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Radioterapia w leczeniu skojarzonym /
Radiotherapy in the combined treatment

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2023, tom 8, nr 1, 22–31

ISSN: 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Radiotherapy and immunotherapy

Ewa Sierko[1, 2]

[1]*Radiotherapy Department 1, Maria Sklodowska-Curie Bialystok Oncology Center, Bialystok, Poland*
[2]*Department of Oncology, Medical University of Bialystok, Bialystok, Poland*

Radiation therapy is one of the standard treatment methods for cancer patients. Apart from killing cancer cells, it produces a modulation effect on local and systemic disease. Recently, immunotherapy, aiming mainly to immune checkpoint blockade, has become widely used in many clinical situations. Experimental and clinical studies indicate that the combination of both radiation therapy and immunotherapy may be beneficial in the cancer patient population in different clinical scenarios. Durvalumab maintenance therapy after radiochemotherapy in stage III non-small-cell lung cancer (NSCLC) patients was introduced to standard clinical care. The paper discusses the pathogenesis of the mutual interaction between radiation therapy and immunotherapy, as well available preclinical and clinical data concerning this promising treatment combination.

Key words: radiation therapy, radiotherapy, immunotherapy, checkpoint inhibitors, cancer

Introduction

Radiation therapy (RT) plays an important role in cancer patients' cure, the prolongation of their lives and the alleviation of cancer-related symptoms. The death of cancer cells due to DNA damage (e.g. apoptosis, autophagy) during cell division or in interphase (e.g. lymphocytes) is the main mechanism of RT. Recent evidence revealed that the efficacy of RT results from the optimal immune response triggered in irradiated tissue. Experimental studies demonstrated that mice lacking T and B cells required a higher radiation dose to achieve the same antitumor effect as mice harboring a properly active immune system. [1]. Additionally, preclinical studies demonstrated reduced RT efficacy in natural killer cells (NK) or macrophages or dendritic cells (DC) – deficient animals [2]. Furthermore, interferon gamma (IFN-γ) was documented to serve as the main factor in CD8+T cells activation, as key effectors in response to RT [3, 4].

Cancer cells accumulate genetic alterations and loss of normal regulatory processes. This results in expression of the neoantigens, differentiation antigens, and/or cancer nuclei antigens, which may lead to presentation of the peptides through binding to major histocompatibility class I (MHC I) molecules on the surface of cancer cells [5, 6]. Such cancer-specific antigens may be recognized by CD8+ T cells produced spontaneously in cancer patients [7], and thus cancer cells may be distinguished from normal cells. Recent studies revealed that at the tumor bed, cancer cells rely on different normal cells and recruit accessory cells to support progression of the tumor [8]. Accessory cells include cells forming hematogenous and lymphatic vasculature, tissue stroma components (among them – tissue-specific mesenchymal support cells, soluble and insoluble matrices), as well as myeloid and lymphoid-lineage cells [5, 8]. Reciprocal interaction between cancer cells, accessory cells, and their mediators, as well as extracellular matrix components exists and is a dynamic process [5]. During the early phase of cancer development, cancer cells are visible to the immune system (through cancer-specific antigens and proinflammatory "danger" signals, and most of them are eliminated (cancer immunosurveillance). Further, the process is not so successful, and the tumor cells may enter

Jak cytować / How to cite:
Sierko E. ***Radiotherapy and immunotherapy.*** *NOWOTWORY J Oncol* 2023; 73: 22–31.

the equilibrium phase, where they may be either maintained chronically or immunologically sculpted by immune "editors" to produce new populations of tumor variants [9]. Finally, during the escape phase, cancer cells are invisible to the immune system and this is clinically visible phase of cancer progression [9]. Well designed studies in mice revealed that the continued deletion of cancer cells expressing T cell targets (immune editing) may enable cancer cells to avoid attacking the immune system [9]. There are multiple other factors contributing to the cancer cells escape from immunosurveillance: cancer cells variability (e.g. proteasome dysfunction, loss of classic MHC I molecules, presence of ligand 1 for programmed cell death (PD-L1), immunosuppressive activity of tumor matrix, presence of cells promoting escape phase (e.g. myeloid-derived stem cells, M2 macrophages, regulatory T cells – Treg, fibroblasts), soluble in tumor extracellular matrix suppressive factors, e.g. adenosine, transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF) [5, 6].

Immune responses in tumors reflect a series of carefully regulated events [6]. Both innate and adaptive immunity contributes to the immune system's optimal activity. The difference between them is based on antigen specificity. Innate immunity, composed mainly from DC, myeloid cells/macrophages and NK, serves as an early warning system and the gatekeeper to T cell activation [6]. The specialized receptors located on the innate immunity cells recognize potential danger targets, which should be eliminated by the host. Pathogen associated molecular patterns (PAMPs) or signals indicating tissue damage ("danger") – danger-associated molecular patterns (DAMPs) are recognized by the innate system, which leads to an immune response [10]. Cells of the innate system play a role in the early phase of the multistep inflammation process and facilitate a full and robust immune adaptive response. The adaptive immunity consists primarily of B and T cells and provide different specificity of the immune system through B and T cell receptor activation [6, 11].

Radiation therapy and innate immunity

At the tumor burden, innate immunity allows for detection of signals indicating the presence of cell damage or danger (fig. 1) [12]. Radiation induces both cancer and normal cells leading to release of specific danger signals that consequently activate multiple inflammatory pathways in innate immune cells. The danger signals include, among others, high-mobility group box protein-1 (HMGB1), calreticulin, complement, heat shock protein 70 (hsp70), cytosolic DNA, and adenosine triphosphate (ATP) [2]. These molecules are sensed by the innate immune cells, such as macrophages, DC *via*: toll-like receptor 4 (TLR-4), cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING), CD47 and NLR family pyrin domain containing protein 3 (NLRP3). These lead to the release of mediators, such as cytokines and chemokines, which trigger an immune response [2].

Damaged cells release HMGB1protein, which binds to TLR-4 on the macrophages and DC. The innate immune cells are characterized by high levels of the receptor. The TLR-4 is the main receptor for bacterial lipopolysaccharide (LPS) as well. Similarly to LPS, HMGB1 stimulates innate immune cells to cytokine release and upregulation of different molecules, like MHC, CD80, CD86, which leads to T cell activation [2].

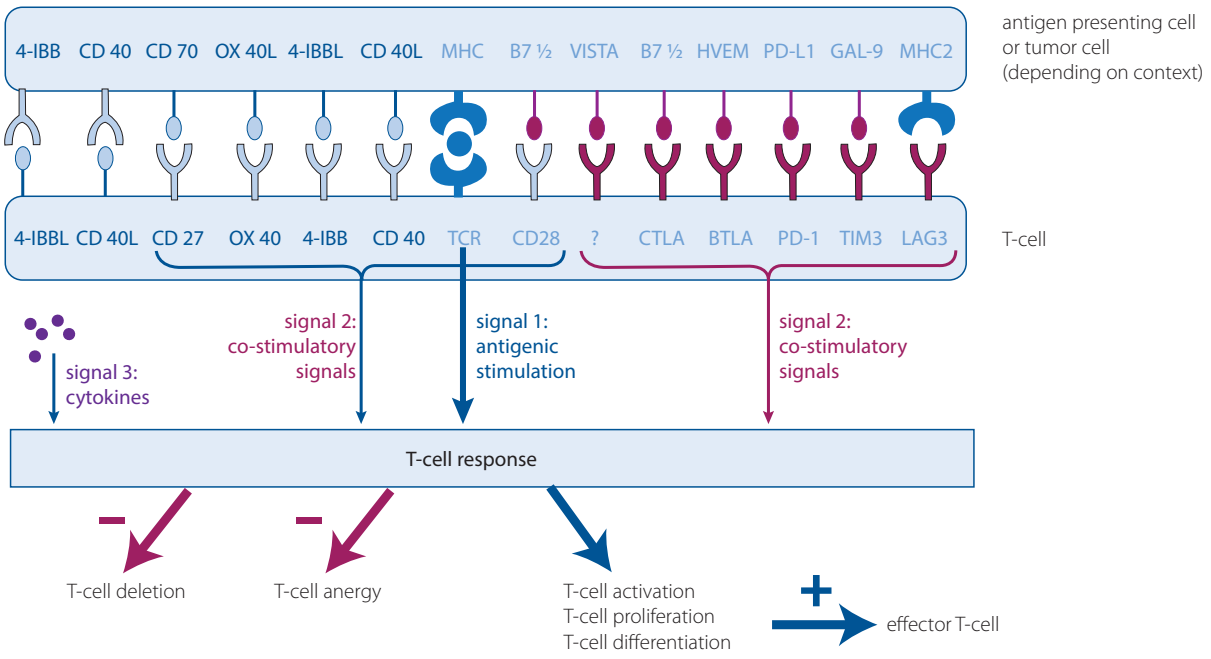


Figure 1. Innate immunity and radiation therapy

Following radiation damage, cells express calreticulin on their surface, which is a phagocytic signal for macrophages and DC. The former cells engulf the dead cells and subsequently may present tumor antigens [13]. Recently, cytosolic DNA was indicated as a critical inflammatory signal induced by radiation [12,14]. Direct and indirect, radiation damage of nuclear and mitochondrial DNA causes DNA fragment formation in the nucleus and in the cytosol. Cytosolic DNA fragments are recognized by an intracellular protein called cyclic GAMP synthase (cGAS) that leads to cGAMP synthesis. It activates the endoplasmic reticulum-bound STING pathway leading to the activation of IFN-regulatory factor 3 (IRF3), and subsequent INF production [15, 16]. Innate immune cells, like macrophages and dendritic cells, are highly abundant in cGAS and STING, which are required for optimal production of type I INF. Synthesis of type I INFs after RT is the prerequisite for inducing the anti-tumor cytosolic CD8+ T cell response, since it induces tumor associated antigens presentation on T cells [16–19]. A recent elegant study demonstrated that DNA exonuclease – 3'repair exonuclease 1 (Trex1) regulates RT-induced activation of cGAS-STING-IFN pathway through cleaving cytosolic DNA formed after radiation exposure [20]. It was revealed that sensitivity of radiation in part depends on Trex1 levels. Namely high levels of Trex1 prevent RT-induced INF production [20].

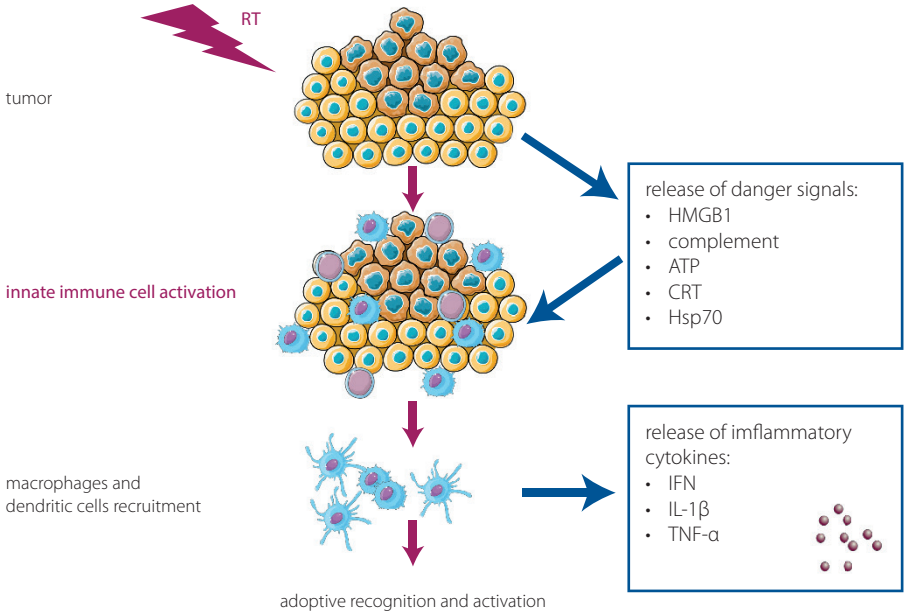
Radiation therapy and adaptive immunity

Cancer antigens are presented to T cells both at tumor burden or in draining lymph nodes mainly by extremely efficient DC. After antigen recognition and capture, DC migrate to draining lymph nodes along with free tumor associated antigens (TAA). Soluble TAA are captured by DC localized at lymphatic tissue. At the lymphoid tissue DC present captured antigens, in the form of peptide-MHC I or MHC II molecule complexes, to naive (antigen inexperienced) T cells (first signal). Additional co-stimulation should proceed through CD80, CD70 and/or 4-1BB (second signal) as well trough cytokines e.g. interleukin 12 (IL-12), type I IFN, IL-15 (third signal) (fig. 2). Naive CD8+ T cells differentiate into cytotoxic T lymphocytes (CTLs) exerting antitumor activity, whereas naive CD4+ cells differentiate into helper cells (T_H) or to Treg – Treg, which role is to decrease the immune response [21, 22].

Immunologic synapse (adaptive response)

T cells migrate through blood and lymphatic vessels to the tumor microenvironment, where they face numerous barriers, like intrinsic regulators (e.g. CD28 – CTLA-4 or PD-1 – PD-L1 systems – called check point regulators), extrinsic factors (Treg, Breg, myeloid cells), pro-tumor inflammatory microenvironment, tissue microenvironment-related DC inhibition, immune evasion of tumor target, tissue-specific alteration, like the presence of fatty cells, desmofibrosis [23]. The killing of cancer cells via T cells release leads again to endogenous tumor-associated antigen (TAA) release and further DC activation, closing so-called "cancer-immunity cycle" [5, 6].

Radiation therapy causes the death of cancer cells due to DNA damage (e.g. apoptosis, autophagy) during cell division or in interphase (e.g. lymphocytes) [24]. In this way it essentially contributes to an exacerbation of the immune system response. Radiation leads to TAA and DAMPS release from cancer cells, deletion of anergic T cells and Treg, increases in antigen processing, and increases in the expression of death receptors, an increase of cytokine and chemokine production as well as



HMGB1 – high-mobility group box protein 1, ATP and adenosine triphosphate; CRT – calreticulin; Hsp70 – heat shock protein 70; IFN – interferon; IL-1β – interleukin 1β; TNF-α – tumor necrosis factor α; RT – radiation therapy

Figure 2. Immunologic synapse (adaptive response)

stimulation of immune cell circulation through the bloodstream [5]. On the other hand, stereotactic radiation therapy (SRT)/ stereotactic body radiation therapy (SBRT) contributes to a diminished number of lymphocytes within the tumor burden, myeloid-derived stem cells increase within the tumor and in the bloodstream, Treg increase, all of which leads to immunosuppression and resistance to immunotherapy [24].

In 1953, for the first time an "abscopal effect" of RT was described. Namely, after RT delivery to one site, the systemic response arises and nonirradiated tumors, being located far away from radiation fields diminished in size or disappeared [25]. From that time such cases were documented in the literature, particularly after hypofractionated regimens [26]. However, in real clinical practice this phenomenon is not frequently observed, probably due to existing, dominant immunologic tolerance mechanisms [24]. Many studies demonstrated that combining RT and immunotherapy increases the antitumor response [24, 27].

Combination of RT and immunotherapy

Currently two concepts between an interplay of RT and immunotherapy exists:

- RT acts as a vaccine, and increases/stimulates the abscopal effect. This is an issue in cancer metastatic setting,
- RT contribution to immunologic modulation in case of radical treatment [26, 27].

It should be stressed that the maximal effect is seen when patients' immunological system is well-functioning. Thus, frail patients are less likely to respond to RT combined with immunotherapy.

Influence of RT dose on immunologic response

Preclinical studies demonstrated that the best effect of combining checkpoint inhibitors with RT is achieved when hypofractionation is used compared to conventionally fractionated RT [28]. However, data from preclinical studies and early clinical experience are not uniform. Brooks et al. [29] demonstrated that a single fraction of 30 Gy resulted in higher CD8+ T cells infiltration and better tumor response than a single 5 Gy fraction, single 20 Gy fraction or 10 x 3 Gy fractionation regimen.

In a PEMBRO-RT phase III trial, SBRT administration (3 x 8 Gy) to the non small-cell lung cancer (NSCLC) metastatic sites combined with pembrolizumab increased relative responses compared to pembrolizumab alone (36% *vs.* 18%) [30]. Of note, the patients were irradiated to the lung tumors or lymph nodes metastases. On the other hand, Luke et al. [31] demonstrated that SBRT administration to 2–4 metastatic sites (30–50 Gy/3–5 fractions) and subsequent pembrolizumab therapy resulted in only a 13% relative response rate. Interestingly, in the study increased expression of 4 preselected IFN-γ genes in postradiation biopsy samples significantly corelated with observed responses in non-irradiated metastatic lesions [31].

The experimental study implies that fractionated RT (8 Gy) induces a better antitumor immune abscopal effect when compared to a single RT dose (20 Gy) [32]. The study, performed by Vanpouille-Box et al. [20], demonstrated that after 3 x 8 Gy-fraction regimen, double strand DNA fragments are present in the cell cytoplasm, whereas a 20 Gy dose produces no such effect [20]. Doses above 12–18 Gy induces the activity of DNA exonuclease Trex1 in cancer cells and attenuates their immunogenicity by degrading DNA that accumulates in the cytosol upon RT [20]. Contrary, RT used at immunogenic doses (oscillating around 8 Gy per fraction) leads to the accumulation of cytosolic double-stranded DNA (dsDNA) in cancer cells, which activates type I IFN (IFN-I) *via* the cGAS/STING pathway [20, 33]. The abscopal effect in mice is seen when a high dose of RT (but not too high) is combined with anti-CTLA-4 and anti-PD-L1 treatment (tab. I) [20].

Table I. Influence of radiation does on immune response

	Radiation dose per fraction (Gy)		
	≤2	4–10	>10
tumor cells	• cancer cell apoptosis • not effective in boosting TAA and DAMPs generation	• cancer cell death • no immunosupression	• cancer cell necrosis • tissue damage • increased cancer cell killing • increased TAA and DAMPs release
immune response	• no change in DCs phenotype and function • increased immunosuppresion • increased number of MDSC, TGF-β, TAM M2 at the tumor burden • immune adjuvant effects • increased number of CD8+ and CD4+ T cells • some TAMs repolarize toward M1 phenotype • lack of efficient antitumor response	• MHC-I up-regulation • DCs capture TAA • promotion of DCs migration tom the lymph nodes • MDSCs, Treg, M2-phenotypic traits decrease • macrophage increase • transient induction of proinflammatory microenvironment	• MHC-I up-regulation and expression on DCs • increased maturation of DCs, APCs • increased Type-I IFN production by DCs • increased number of CD45+ cells and CD8+ T cells • hipoxia-driven immunosuppresive microenvironment • increased number of MDSCs, tolerogenic TAMs M2, Tregs, TGF-β • triggering of innate and adaptive response

TAA – tumor associated antigen; DAMPs – damage and molecular patterns; DCs – dendritic cells; MDSCs – myeloid-derived stem cells; TGF-β – transforming growth factor beta; TAM M2 or -M1 – tumor associated macrophages-M2 or -M1; MHC-I – main histocompatibility complex I; Treg – regulatory T cell; APCs – antigen presenting cells; Type-I IFN – interferon type I; Gy – grey

Interestingly, Menon et al. [34] demonstrated that the addition of low-dose radiation (to tumors nonirradiated with high-dose) to SBRT combined with immunotherapy increases the systemic response rates of metastatic disease. Furthermore, the addition of very low radiation (2 x 1 Gy) to secondary tumors delivered with immunotherapy and high-dose RT to primary tumors (3 x 12 Gy), the so-called RadScopal technique, enhances systemic antitumor immune responses through overcoming the inhibitory tumor stroma [35].

Is what is irradiated important?

Distinct results were obtained in different trials combining treatment with immunotherapy and SBRT delivered to the lymph nodes/lung tumors in the PEMRO-RT trial resulting in doubling of the response rate of combined treatment [30], whereas SBRT to different tumor sites included a substantial number of bony sites (25% of irradiated lesions) did not result in high response rate [31]. Thus, the type of irradiated site may by important to induce immunogenic cell death and durable antitumor immunity.

MacGee et al. [36] revealed that SBRT delivered to parenchymal sites (lung, liver) induces systemic immune changes, including a decrease in the total number of NK and cytotoxic ($CD56^{dim}CD16^{+}$) NK cells, an increase in TIM-3+ NK cells, and an increase in activated memory CD4+ and CD8+ T cells. On the other hand, SBRT administered to non-parenchymal sites (the bones, central nervous system) did not induce such changes. By comparing the immune response after RT to different organs, the data suggest that SBRT induces systemic immunologic changes dependently upon the irradiated site. Based on the forementioned data, a question raises, if all or some metastatic sites should be irradiated to most efficiently increase the chance of immunogenic cell death and to achieve the best effect of combined RT and immunotherapy [29]. Brooks et al. [29] propose delivering SBRT to all or multiple lesions to enhance the probability of immunogenic cell death. Future trials directed to assess the efficacy of SBRT/ immunotherapy should address the issue of number and localization of irradiated lesions as well as define biomarkers of the immunologic cell death [37].

The main effector cells of the immune system are lymphocytes. Radiation therapy volumes including large vessels, the heart, lymphatic structures (e.g. lymph nodes, the spleen, bone marrow, thymus in children) may lead to transient or persistent lymphopenia [38]. Numerous clinical trials demonstrate that lymphopenia correlates with decreased overall survival [39]. There is no data on radiation dose/lymphatic organ volume ratio to guide the safety of RT to lymphatic sites, thus the as low as rationally allowed (ALARA) rule should be used. In so-called "lymphocyte spraying RT", modern imaging methods and sophisticated RT techniques should be used to spare lymphatic organs and bone enriched with bone marrow as much as possible [38, 39]. Utilization of functional imaging, like positron emission tomography (PET) with different tracers, magnetic resonance imaging (MRI) or spectroscopy (SPECT) allow to identify active and inactive volumes of bone marrow, which may help for optimal RT planning to reduce the active volume of the tissue in the radiation volume [39].

Another conception of improving the efficacy of SBRT/ immunotherapy combination is based on partial tumor irradiation. An example is the SBRT-PATHY trial, where SBRT (1–3 fractions, 10–12 Gy each) was delivered to exclusively hypoxic segment of bulky tumors [40]. Such treatment resulted in better SBRT outcomes by exploiting both bystander and abscopal effects [40]. The addition of immunotherapy to such RT might further improve survival. To date, no data exists on such combination efficacy.

Recently, a ultrarapid ultrahigh dose rate FLASH RT was introduced. It delivers very high doses of radiation (8–20 Gy) in less than 1 second(s) [26, 38]. FLASH produces changes in the immunologic microenvironment in both tumor and normal tissues and allows for normal tissue sparing. Furthermore, spatially fractionated radiation therapy (SFRT), the intentional use of heterogeneous doses of radiation to different subvolumes within the same tumor (high dose peaks separated by low dose areas) [26, 38]. Early studies revealed that FLASH induces the release of TNF-α, which correlates with a complete clinical response [26, 38]. The introduction of the novel technologies in combination with immunotherapy is interesting, but requires further thorough studies.

Tumor immunoreactivity

Many studies revealed that the patients who most benefit from immunotherapy are those with cancers that have a high mutational burden [41, 42]. These are for example skin melanomas or microsatellite-instability-high colorectal cancers. Sensitivity of such tumors results from formation of immunogenic, tumor-specific mutant neoantigens [41]. On the other hand, some tumors do not respond to immunotherapy, like: estrogen receptor-positive breast cancer, prostate cancer. These tumors are characterized by limited mutational burden. Cancer cell clones with high mutational burden may be eliminated during progression of the disease as a result of cancer immunoediting, leading to the outgrowth of tumor cell clones with reduced immunogenicity. It was documented that RT-induced neoantigens broaden the immunotherapeutic window of cancers with low mutational loads [41]. As mentioned earlier, the cancer subtype matters in terms of immunoreactivity. Microsatellite-instability-high colorectal cancers are characterized by high mutational burden, contrary to other subtypes of colorectal cancers. Triple negative and HER positive breast cancers are enriched with lymphocyte infiltrations and are characterized by higher immunogenicity, contrary to estrogen receptor/ progesterone receptor positive breast cancers [43].

Optimal timing and sequencing of SRT/SBRT and immunotherapy

Optimal sequence and timing of RT and immunotherapy combinations is the subject of numerous experimental and clinical studies [42, 44]. It should be taken into account that tumors are largely distinct in terms of primary site, histopathology, immunogenicity, and clinical stage. There are several therapeutic mechanisms exploited by immunotherapy. Currently, the most widely implemented is immune checkpoint blockade (ICB).

CTLA-4 blockade and RT

CTLA-4 inhibits an early stage T-cell development, thus contributing to maintaining immune tolerance. CTLA-4 inhibition prevent the downregulation of T-cell activity and reduce Treg activity [44]. Many experimental studies documented promising synergy between RT and anty-CTLA-4 inhibition in neoadjuvant, concurrent, and adjuvant settings [44]. However, to date the optimal sequence is elusive. In experimental studies adding CTLA-4 inhibitors after RT produced increased tumor response and improved survival (in primary and metastatic situations) [44]. CTLA-4 inhibitor administration before RT followed by OX40 inhibitor produced better effects than giving them after RT [45].

In clinical settings ipilimumab administration within 4 weeks after SRT due to melanoma brain metastases resulted in a higher response rate than giving the inhibitor after 4 weeks [46]. In a retrospective study (46 patients), it was observed that ipilimumab administration before or during SRT (single fraction of 21 Gy) for brain metastases produced the best survival benefit and lowest rate of recurrence [47]. Closer to the last dose of ipilimumab delivery of SRS to brain metastases (within 5.5 months) corelated with the best intracranial control [48]. Baker et al. [49] demonstrated that in stage III–IV, unresectable melanoma patients who received nonbrain RT, the longest median survival time was achieved when ipilimumab was administered after RT as maintenance therapy compared to induction delivery – before RT (39 *vs.* 9 months). Knisely et al. [50] reported similar outcomes in 77 melanoma brain metastatic patients after combining SRS and ipilimumab, irrespective of the sequence of administration of the two modalities. In IMCISION (NCT03003637), a non-randomized phase Ib/IIa trial, 32 head and neck squamous cell carcinoma patients were treated with 2 doses (in weeks 1 and 3) of ICB using nivolumab (NIVO MONO, n = 6) or nivolumab plus a single dose of ipilimumab (COMBO, n = 26) prior to surgery [51]. A major pathological response was achieved in 35% of patients after COMBO ICB, whereas after NIVO MONOs – the rate was only 17% [51].

In a prospective trial, enrolling 24 locally advanced melanoma patients, ipilimumab was delivered at 3 mg/kg every 3 weeks for four doses in conjunction with RT (the median dose was 40 Gy). In inoperable patients undergoing neoadjuvant/definitive combined treatment, the objective response rate was 64%, with 4 of 10 evaluable patients achieving a radiographic complete response. An additional 3 patients in this cohort had a partial response and went on to surgical resection [52]. Furthermore, in the second cohort, where the high-risk of recurrence melanoma patients received the combined treatment postoperatively, as adjuvant therapy, the 6-, 12-, and 24-month relapse-free survival was 85%, 69%, and 62%, respectively (with 2 years of follow-up) [52].

In a prospective phase I trial, conducted by the Gynecology Oncology Cooperative Group enrolling 34 cervical cancer patients in clinical stage IB2 to IVA with positive pelvic lymph nodes (LNs), para-aortic LNs, or both, ipilimumab was administered after definitive radiochemotherapy. Treatment was well tolerated, and the 12-month overall survival (OS) was 90%, and progression-free survival (PFS) was 81% [53].

PD-1 blockade and RT

PD-1 present on the mature T lymphocytes inhibits the activation of T cells. It binds with PD-L1 and PD-L2 expressed on tumor cells and antigen-presenting cells. Nivolumab, pembrolizumab, and cemiplimab are PD-1 inhibitors currently used in the clinic [42].

In murine breast cancer model Verburgge et al. [54] observed that PD-1 inhibition given concurrently with RT enhances its efficacy. Furthermore, SBRT delivered 1 day before PD-1 blockade resulted in increased PD-1 blockade antitumor response [55].

A pooled analysis of the phase II PEMBRO-RT trial (NCT 02492568) and phase I and II MD Anderson Cancer Center (MDACC) trial (NCT02444741) revealed that in metastatic NSCLC patients adding radiotherapy to pembrolizumab immunotherapy increased outcome responses [56]. Pembrolizumab was administered intravenously (200 mg every 3 weeks) with or without RT in both trials. In the PEMBRO-RT trial, the first dose of pembrolizumab was given sequentially less than 1 week after the last dose of SBRT (3 x 8 Gy), whereas in the MDACC trial, pembrolizumab was given concurrently with the first dose of RT (4 x 12.5 Gy or 15 x 3 Gy). Only unirradiated lesions were measured for response. Median PFS was 4.4 months with pembrolizumab alone *versus* 9.0 months with pembrolizumab plus RT (p = 0.045), and median OS was 8–7 months with pembrolizumab *versus* 19.2 months with pembrolizumab plus RT (p = 0·0004) [57]. In a phase II NICOLAS trial, 79 stage IIIA–B unresectable treatment-naive NSCLC patients underwent standard, definitive radiochemotherapy plus nivolumab and subsequent nivolumab monotherapy as maintenance setting [58]. The 1-year PFS was 53.7% and the median PFS was 12.7 months. At an extended follow-up (median 32.6 months) median OS was 38.8 months and a 2-year OS rate was 63.7% [58]. Secondary analysis of results from the KEYNOTE-001 trial revealed that patients who had received RT before pembrolizumab administration had longer PFS and OS than those undergoing pembrolizumab therapy alone [59]. Multiple studies (mainly phase I and II) testing various sequencing

Table II. Phase III pending trials involving PD-1 inhibition and radiation therapy

Clinicaltrials.gov identifier [reference]	Setting	Treatment	Endpoint
NCT03700905 [60]	postoperative head and neck cancer	nivolumab or nivolumab plus ipilimumab after surgical resection and adjuvant RT or RT-CT	DSF
NCT04365036 [61]	early stage natural killer/T-cell lymphoma	toripalimab and induction CT followed by RT with concurrent toripalimab vs induction CT followed by RT	PFS
NCT04221945 [62]	locally advanced cervical cancer	CH-RT with or without concurrent pembrolizumab	PFS, OS

RT – radiation therapy; CT – chemotherapy; RT-CT – concurrent radiochemotherapy; DFS – disease free survival; PFS – progression free survival; OS – overall survival

of RT and anti-PD-1 combinations have been published or are ongoing, among others in: in head and neck, cervical, lung, gastrointestinal, genitourinary, breast cancer patients as well as in the central nervous system or hematologic malignancies [42]. Ongoing phase III clinical trials are presented in table II.

PD-L1 blockade and RT

Increased PD-L1 expression on cancer cells allows tumors to evade the immune system. RT increases the expression of PD-L1 in the tumor microenvironment and on CD8+ T-cells [42].

In experimental models, concurrent administration of the PD-L1 inhibitor and RT led to improved survival compared to sequential treatment [63]. A study in a murine pancreatic cancer model demonstrated that adding anti-PD-L1 antibody to high-dose RT significantly improved tumor response and the delay of 7 days between RT and receipt of PD-L1 inhibition abolished the radiosensitization effect [64]. Durvalumab, atezolizumab, and avelumab are PD-L1 inhibitors currently used in the clinic.

The efficacy of combining durvalumab as maintenance therapy after concomitant chemoradiation in clinical stage III NSCLC patients was demonstrated in an elegant phase III PACIFIC trial. Namely the 12-month PFS rate was 55.9% *versus* 35.3%, and the 18-month PFS rate was 44.2% *versus* 27.0%. The response rate was higher with durvalumab than with the placebo (28.4% *vs.* 16.0%; $p < 0.001$), and the median duration of response was longer (72.8% *vs.* 46.8% of the patients had an ongoing response at 18 months) [65]. Of note, subgroup of patients who received durvalumab within 14 days after completing radiochemotherapy had increased survival compared to those who were randomized after this period. Furthermore, durvalumab significantly prolonged OS, as compared with the placebo ($p = 0.0025$) [66]. Estimated 5-year rates for durvalumab and placebo were 42.9% *versus* 33.4% for OS and 33.1% *versus* 19.0% for PFS [67]. Such spectacular results led to incorporating a new benchmark for standard of care in this setting.

Another, phase III randomized study (PACIFIC-4) examines the efficacy and safety of durvalumab with SBRT versus placebo with SBRT in patients with unresected clinical stage I/II lymph node-negative (T1 to T3N0M0) NSCLC [68]. An interesting randomized phase II study (NCT04786093) is ongoing, which is designed to determine the impact of SBRT and durvalumab on quality-of-life and oncologic outcomes in patients with advanced NSCLC. Durvalumab and SBRT, with each fraction of RT given every other day on a standard stereotactic ablative RT schedule or every four weeks on the personalized ultra-fractionated stereotactic adaptive RT (PULSAR) schedule [69].

A randomized, phase III CALLA study to determine the efficacy and safety of durvalumab plus chemoradiotherapy versus chemoradiotherapy alone as a treatment in locally advanced cervical cancer patients is active (NCT03830866) [70]. The results (PFS) are awaited.

Toxicity and tolerability of ICB and RT

In most cases RT and immunotherapy are characterized by a distinct toxicity profile.

Meta-analysis of results obtained in 51 studies showed comparable grade 3–4 toxicity in using ICB plus RT compared to ICI alone in CNS melanoma metastases, NSCLC, and prostate cancer. The author concluded that ICIB plus RT is safe for future clinical trials in these cancers [71]. Additionally, a pooled analysis of trials in the US Food and Drug Administration Database revealed that immune checkpoint inhibitors given within 90 days following RT did not appear to be associated with an increased risk of serious adverse effects [72].

RT combination with other forms of immunotherapy

Apart from immune checkpoints inhibitors, which are the most frequently applied during clinical practice, many other options of immunotherapy combined with RT are currently tested [44]. One of the options are combinations of RT with cancer vaccines, e.g. dendritic cell vaccine (Sipuleucel-T), viral vaccines (rV-CEA/TRICOM or rV-PSA/rV-B7), or protein and peptide vaccines (Vitespene/Oncophage) [44]. Administration of RT with adoptive immunotherapy (T-cell therapy, CAR-T cell therapy, or NK cell therapy) is under early clinical investigation as well [44]. Inclusion of cytokines (TGF-β, TNF-α, GM-SCF, IL-2, Il-7 and IL-15) to stimulate the innate and adaptive immune cells along with RT is also an interesting option, however cytokine

toxic side effects may limit their usage in combination treatment with RT [44].

RT and steroids

Glucocorticosteroids are potent immune suppressants. They trigger T cell apoptosis and may increase the number of Treg. Since the purpose of RT is to stimulate the immune system to act against tumor cells, steroids may prevent this function and abolish the production of new T cells and their priming and activation. In clinical studies with ipilimumab in melanoma patients undergoing SRS, steroids were given prophylactically to avoid brain edema [73–75]. Patients receiving steroids have had lower median survival rates than those who were not given the regimen. However, administering steroids during RT did not interfere with the treatments results, since T cells may already be activated. This needs to be more precisely explained in dedicated studies. The optimal interval between steroid usage and beginning of immunotherapy should be also assessed.

Currently it is recommended to avoid usage of steroids before administration of RT combined with immunotherapy. However, there is an indication that using steroids can mitigate side effect of immunotherapy [76].

Conclusions and future perspective

Despite the encouraging results of many experimental and clinical studies on the combination of radiation therapy and different types of immunotherapy, there is a lack of uniform recommendation concerning the optimal composition of the two modalities in different clinical scenarios (primary or metastatic settings). There is a need to analyze the optimal combinations of RT and immunotherapy in terms of their influence on particular tumors, tumor microenvironment, and immune response. The influence of histopathology, the biological characteristics of the tumor, its localization, primary or metastatic site irradiation, RT delivery to one or multiple sites, the type of site undergoing irradiation (e.g. bone or lung tissue), optimal sequence of the combined therapy, the duration of immunotherapy, the total and fractional radiation dose, etc. should be widely studied. There is a need to find predictive factors (e.g. total mutation burden, total lymphocyte count, p53 status, calreticulin expression, Trex1 level or activity of STING) that allow for the best choice of proper treatment options for the individual patient.

Conflict of interest: none declared

Ewa Sierko
Radiotherapy Department 1
Maria Sklodowska-Curie Bialystok Oncology Center
ul. Ogrodowa 12, 15-027 Białystok
Poland
e-mail: esierko@onkologia.bialystok.pl

Received: 12 Oct 2022
Accepted: 23 Nov 2022

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