The recent years have brought rapid development of immunotherapy (reviewed in 3,4). New drugs which modulate the immune system are progressively used not only in immunogenic tumors, such as melanoma (5), but also in lung cancer (6), esophageal, gastric and even colorectal cancer (7). It should be noted that head and neck squamous cell cancer, cervical cancer, colorectal cancer, and lung squamous cell cancer are also cancers with high T-cell infiltration scores, which suggests the possibility of efficacy of combined immunotherapy and radiotherapy treatment.

This has once again brought light on the abscopal effect, prompting questions whether immunotherapy can potentially trigger abscopal effect of radiotherapy.

THE MECHANISM OF ABSCOPAL EFFECT

Radiation induces cell death via a specific process known as *immunogenic cell death*. During this process a number of immunogenic factors, such as DAMPs (*damage-associated molecular patterns*), are released. DAMPs include ATP (*adenosine triphosphate*), HMGB1 (*high mobility group box 1*) protein and calreticulin [8]. More specifically, during immunogenic cell death calreticulin is translocated to the cell surface, where is recognized and processed by dendritic cells (DCs). Mature DCs present tumor antigens to cytotoxic T lymphocytes (CTLs) and activate systemic antitumor response (9). HMBG1 binds to Toll-like receptor 4 (TLR4) on the surface of DCs, thus increasing antigen presentation (10). ATP can also bind on receptors on DCs, which results in interleukin 1β release (11). In addition to that, nucleic acids released from dead cells can act as ligands to Toll-like receptors (TLR3, 7, 8 and 9), which results in the release of various cytokines and interferons, and also enhances DC cross-priming (12).

Radiation also causes the upregulation of Fas molecule, a known trigger of apoptosis, as well as MHC I (*major histocompatibility complex*) complex, thus additionally increasing antigen presentation to the cytotoxic T lymphocytes) (2,13).

It has been shown that the activation of cytotoxic T lymphocytes is a marker of radiosensitivity (14), and is a key in the development of the abscopal effect (15).

Abscopal effect in clinical setting is a very rare event. This is probably due to the fact that radiation can exhibit immunosuppressive effects, mainly through upregulation of TGFβ (*transforming growth factor beta*), enhancement of regulatory T-cell representation, and recruitment of myeloid-derived suppressor cells (16-19). These immunosuppressive effects in most cases likely counteract the immunostimulatory effects, which results in rarity of the abscopal effect.

However, the emergence and rapidly growing use of immunotherapy has brought into focus the potential of radiation therapy to induce systemic antitumor responses, by tipping the scale in favor of immunostimulatory, rather than immunosuppressive effects of radiation.

CLINICAL EVIDENCE OF THE ABSCOPAL EFFECT

In 2019 Dagoglu et al. published a systematic review of the reported cases of abscopal effect (disregarding the articles where current cytotoxic treatment was given with radiotherapy) between 1960 and November 2018 and found 94 reported cases in 52 articles. It is notable that half of the reported cases were treated with radiotherapy only, and were reported between 1969 and 2018, while the other half of the cases were treated with a combination of radiotherapy and immunotherapy and reported between 2012 and 2018. The majority of the latter subgroup of patients were treated for non-small cell lung cancer and melanoma, while the other included Hodgkin's lymphoma, gastric cancer, esophageal cancer, pancreatic cancer, renal cell cancer and cervical cancer (large cell neuroendocrine histology) (20).

One of the more notable examples of abscopal effect in combined immune- and radiotherapy treatment was the report of a patient with metastatic melanoma treated with ipilimumab as maintenance therapy who suffered from back pain as a result of a paraspinal mass. Total dose of 28.5 Gy in three fractions was administered to a paraspinal mass. Four months after radiotherapy, CT scan showed not only paraspinal mass regression, but also regression of nonirradiated lesions in spleen and right hilar node. Stable, minimal disease persisted even after 10 months (21). Later report showed a complete regression of primary and metastatic lesions in a patient with metastatic melanoma treated with ipilimumab and radio-

Table 1.

CLINICAL TRIALS USING CHECKPOINT INHIBITORS IN COMBINATION WITH RADIOTHERAPY
[ADAPTED FROM 28]

NCT Number	Status	Condition	Intervention	Characteristics
NCT03042156	Recruiting	Advanced cancer	Radiotherapy (palliative dose)	Observational Model: Cohort Outcome measures: Number of patients developing grade 3 or higher toxicity; In-field and out of field (abscopal) response; The number of completed ESAS questionnaires; Biomarkers analyses
NCT03322384	Recruiting	Advanced solid tumors Lymphoma	Epacadostat; SD-101; Radiotherapy	Phase 1 Phase 2 Outcome Measures: Incidence of adverse events; Abscopal response rate; Maximum tolerated dose
NCT04193696	Not yet recruiting	Advanced hepatocellular carcinoma	Systemic anti-PD-1 immunotherapy; Radiotherapy	Phase 2 Outcome measures: Objective response rate; Overall survival; Abscopal effects rate
NCT03774732	Recruiting	Non-small cell lung cancer	Anti-PDL-1; Radiotherapy	Phase 3 Outcome measures: Overall survival; Progression-free survival; Tumor response; Local and distant control; Quality of life of the patients; Acute/late toxicities
NCT03453892	Recruiting	Metastatic cancer	Nivolumab; Pembrolizumab; Ipilimumab; Radiotherapy	Observational Outcome measures: Overall survival; Progression-free survival; Local and systemic response of detected metastases; Adverse events; Change of circulating immune cells of treated patients by deep immunophenotyping
NCT02406183	Completed	Melanoma	Ipilimumab; Stereotactic body radiotherapy (SBRT)	Phase 1 Outcome measures: Overall survival; Progression-free survival; Maximal tolerated dose that is associated with dose-limiting toxicity in 25% of patients; Immunomonitoring; Preliminary anti-tumor activity (using the immune related response criteria) following ipilimumab combined with escalating doses of radiation
NCT03277482	Recruiting	Recurrent gynecological cancer	Durvalumab; Tremelimumab; Radiotherapy	Phase 1 Outcome Measures: Maximum tolerated dose of combined treatment; Abscopal response; Local response; Overall response; Response duration; Local control; Progression-free survival; Overall survival

Table 1.

CONTINUED

NCT Number	Status	Condition	Intervention	Characteristics
NCT03548428	Not yet recruiting	Sarcoma	Atezolizumab; SBRT	Phase 2 Outcome Measures: Progression-free survival (PFS) rate at 6 months; PFS after radiotherapy/PFS during the previous line of treatment ratio; PFS by immune response criteria; Overall survival; Objective response rate; Treatment toxicity; Quality of life; Rate of PET-CT at inclusion; Treatment cost
NCT03283605	Recruiting	Head and neck squamous cell carcinoma; Metastatic squamous cell carcinoma	SBRT; Durvalumab; Tremelimumab	Phase 1; Phase 2 Outcome Measures: Acute toxicity; Abscopal events; Local control; Overall survival; Progression-free survival
NCT03539198	Recruiting	Head and neck cancer	Nivolumab; Proton Stereotactic Body Radiation Therapy (SBRT) (35-45 Gy in 5 fractions)	Observational Outcome Measures: Objective response rate; Local control rate; Overall survival; Progression-free survival; Time to progression; New development of distant metastasis; Quality of life; Adverse effects; Predictive and prognostic biomarkers
NCT03509584	Not yet recruiting	Non-small cell lung cancer	Nivolumab; Ipilimumab; Radiotherapy (hypofractionated)	Phase 1 Outcome Measures: Incidence of immune related adverse events
NCT04042506	Recruiting	Metastatic melanoma	Nivolumab; SBRT	Phase 2 Outcome Measures: Adverse events; Clinical abscopal effect
NCT03927898	Recruiting	Metastatic colorectal cancer	Toripalimab; SBRT	Phase 2 Outcome Measures: Progression-free survival (PFS) at 1 year; Grade 3-5 acute adverse events; Objective response rate; Local control rate at 2 years; Overall survival at 2 years; T cell clones in peripheral blood and T cell receptor repertoire; PD-1, Ki-67 expression on T cell; PD-L1 expression on exosomes in peripheral blood and on circulating tumor cells
NCT02992912	Recruiting	Metastatic tumors	Atezolizumab; SBRT	Phase 2 Outcome Measures: Progression-free survival

Table 1.

CONTINUED

NCT Number	Status	Condition	Intervention	Characteristics
NCT03176173	Recruiting	Stage IV non-small cell lung cancer	Immunotherapy (standard of care); Image Guided Radiation Therapy	Phase 2 Outcome Measures: Progression-free survival; Change in circulating tumor deoxyribonucleic acid levels (by deep sequencing); Change in levels of immune markers; Incidence of acute and late grade 3-5 toxicity; Overall survival
NCT04221893	Not yet recruiting	Clinical stage IV esophageal, GEJ and gastric cancer	Radiotherapy	Phase: not applicable Outcome Measures: Overall response rate; Progression-free survival; Overall survival; Tumor measurement change by RECIST or iRECIST; Local control in radiated lesion(s); Incidence of new metastatic lesions; Frequency of grade 3 or higher adverse events; Time to new systemic therapy
NCT02888743	Active, not recruiting	Metastatic colorectal carcinoma; Metastatic lung non-small cell carcinoma	Durvalumab; Tremelimumab; Radiotherapy	Phase 2 Outcome Measures: Incidence of adverse events; Abscopal response rate; Local control rate; Overall response rate; Progression-free survival; Overall survival; Objective response per immune-related response criteria; Prognostic effect of PD-L1 expression; Prognostic effect of T-cell infiltration
NCT02587455	Recruiting	Thoracic tumours	Pembrolizumab; Radiotherapy	Phase 1 Outcome Measures: Maximum tolerated dose of pembrolizumab in combination with radiotherapy; Toxicity rate; Progression-free survival rates at 6 and 12 months (all and PDL-1 strong patients); Overall survival rates at 6 and 12 months (all and PDL-1 strong patients); Duration of clinical benefit; Response rate comparison between squamous and non-squamous cancers
NCT03085719	Recruiting	Head and neck cancer	Pembrolizumab; Radiotherapy	Phase 2 Outcome Measures: Overall response rate; Local response determined using CT imaging; Abscopal response determined using CT imaging; Overall survival; Progression-free survival; Adverse events; Objective response by immune related response criteria; Clinical benefit rate

therapy. Total dose of 54 Gy was given in three fractions (22). In another clinical study, 34 patients with castration-resistant prostate cancer were treated with ipilimumab and palliative bone radiotherapy (one to three 8 Gy fractions). The results showed complete clinical response in one patient, while six other had stable disease (23).

Hiniker et al. have shown 13.6% complete response rate in a prospective trial of combination ipilimumab plus radiotherapy in metastatic mela-

noma patients (24), as opposed to 1.5% complete response rate reported in patients treated with ipilimumab only (25).

The efficacy of combined ipilimumab and radiotherapy treatment was also studied in a phase I study of 22 patients with metastatic melanoma. The results showed that 36% of patients had partial response or stable disease, while the rest had disease progression (26). It was later shown that the resistance to combination of radiotherapy and anti-CTLA4 treatment was partially linked to the upregulation of PD-L1 (27).

Currently, there are numerous ongoing clinical trials investigating combinations of radiation and immunotherapy. Some of the ongoing trials are shown in Table 1.

As can be noted, most of the trials are phase I and II, and aim to investigate the potential synergistic effects of radiation and immunotherapy in a myriad of cancers, including non-small cell lung cancer, head and neck cancer, colorectal cancer, esophageal, gastric and GEJ cancer, gynecological cancer, sarcoma and lymphoma. The most interesting, however, may be a phase III French NIRVANA-Lung trial, which is examining the feasibility and efficacy of the combination of anti-PD-L1 therapy and radiotherapy to advanced NSCLC. In this trial, 510 patients with stage IIIB-IV NSCLC are being randomized to receive immunotherapy (nivolumab, pembrolizumab or atezolizumab) or immunotherapy plus radiation (3D-CRT or SABR) to a total dose of 18 Gy in three fractions. Primary outcome of the trial is overall survival, which will be evaluated after a follow-up of 2 years. Local and distant disease control, tumor response, progression-free survival, quality of life and toxicities will be determined after a follow up of 6 months, 1 year and 2 years, respectively.

THE OPTIMAL TIMING, DOSAGE AND FRACTIONATION OF RADIOTHERAPY

Currently, the optimal parameters of radiotherapy to induce abscopal effect remain unknown. The dosage, fractionation and timing seem to vary across different studies.

Some preclinical studies seem to favor fewer fractions. One study on murine melanoma showed better response after a single fraction of 8 Gy than five fractions of 4 Gy (29), while the other favored two fractions of 7.5 Gy over a single fraction of 15 Gy (30).

Dewan et al. compared a single fraction of 20 Gy, three fractions of 8 Gy and five fractions of 6 Gy in combination with anti-CTLA4 antibody on a murine breast cancer, and reported that the fractionated regimes had better antitumor effect than a single dose of 20 Gy [31]. One retrospective analysis of 47 metastatic melanoma patients showed a significant correlation between abscopal effect and fractionated radiation, particularly with fractions equal and smaller than 3 Gy (32).

Currently, MD Anderson phase II trial (NCT02710253) is comparing different radiotherapy regimes in inducing response rates in metastatic patients who have been treated with immunotherapy within past 6 months. The regimes include 50 Gy in 4 fractions using stereotactic radiation or 60-70 Gy in 10 fractions, 20-30 Gy in 5 fractions, or 30-45 Gy in 10-15 fractions using conventional external-beam radiation. A phase I trial (NCT02406183), is comparing 24 Gy in 8 fractions using stereotactic radiation with 30 Gy in 10 fractions and 36 Gy in 12 fractions using conventional external-beam radiation; in combination with ipilimumab for metastatic melanoma.

The optimal sequencing of immunotherapy and radiotherapy is also controversial. While it seems that combination of ipilimumab and radiotherapy works best if given concurrently (31), durvalumab seems to be most effective if given after the chemoradiation (33).

One ongoing phase I study (NCT02826564) is evaluating the optimal sequencing of pembrolizumab and stereotactic body radiation in patients with urothelial carcinoma.

RADIOIMMUNOTHERAPY TOXICITY

There has been some concern that the combination of radiotherapy and immunotherapy may increase their respective toxicities. However, several clinical trials have shown that this is not the case (33-39). One trial in metastatic melanoma, however, showed higher rates of radiation necrosis when radiotherapy was combined with ipilimumab (30% vs. 21%), while the other reported higher rate of treatment-related pulmonary toxicity in comparison with pembrolizumab alone in treatment of non-small cell lung cancer (13% vs. 1%) (39).

CONCLUSION

Although abscopal effect is a phenomenon that has been known for many years, it has only recently been put under the spotlight, mostly due to the rapid advancements in immunotherapy. Although some of the underlying mechanisms behind this phenomenon have been understood, including its immunogenic nature, there are still several unknown variables needed to be determined in order to maximize the abscopal response in clinical setting. These include dose-fractionation regimes of radiotherapy, as well as determination of optimal treatment sequence. Increasing number of ongoing trials will hopefully give answers to these questions, allowing utilization of local radiotherapy in achieving systemic antitumor effects.

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Sažetak

APSKOPALNI UČINAK RADIOTERAPIJE: STARI KONCEPT U NOVOM DOBU

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Apskopalni učinak je fenomen koji opisuje sustavni antitumorski odgovor koji može nastati kao rezultat lokalizirane radioterapije. Premda su sporadični slučajevi prijavljivani još od 1960-tih godina, njihov je broj značajno porastao u eri imunoterapije. Čini se da imunoterapija stimulira imunogenične učinke radioterapije, pojačavajući na taj način sistemski antitumorski odgovor. Iako je kombinacija radioterapije i imunoterapije obećavajuća strategija u liječenju metastatskih tumora, još uvijek nemamo odgovore na brojna pitanja vezana za optimalni protokol liječenja. Sve veći broj istraživanja koja su u tijeku vjerojatno će dati odgovore ta neriješena pitanja, što će omogućiti korištenje ove strategije u sustavnom liječenju raka.

KLJUČNE RIJEČI: *apskopalni učinak, radioterapija, imunoterapija*