Radiotherapy and immune checkpoint blockades: a snapshot in 2016

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Immune checkpoint blockades including monoclonal antibodies (mAbs) of cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), and programmed death-ligand 1 (PD-L1) have been emerged as a promising anticancer therapy. Several immune checkpoint blockades have been approved by US Food and Drug Administration (FDA), and have shown notable success in clinical trials for patients with advanced melanoma and non-small cell lung cancer. Radiotherapy is a promising combination partner of immune checkpoint blockades due to its potent pro-immune effect. This review will cover the current issue and the future perspectives for combined with radiotherapy and immune checkpoint blockades based upon the available preclinical and clinical data.

Keywords: Radiotherapy, Immune checkpoint blockades, Cytotoxic T-lymphocyte antigen-4, Programmed cell death 1 receptor

Introduction

Radiotherapy (RT) is a main modality for anticancer treatment. Radiation directly ionizes atoms of the cancer cells and makes excited electrons. These secondary electrons directly damage the DNA of cancer cells. The electrons also make free radicals by interacting with water in the tissue, which can damage the DNA of cancer cells. This is the indirect action of radiation. Incomplete repair of these damaged DNA causes several modes of cell death, such as apoptosis, autophagy, or senescence. Radiosensitivity varies according to cells, tissues, and organs. In particular, lymphocytes show high radiosensitivity even in a low dose, so RT has been used as an immunosuppressive therapy, such as total body irradiation for conditioning prior to bone marrow transplantation. Also, RT can activate immunosuppressive transforming growth factor-β (TGF-β) and tumor promoting macrophage [1]. However, RT can induce immunologic cell death providing tumor specific peptides presented by major histocompatibility complex (MHC) class I of antigen-presenting cells (APCs) and recognized by cytotoxic T cells [2]. Furthermore, RT also can activate APCs possessing anti-tumor immunity [3]. These T cells infiltrate to the tumor site, secrete interferon γ (IFN-γ), and kill tumor cells [4]. Specific combination of signals could be released either, which stimulate tumor-specific cytotoxic T lymphocytes even in the distant sites, so-called “abscopal effect.” The systemic effects induced by local RT have been reported in patients with several types of solid tumors, such as melanoma, renal cell carcinoma, and lung adenocarcinoma [5] (Table 1).
Immune checkpoint blockades have been showing remarkable progress in the field of immunotherapy, regulating key immunosuppressive pathways of cancer cells. Targets of checkpoint blockades are cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1), crucial molecules for peripheral CD8+ T cell tolerance induced by APC. CTLA-4, a trans-membrane protein receptor which expressed in T cells, affects priming phase of immune response. It is transported to the surface when T cell receptor (TCR) recognizes an antigenic peptide in association with MHC of APC. For the complete T cell stimulation, CD28 receptor of T cell and B7 ligand of APC are needed to be bound for a co-stimulatory pathway [6]. CTLA-4 has higher affinity, thus inhibits proliferation of T cells by outcompeting CD28 receptor for ligand binding. CTLA-4 mediated T cell immune tolerance also can be achieved by production of cytokines such as TGF-β in regulatory T cells [7].

Another key inhibitory receptor PD-1 is on surface of T cell and B cell, and binds to programmed death-ligands 1 and 2 (PD-L1 and PD-L2). PD-L1 is widely expressed on hematopoietic and non-hematopoietic cells. The main role of PD-1/PD-L1 system is to limit the response of effector T cell and the immune-mediated damage of tissues. PD-L1 is also expressed on various types of solid tumors and hematologic malignancies. Tumor cells with PD-L1 expression can escape from T cell related immune reaction, and this adaptive resistance is regulated by cytokines, such as tumor necrosis factor-α (TNF-α) and IFN-γ [8].

In clinical trials using the checkpoint blockades, anti-CTLA-4 and anti-PD-1 monoclonal antibodies (mAbs), improved survival outcomes were reported for patients with advanced solid tumors, in particular melanoma and non-small cell lung cancer (NSCLC). Ipilimumab, an anti-CTLA-4 mAb, was administered for metastatic melanoma. Response rate was 11% to 15.2% and median overall survival (OS) time was 10.1 to 11.2 months. Adverse effect rate was higher, grade 3 to 4 events occurred in 45% to 60% of patients. Of these, immune-related adverse effects were 10% to 41.7%. Common side effects were skin reaction, diarrhea, and increased liver enzyme [9,10]. Interestingly, survival benefit was lasted for long time, a plateau was found after 3-year, and OS rate was 18.2% at 5-year [11]. Anti-PD-1 mAbs (nivolumab and pembrolizumab), comparing with ipilimumab, were reported to prolong survival and response rate, while decrease adverse effect in metastatic melanoma patients [12,13]. In the trial using pembrolizumab (vs. ipilimumab), 1-year OS rate was 68.4%–74.1% (vs. 58.2%), response rate was 32.9%–33.7% (vs. 11.9%), and grade 3 to 5 adverse effect rate was 10.1% to 13.3% (vs. 19.9%) [13].

In the patients with chemo-refractory NSCLC, nivolumab showed better treatment outcomes than docetaxel. Median OS was 9.2–12.2 vs. 6.0–9.4 months and response rate was 19%–20% vs. 9%–12%. Grade 3 to 4 adverse events were less in nivolumab group, 7%–10% vs. 54%–55%. Of these patients having response to nivolumab, response duration time was very long, median time was 17.2 months or unreached [14,15]. Pembrolizumab also compared with docetaxel in PD-L1-positive NSCLC patients who had history of treatment. Median OS was 10.4–12.7 months vs. 8.5 months, and response rate was 18.0%–18.5% vs. 9.3%. Patients with PD-L1 positive in 50% or more tumor cells had more improved outcomes, median OS was 14.9–17.3 months vs. 8.2 months, and response rate was 29.1%–30.2% vs. 7.9%. Grade 3–5 treatment-related toxicity rate was lower with pembrolizumab, 13%–16% vs. 35% [16].

Checkpoint blockades have shown improved treatment outcomes in the clinical trials for advanced melanoma and NSCLC patients with previous systemic treatments. Notably, the response rate of pembrolizumab was not significantly lower even in the patients with ipilimumab history [17,18]. Nonetheless, advanced solid tumors other than melanoma or NSCLC have not been reported to have considerable efficacy or safety of checkpoint blockades [19,20]. Hence, combination strategies are actively discovered to extend the target of checkpoint blockades, using chemotherapy or small molecules. RT is also a promising partner of checkpoint blockades in terms of the immunogenic effect as mentioned above.

**RT Combined with Checkpoint Blockades: Preclinical Data**

Regulatory T (Treg) cells are more radioresistant than other T cells, consequently increased by RT [21]. Naturally, an important role of Treg cells is to maintain immune tolerance, even in tumorous condition. CTLA-4 is reported to be a key target to control the suppressive function of Treg cell [22]. Thus, the combination of RT and anti-CTLA-4 mAb has been investigated to overcome tumor immunity. Demaria et al. [23] injected poorly immunogenic 4T1 metastatic mouse mammary carcinoma cells into mice, and then performed 2 by 2 arms of treatment: (RT or no-RT) × (CTLA-4 mAb or control immunoglobulin G [IgG]). When RT was combined with anti-CTLA-4 mAb, the survival was significantly extended and lung metastasis was controlled. In this study, CD8+ T cell was
shown to have crucial role, while CD4+ T cell did not. Anti-tumor immunity was also confirmed in other types of cell lines, such as mesothelioma [24] and glioma [25].

Though the combination of RT and anti-CTLA-4 mAb has been reported to have improved response, the unresponders are more common than the responders. In this point of view, the importance of PD-L1/PD-1 co-inhibitory pathway has been noted, which modulate microenvironment to facilitate activation of CD8+ T cells [26]. Twyman-Saint Victor et al. [27] obtained resistant murine melanoma cells from mice with relapsed tumor after the combination of RT and anti-CTLA4 mAb. The authors found that the resistance was associated with the exhaustion of CD8+ T cell and the upregulation of PD-L1 by cancer cells. After the addition of anti-PD-L1 mAb, exhausted CD8+ T cell was reversed and the response was improved. In addition to effector T cells, down-regulation of tumor-infiltrating myeloid-derived suppressor cells by TNF-α was reported to be associated with antitumor immunity [28], and blocking of TGF-β might be a another strategy [29]. Thus, murine melanoma cell line was a preceding model to confirm the effect of the combination of anti-PD-1/PD-L1 mAb and RT [30].

Furthermore, impressive feature of immunotherapy, immune memory was confirmed. Zeng et al. [33] selected "cured mice," which survived more than 90 days after the combined treatment of RT and anti-PD-1 mAb for murine glioma, and injected same cell line. All of naive mice had >1 cm³ tumors after 21 days of implantation, while none of cured mice had tumors after 60 days of implantation. Enhanced abscopal effect was also reported in other study, combined treatment of RT and anti-PD-1 mAb significantly inhibited the growth of secondary unirradiated tumors, comparing with single treatment of RT or anti-PD-1 mAb [32] (Table 1).

### Table 1. Checkpoint blockades and effect of radiotherapy

| Ligands on tumor cell | Receptors on T cell | Ligands on antigen-presenting cell | Checkpoint blockade |
|-----------------------|---------------------|----------------------------------|---------------------|
| PD-L1 and L2          | PD-1                | -                                | Anti-PD-1/L1 (atezolizumab, nivolumab, pembrolizumab) |
|                       |                     | CTLA-4                           | Anti-CTLA-4 (ipilimumab) |

**Effect of radiotherapy** To increase antigen presentation and CD8+ T cell infiltration

To stimulate tumor-specific cytotoxic T lymphocytes in the distant sites: abscopal effect

PD-L1 and L2, programmed death-ligand 1 and ligand 2; PD-1, programmed death-1; CTLA-4, cytotoxic T-lymphocyte–associated protein 4.

At this time, a limited number of clinical trials reported results of combined RT and checkpoint blockades, moreover, most of them used anti-CTLA-4 mAb. A phase I/II study for patients with metastatic castration-resistant prostate cancer evaluated safety and efficacy of ipilimumab, an anti-CTLA-4 mAb with or without radiotherapy. RT was delivered to metastatic bone lesion with 8 Gy single fraction 1 to 2 days before the first ipilimumab. The dose of ipilimumab was escalated as 3, 5 or 10 mg/kg without RT, or 3 or 10 mg/kg with RT. Response was assessed after up to 4 cycles (3 weeks per cycle). Among 34 patients with 10 mg/kg ipilimumab and RT, grade 3 to 4 immune-related adverse effects occurred in 18% of patients (colitis, 6%; hepatitis, 6%; and diarrhea, 6%), and ≥50% prostate-specific antigen (PSA) decline was confirmed in 12% of patients [34]. In a phase III trial, ipilimumab was compared with placebo for metastatic castration-resistant prostate cancer patients. Single fraction RT (8 Gy) was given for metastatic bone lesion within the 2 days before the medication. Ipilimumab (10 mg/kg) or placebo was administered every 3 weeks for up to 4 cycles, and continued every 3 months until disease progression or severe toxicity. A total of 799 patients were randomly assigned to ipilimumab (n = 399) and placebo (n = 400) groups. Though OS for the entire patients was not increased with ipilimumab (11.2 vs. 10.0 months, p = 0.053), progression-free survival (4.0 vs. 3.1 months, p < 0.0001) and ≥50% PSA decline (13.1% vs. 5.2%) was improved. Grade 3 to 4 immune related adverse effects were noted in 26% of ipilimumab group and 3% of placebo group, and common immune related events were diarrhea (15% vs. <1%) and colitis (5% vs. 0%). Four patients (1%) in ipilimumab group had ipilimumab-related death [35]. These two clinical trials reported similar rate of severe immune-related toxicity comparing with aforementioned phase III.
Immunotherapy trials without RT, hence we can expect the combination of RT and checkpoint blockades could be a useful treatment modality. More data can be found in retrospective studies, and they may give us additional clue to identify the benefit of the combination.

In the real world, immunotherapy is usually tried for patients with systemic metastasis, thus RT may be particularly used as palliative intent. As expected, palliative RT (median dose of 30 Gy) combined with ipilimumab (median dose of 10 mg/kg) was reported to have appropriate palliative effect without significant increase of immune-related adverse effects [36]. If the abscopal effect is confirmed in clinical data, the combination of RT and immunotherapy can be more useful. Several case reports have observed the abscopal effect of local RT. A metastatic melanoma patient who had showed stable disease with ipilimumab received palliative RT (28.5 Gy in 3 fractions) when the disease progressed. Shortly after RT, there was not a response. However, a significant regression was observed in both of irradiated lesion and distant non-irradiated lesions after an additional dose of ipilimumab [37]. In another case report, a patient with metastatic lung adenocarcinoma underwent palliative RT (30 Gy in 5 fractions) concomitantly with ipilimumab. After the concomitant treatment, significant reduction of tumor size and metabolic uptake was detected in whole body, furthermore, the carcinoembryonic antigen level was normalized either [38].

Brain metastasis can be a typical model of combined treatment of RT and immunotherapy, since complete resection is difficult and systemic agents hardly penetrate the blood–brain barrier. Survival benefit of the combination of brain RT and ipilimumab was reported in a study for brain metastatic melanoma patients, the combined treatment showed better OS (median, 21.3 vs. 4.9 months; p = 0.044) than radiosurgery alone [39]. The abscopal effect observed either. A retrospective study reported treatment results of 13 patients with brain metastatic melanoma who treated with ipilimumab (3 mg/kg) and whole-brain RT (WBRT; median 30 Gy in 10 fractions) within 30 days of one another. Extracranial response rate was evaluated in 10 patients, and the response rate was 20% (complete response 1, partial response 1, and stable disease 2). The rate of grade 3 to 4 central nervous system-related acute toxicity was low, reported in only 1 patient. Notably, all patients who had post-WBRT imaging had new or worsened intratumoral hemorrhage (median, 53 days) [40]. However, the influence of RT or ipilimumab on hemorrhage should be cautiously considered, because intratumoral hemorrhage is commonly occurred in melanoma metastases. Actually, in another study for brain metastatic melanoma patients, more intratumoral hemorrhage was occurred in brain RT alone group than brain RT and ipilimumab group (12.5% vs. 3.9%) [41].

In summary, clinical data for the combination of RT and checkpoint blockades are still scanty and concentrated on a certain agent, ipilimumab. Nonetheless, based on the results of several retrospective studies, we can expect that the combined treatment may be synergistic without significant increase of immune-related adverse effects.

How to Combine RT with Checkpoint Blockades?

Several technical issues should be considered for combination of immune checkpoint and RT, such as fractionation schedule and sequence of RT. We should look back on preclinical data to find appropriate fraction size. In a mouse model using B16 melanoma cells, 20 Gy was delivered in 1 fraction or 5 fractions. Increased reduction of primary tumor or distant metastasis was reported in single fractionation group rather than fractionation group. This ablative RT-initiated immunity was CD8+ T-cell dependent [42]. In other study using a fractionated schedule of RT (2 Gy × 5), upregulation of PD-L1 was observed in murine colon carcinoma cells of mice [43]. This is the adaptive immune-evading mechanism of tumor cells, depending on IFN-γ produced by CD8 T cell. In contrast, single fraction RT with higher dose (10 Gy) decreased the expression of PD-L1 in human prostate cancer cell lines in vitro [44].

Based on these results, ablative RT with single fraction might be suggested to initiate immunologic response better than fractionated RT. However, 2 to 5 Gy per fraction which used in aforementioned studies is a relatively conventional schedule. Fractionated RT with conventional low daily dose may be less immunologic, at least in the setting of metastatic disease. Silk et al. [41] reported that survival benefit of ipilimumab was confirmed in radiosurgery group (19.9 vs. 4.0 months; p = 0.009), while not in WBRT (3.1 vs. 5.3 months; p = 0.60). In this study, RT dose was 30–37.5 Gy in 10–13 fractions and 14–24 Gy in 1–5 fractions for radiosurgery. Therefore, fractionated RT with higher daily dose should be compared with single fraction RT. Actually, Dewan et al. [45] injected TSA mouse breast carcinoma or MCA38 mouse colon carcinoma cells into the both flanks of mouse. RT was given to “primary site” as 20 Gy in single fraction, 8 Gy in 3 fractions, and 6 Gy in 5 fractions. 9H10 monoclonal antibody against CTLA-4 was
**Table 2. Selected ongoing trials**

| Trial no. | Phase | n | Condition | Intervention | Sequence | Radiotherapy schedule | Institute |
|-----------|-------|---|-----------|--------------|----------|------------------------|-----------|
| NCT02406183 | I | 21 | Metastatic melanoma | Ipilimumab + SBRT | Ipilimumab → RT (at day 39, 41, 43) | SBRT 24, 30 or 36 Gy in 3 fractions | Radiotherapie, University Hospital Ghent |
| NCT02821182 | II | 40 | Metastatic melanoma | Anti-PD-1 + SBRT | Concomitant | 24 Gy in 3 fractions (separated 2–3 days) | University Hospital Ghent |
| NCT02115139 | II | 66 | Melanoma and brain metastases | Ipilimumab + WBRT | Ipilimumab → WBRT (between cycle 1 day 2 and cycle 2 day 1) | 30 Gy in 10 fractions | Grupo Español Multidisciplinar de Melanoma |
| NCT02407171 | I/II | 60 | Metastatic melanoma or non-small cell lung cancer | MK-3475 + SBRT | Concomitant | 30 Gy in 3 or 5 fractions | Yale University |
| NCT02866747 | I/II | 62 | Recurrent glioblastoma | HFRT Durvalumab + HFRT | RT → durvalumab (on day 5 of RT) | 24 Gy in 3 fractions (days 1, 3, and 5) | Institut Claudius Regaud |
| NCT02617589 | III | 550 | Glioblastoma | Nivolumab + RT Temozolomide + RT | - | - | Bristol-Myers Squibb |
| NCT01935921 | I | 18 | Stage III-IVB head and neck cancer | Cetuximab + RT + ipilimumab | Cetuximab + RT → ipilimumab (at week 4) | 66–70 Gy for 7 weeks | National Cancer Institute |
| NCT02764593 | I | 120 | Advanced head and neck squamous cell carcinoma | Nivolumab + cisplatin Nivolumab + cetuximab Nivolumab + RT | Nivolumab → (after 14 days) RT | 70 Gy in 35 fractions | RTOG |
| NCT02759675 | II/II | 47 | Locally advanced laryngeal squamous cell carcinoma | Pembrolizumab + cisplatin + RT | Concomitant | 70 Gy in 35 fractions | Nooshin Hashemi-Sadraei |
| NCT02609503 | II | 29 | Locally advanced squamous cell carcinoma of the head and neck | Pembrolizumab + IMRT | Concomitant | 7 weeks | UNC Lineberger Comprehensive Cancer Center |
| NCT0277385 | II | 44 | Head and neck squamous cell carcinoma | Pembrolizumab + cisplatin + IMRT | CCRT → (3 weeks after pembrolizumab) Pembrolizumab → (1 week after) CCRT | 35 fractions | University of Pittsburgh |
| NCT02289209 | II | 48 | Inoperable recurrence or second primary squamous cell carcinoma of the head and neck | Reirradiation + MK-3475 | Concomitant | 1.2 Gy BID for 5 days weekly | Dan Zandberg, University of Maryland |
| NCT02642809 | 0 | 15 | Metastatic esophagel cancers | Brachytherapy + pembrolizumab | Brachytherapy → pembrolizumab (within 1 week) | 16 Gy in 2 fractions | Washington University School of Medicine |

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| Trial no.     | Phase | n   | Condition                          | Intervention                                                                 | Sequence   | Radiotherapy schedule                                                                 | Institute                                                                                     |
|--------------|-------|-----|------------------------------------|-----------------------------------------------------------------------------|------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| NCT02844075  | II    | 28  | Esophageal squamous cell carcinoma | Neoadjuvant CCRT with taxol, carboplatin, and pembrolizumab                | Concomitant | 44.1 Gy in 21 fractions                                                               | Yonsei University                                                                           |
| NCT02621398  | I     | 30  | Stage II-IIIB non-small cell lung cancer | Paclitaxel + carboplatin + RT + pembrolizumab                        | Concomitant | 5 Days a week for 6 weeks                                                               | Rutgers, The State University of New Jersey                                                   |
| NCT02221739  | II    | 39  | Metastatic non-small cell lung cancer | Ipilimumab + local RT                                                      | RT → ipilimumab (within 24 hours) | 6 Gy × 5 fractions                                                                    | New York University, School of Medicine                                                     |
| NCT02525757  | II    | 40  | Non-small cell lung cancer         | CCRT with carboplatin and paclitaxel + MPDL3280A                        | Concomitant MPDL3280A → CCRT | 60–66 Gy in 30–33 fractions                                                            | MD Anderson Cancer Center                                                                     |
| NCT02888743  | II    | 180 | Metastatic colorectal or non-small cell lung cancer | Tremelimumab + durvalumab + high dose RT                                      | Immunotherapy → RT (at week 2) | Arm B: over 10 days for up to 3 fractions Arm C: every 6 hours BID on weeks 2, 6, 10 and 14 | National Cancer Institute                                                                   |
|              |       |     |                                     | Tremelimumab + durvalumab + low dose RT                                    |            |                                                                                        |                                                                                               |
| NCT02768558  | III   | 660 | Stage III unresectable non-small cell lung cancer | RT + cisplatin + etoposide +/- nivolumab                               | CCRT → nivolumab | 60 Gy                                                                                  | RTOG                                                                                          |
| NCT02303366  | I     | 15  | Oligometastatic breast cancer       | MK-3475 + SBRT                                                            | SBRT → MK-3475 | 20 Gy in 1 fraction                                                                   | Peter MacCallum Cancer Centre                                                               |
| NCT02730130  | II    | 17  | Metastatic triple negative breast cancer | Pembrolizumab + RT                                                        | RT → pembrolizumab (at day 2) | 30 Gy in 5 fractions                                                                   | Memorial Sloan Kettering Cancer Center                                                      |
| NCT01853618  | I     | 100 | Liver cancer                        | TACE or RFA once only Repeat TACE Tremelimumab + SBRT Tremelimumab + cryoablation Tremelimumab + RFA | Tremelimumab → SBRT (at day 36) | 1 fraction                                                                               | National Cancer Institute                                                                  |
| NCT02837263  | I     | 15  | Liver metastatic colorectal cancer  | SBRT + pembrolizumab                                                       | SBRT → pembrolizumab | 40–60 Gy in 5 fractions                                                                | University of Wisconsin, Madison                                                            |
| NCT0298946   | I     | 17  | Metastatic colorectal cancer        | Cyclophosphamide + SBRT + AMP-224                                         | SBRT (days –2, –1, 0 or day 0) → medication | 8 Gy × 1 or 3 fractions                                                               | National Cancer Institute                                                                  |
| NCT02948348  | I/II  | 50  | Rectal cancer                       | Preoperative CCRT with capecitabine + nivolumab                           | Concomitant | 45 Gy in 25 fractions                                                                  | Takayuki Yoshino, National Cancer Center Hospital East                                    |
| NCT02868632  | I     | 36  | Unresectable, non-metastatic pancreatic cancer | MEDI4736 + SBRT Tremelimumab + SBRT MEDI4736 + tremelimumab + SBRT | SBRT → immunotherapy (within 4 hours) | 6 Gy × 5 fractions                                                                    | New York University, School of Medicine                                                    |

Continued on the next page.
Table 2. Continued

| Trial no. | Phase | n | Condition | Intervention | Sequence | Radiotherapy schedule | Institute |
|----------|-------|---|-----------|--------------|----------|-----------------------|-----------|
| NCT02311361 | I | 60 | Unresectable pancreatic cancer | MEDI4736 + SBRT | | | National Cancer Institute |
| NCT02648282 | II | 54 | Locally advanced pancreatic cancer | Cyclophosphamide + pembrolizumab + GVAX + SBRT | Immunotherapy → SBRT (at second dose) | 6.6 Gy for 5 days (at 2nd cycle) | Sidney Kimmel Comprehensive Cancer Center |
| NCT02855203 | I/II | 30 | Oligometastatic renal tumors | Pembrolizumab + SBRT | SBRT → pembrolizumab | 18-20 Gy × 1 fraction | Peter MacCallum Cancer Centre, Australia |
| NCT02599779 | II | 35 | Stage IV renal cell cancer | Pembrolizumab + SBRT | | | Sunnybrook Health Sciences Centre |
| NCT02880345 | - | 14 | Advanced urothelial cancer | Pembrolizumab + HFRT or SBRT | | 8 Gy × 3 fractions | Abramson Cancer Center of the University of Pennsylvania |
| NCT02891161 | I/II | 42 | Urothelial cancer (T2-4 N0-2 M0) of the bladder | Durvalumab + RT | Concomitant | 64.8 Gy in 36 fractions | Monika Joshi, Big Ten Cancer Research Consortium |
| NCT02843165 | II | 146 | Metastatic cancer | Anti-CTLA-4 or anti-PD-1/L1 mAb +/- SBRT | Concomitant | 9.5 Gy × 3 fractions (1-21 days) | University of California, San Diego |
| NCT01711515 | I | 28 | Locally advanced cervical cancer | Cisplatin + EBRT and brachytherapy + ipilimumab | Cisplatin + RT → ipilimumab (within 2 weeks) | | National Cancer Institute |

Anti-CTLA-4 (ipilimumab, tremelimumab); Anti-PD-1/L1 (AMP-224, durvalumab, MEDI4736, MPDL3280A, MK-3475, nivolumab, pembrolizumab). SBRT, stereotactic body radiotherapy; RT, radiotherapy; WBRT, whole brain radiotherapy; HFRT, hypofractionated radiotherapy; RTOG, Radiation Therapy Oncology Group; IMRT, intensity modulated radiotherapy; CCRT, concurrent chemo-radiotherapy; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; mAbs, monoclonal antibodies; EBRT, external beam radiation therapy.
combination with RT or not. Interestingly, the RT regimen with 8 Gy × 3 fractions showed most enhanced response regardless of tumor sites.

Regarding the sequence of RT and immunotherapy, it is another uncertainty. In one study for brain metastatic melanoma, response rate was 40% in RT after ipilimumab and 16.7% in RT before ipilimumab [41]. On the contrary, in another study for melanoma brain metastases, patients underwent radiosurgery during or before ipilimumab had better OS than those underwent radiosurgery after ipilimumab (at 1 year, 65% vs. 56% vs. 40%, p = 0.008). However, patients underwent radiosurgery during ipilimumab showed more frequent central nervous system toxicities, for example, hemorrhage was found in 40%, compared with 18% in patients underwent radiosurgery before or after ipilimumab [46]. However, small number of patients and retrospective nature is the limitations of these studies to clarify the optimal sequence of RT and immunotherapy.

Ongoing Trials and Future Perspectives

Major issues for the combined treatment of RT and checkpoint blockades can be summarized as follows. Above all, more types of cancer, beyond melanoma and NSCLC, must be considered as the indication of combined treatment. Especially, several cancers with poor prognosis or limited applicable systemic agents, such as pancreas and triple negative breast cancers, were reported to be possibly immunogenic [47,48], so multiple studies have been conducted for varied types of cancer (Table 2). Additionally, anti-PD-1/L1 mAb, besides anti-CTLA-4 mAb, should be verified to have synergistic effect by the combined RT and immunotherapy. Most of preclinical and clinical studies used anti-CTLA-4 mAb, especially ipilimumab, being developed earlier than other agents. Tumor tissue studies in patients receiving neoadjuvant chemo-radiotherapy reported that PD-L1 expression was increased in tumor cells, but its influence on prognosis is very conflicting [49,50]. Lastly, optimal combination schedule of RT and checkpoint blockades also has to be clarified, including fractionation schedule and sequence of RT and checkpoint blockades. Although RT with higher daily dose appears more immunogenic than RT with conventional daily dose in several preclinical or retrospective studies, we should take into account that the studies used RT in a palliative setting. For curative intent, conventionally fractionated RT should be investigated in clinical trials whether has synergistic immunogenic effect, as well as the sequence of RT and immune checkpoint blockade. Selected ongoing trials are summarized in Table 2.

Conclusion

Immune checkpoint blockades have been emerged as promising anticancer therapy, showing enormous progression on clinical application. Pro-immune effect of RT is expected to boost efficacy of checkpoint blockades without significant increase of immune-related adverse event. Although the evidence of combined treatment is not sufficient yet, preclinical data suggest a potential benefit of combined RT and checkpoint blockades. Based on ongoing clinical trials, the latitude for clinical application of RT would be extended, from palliation to radical treatment modality, in the field of immunotherapy.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

This work was supported by the grant (No. 0820010) for Cancer Control Program from the Korea Ministry of Health & Welfare to In Ah Kim.

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