Integrating immunotherapy into chemoradiation regimens for medically inoperable locally advanced non-small cell lung cancer

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Abstract: For patients with inoperable stage II–III non-small cell lung cancer (NSCLC), the backbone of curative intent therapy is concurrent chemoradiotherapy (CRT). As checkpoint inhibitors have shown clinical benefit in the setting of metastatic NSCLC, additional study is necessary to understand their role in patients receiving CRT. When integrating immunotherapy with radiotherapy (RT) for cure, clinicians will need to consider synergy, timing, doses, and safety among the combination of therapies. This article seeks to review data evaluating interactions, temporal sequencing, fractionation, and overlapping toxicity profiles of thoracic chemoradiation and immunotherapy.

Keywords: Immunotherapy; chemoradiation; non-small cell lung cancer (NSCLC); PD-1; PD-L1

Introduction

For patients with inoperable stage II–III non-small cell lung cancer (NSCLC), the backbone of curative intent therapy is concurrent chemoradiotherapy (CRT). The supportive evidence for the use of combined CRT is rooted in several decades of methodical clinical studies that established the superiority of concurrent CRT compared to either modality alone or sequential delivery of chemotherapy followed by radiotherapy (RT) (1-5). The customary platform for localized and inoperable NSCLC consists of concurrent chemoradiation with a platinum-based doublet and 60 Gy of RT delivered daily over 6 weeks followed by consideration of two cycles of consolidative chemotherapy, particularly for carboplatin and paclitaxel regimens (6,7). Although consolidative chemotherapy was not found to demonstrate an obvious survival benefit for inoperable, locally advanced NSCLC (8,9), its incorporation into RTOG 0617 has led to its acceptance as the de facto standard of care (7). Despite

its acceptance as a curative intent treatment, concurrent CRT results in relatively meager treatment outcomes with median survival rates of 20–28 months and 5-year overall survival (OS) rates of 15–20%.

The advent of novel immunotherapy agents affords patients and clinicians therapeutic modalities to improve patient longevity and avenues to study innovative combinations of therapies (10-13). Incorporation of immunotherapy with standard therapy provides the potential to build upon the gains of the well-established regimen of CRT for inoperable NSCLC. Since checkpoint inhibitors have shown clinical benefit in the setting of metastatic NSCLC, additional study will be necessary to understand their role in combined modality CRT. When integrating immunotherapy with RT for cure, clinicians will need to consider synergy, timing, doses, and safety among the combined therapies. This article seeks to review data evaluating interactions, temporal sequencing, fractionation, and overlapping toxicity profiles of CRT and

immunotherapy.

Immune modulation in the setting of RT

Local ionizing radiation can interact with the host's immune system by increasing the tumor antigen specific effector cells that traffic to a tumor. In a study comparing xenografts with B16-F0 tumors, irradiated mice (treated with 15 Gy) had greater ability to present tumor antigens and specific T-cells and tumor infiltrating lymphocytes than non-irradiated mice (14). In melanoma murine models, tumor control increased with the size of the RT dose as did tumor-reactive T cells, but a dose of 7.5 Gy per fraction proved to be the regimen with the optimal tumor control and tumor immunity with the lowest number of T-regulatory cells (T-regs) (15).

RT modulates the immune system and can help to mount an immune response that can result in immunogenic cell death. Radiation releases tumor antigens and facilitates tumor antigen release by dendritic cells (DC) and cross-complementation on major histocompatibility complex-1 (MHC-1) (16). RT potentiates calretinin's exposure on the cell surface and release of ATP and high mobility group box 1 (HMGB1), which seems to be required for DC activation and immune priming against malignant cells (17). Therefore, RT also acts as an in-situ tumor vaccine and may immunize the patient against their neoplasm and can provide immunologic memory which may endure for the host's lifetime (18,19).

RT also provides a pro-immunogenic effect on the tumor microenvironment (18). RT elicits activation of both innate and adaptive immunity (20), and these immune responses are potentiated by the cellular damage caused by RT and the cascade of interleukin-1β (IL-1β), tumor necrosis-factor-α (TNF-α), and chemokine (C-C-C motif) ligand 16 (CXCL16), MHC molecules, adhesion molecules and death receptors (21). RT also can reprogram macrophage differentiation to an iNOS+/M1 phenotype that orchestrates effective T cell immunotherapy (18,22).

The interaction of RT and checkpoint inhibitors or other immunotherapies may lead to an abscopal effect whereby after the administration of RT to one location, a non-responding systemic tumor then displays diffuse systemic response at distant sites from the site of irradiation. This concept has gained much attention in the setting of metastatic melanoma patient who had been maintained on ipilimumab with relatively stable disease subsequently received stereotactic body RT to an enlarging paraspinal

mass and was found to have response at their other sites of distant metastases. The authors suggested that the tumor was resistant to T cell mediated antitumor effects until the delivery of RT (23). T cells are thought to be a driver for the abscopal effect, which may require Flt-3 ligand as mice bearing tumor in both flanks responded in both flanks despite irradiation of only one flank when Flt-3 was available (24). This abscopal effect has been demonstrated on multiple occasions but is thought to be relatively infrequent, and no reliable method has been discovered to reproducibly harness these potent series of events clinically.

PD-1 and its interaction with RT

Programmed cell death-1 is an immune checkpoint inhibitory receptor and facilitates immune escape (25). PD-1 primarily curbs the activity of T cells in the periphery during chronic inflammation, infection or cancer and limits autoimmunity. When PD-1 interacts with its ligand PD-L1, it can inhibit T cell growth, survival, and effector function, such as cytokine release and cytotoxicity (26), and leads to tumor specific T cell apoptosis (27), stimulates the differentiation of CD4+ T cells into T-regs (28) and allows for the resistance of tumor cells to cytotoxic T cell (CTL) attack (29).

Inhibition of PD-1, and likely PD-L1, improves tumor rejection. Polyclonal antibody against PD-L1 can promote tumor rejection in models (29). Since PD-1 is expressed directly on tumor surfaces, this is an attractive target for immune-mediated responses. PD-1 blockade can allow for tumor rejection and immune-mediated signaling to allow the immune system to attack the tumor. PD-1 expression is generally increased in tumors with a higher non-synonymous mutational burden in tumors and is associated with improved responses and durable clinical benefit with longer progression-free survival in NSCLC (30). Given the high mutational burden that is often seen in smokers who develop NSCLC, PD-1/PD-L1 inhibition appears to be a logical combination.

Blockade of PD-L1 improves T cell responses leading to tumor rejection (31). PD-L1 can be upregulated in the tumor microenvironment after RT in murine models. The addition of anti-PD-L1 therapy can improve the efficacy of RT through a CTL-dependent mechanism. This combination also reduced tumor-infiltrating myeloid-derived suppressor cells that contribute to altering the tumor microenvironment (32).

Importantly, the interaction of stereotactic RT can

Table 1 Trials of PD-1 or PD-L1 agents combined with chemoradiation for NSCLC

Clinical trial title (phase of trial)	NCT identification (number/institution/status)
Pembrolizumab, Paclitaxel, Carboplatin, and Radiation Therapy in Treating Patients With Stage II-IIIB Non-Small Cell Lung Cancer (I)	NCT02621398/Rutgers Cancer Institute of New Jersey, University of Pennsylvania, Yale/recruiting
Consolidation Pembrolizumab Following Chemoradiation in Patients With Inoperable/ Unresectable Stage III NSCLC (II)	NCT02343952/Hoosier Oncology Group/active, not recruiting
A Global Study to Assess the Effects of MEDI4736 Following Concurrent Chemoradiation in Patients With Stage III Unresectable Non-Small Cell Lung Cancer (PACIFIC) (III)	NCT02125461/AstraZeneca/active, not recruiting
Nivolumab COnsolidation with Standard First-line Chemotherapy and Radiotherapy in Locally Advanced Stage IIIA/B Non-Small Cell Lung Carcinoma (NICOLAS) (II)	NCT02434081/European Thoracic Oncology Platform/recruiting
Cisplatin and Etoposide Plus Radiation Followed by Nivolumab/Placebo for Locally Advanced NSCLC (III)	NCT02768558/RTOG Foundation, Inc./recruiting
MPDL3280A with Chemoradiation for Lung Cancer (II)	NCT02525757/MD Anderson Cancer Center/ recruiting

Ongoing trials incorporating immunotherapy with definitive chemoradiation for inoperable NSCLC.

augment antigen-specific PD-1 mediated antitumor responses by inducing a more robust immune response and cross-presentation of tumor antigen, which was studied in melanoma and breast cancer models (33). In those models, RT resulted in the development of antigen-specific T cell and B cell-mediated immune responses. These immune stimulating effects of RT were increased when RT was combined with anti-PD-1 therapy or regulatory T cell depletion and resulted in improved local control of the tumor.

As discussed in other articles in this series, anti-PD-1 and anti-PD-L1 therapies have shown clinical activity for NSCLC alone and in combination with chemotherapy. Since the clinical effect of anti-PD-1/anti-PD-L1 therapies is evident without the incorporation of RT, it is plausible that the incorporation of RT may provide combinatorial, abscopal or synergistic effects.

Timing, dose, fractionation of immunotherapy with chemoradiation

To date, clinicians have related many of the abscopal responses to hypofractionated irradiation regimens, often with stereotactic body radiotherapy (SBRT), also termed stereotactic ablative radiotherapy (SABR). Dewan et al. evaluated three RT fractionation schemes: 20 Gy × 1, 8 Gy × 3 or 6 Gy × 5 with or without CTLA blockade. CTLA blockade alone was ineffective, but when combined with any of the RT regimens, growth delay was seen. Abscopal effects were evident with the combination of the fractionated RT

designs (34). Clinically, abscopal effects have been seen with 8 Gy × 3, 6 Gy × 5, and 9.5 Gy × 3 fractions (23,35,36). The greatest difference occurred for patients with 8 Gy × 3, and 80% of tumors outside the field regressed (16). Lower RT doses may cause reprogramming of macrophages toward an iNOS+/M1 phenotype, enabling them the ability to allow tumor rejection (37).

Also, concurrent platinum and RT cause calretinin translocation from dying tumor cells at dosages tested in a dose-dependent manner. Calretinin translocation increased due to platinum but remained stable after adding RT. Nevertheless, platinum and RT cause release of HMGB1 from dying tumor cells. When RT was combined with paclitaxel, adding RT caused immunogenic cell death (18).

A study by Gulley *et al.*, demonstrated the possible efficacy of standard radiation fractionation of 1.8–2 Gy per day in combination with a poxviral vaccine. T cell responses were seen in the tumor antigens and not in the vaccine, suggesting irradiation promoted the activation of T cells (16,38). Therefore, the combination of standard fractionation CRT and immunotherapy may be effective when they are used together.

Ongoing trials will help to elucidate the role and timing of PD-L1 or PD-1 blockade for inoperable NSCLC treated with definitive chemoradiation (*Table 1*).

Additional immunotherapy combinations

For locally advanced NSCLC, other agents have been

investigated, including tecemotide (L-BLP25), a mucin 1 (MUC1) specific agent that induced T cell responses to MUC1. The phase III START trial was a double-blind phase III trial that randomly assigned 1,006 subjects to tecemotide and 507 to placebo. Median overall survival (OS) was 25.6 months with tecemotide *vs.* 22.3 months with placebo (HR 0.88, 95% CI: 0.75–1.03, P=0.123). In patients who received prior concurrent CRT, median OS for those who received tecemotide was 30.8 months compared to 20.6 months for the control group (HR 0.78, P=0.016), whereas patients who received sequential CRT did not benefit in terms of OS (39,40). In the group of patients who received prior CRT, high soluble MUC1 and antinuclear antibodies correlated with tecemotide benefit (41). However, in a subsequent study by Katakami *et al.*, which randomized Japanese patients (n=172) with stable or clinical responses after CRT to receive adjuvant tecemotide vs. placebo, no apparent trend toward increased OS or other secondary endpoint with tecemotide was observed (42).

Additionally, study of GV1001, a telomerase peptide vaccine, was administered after CRT in a phase I/II trial of 23 patients. A GV1001-specific immune response developed in 16/20 evaluable patients and long-term immunomonitoring showed persisting responses in 13 patients. Immune responders demonstrated a median progression-free survival of 19 months compared to 3.5 months for nonresponders (P<0.001). Responders all harbored durable GV1001-specific T-cell memory responses with high IFNγ, and low IL-4 and IL-10 levels (43,44).

Toxicities of immunotherapy overlap with RT side effects

Administration of thoracic RT places patients at higher risk of radiation-induced pneumonitis, and the clinical presentation is similar to immunotherapy-induced pneumonitis with dry cough, fever, dyspnea, and tachycardia. Urgent initiation of steroid therapy is often required. A study evaluating 915 patients who were treated with PD-1/PD-L1 antibody demonstrated that 43 patients developed pneumonitis (about 5% of patients). Pneumonitis was more likely to occur when anti-PD-1/anti-PD-L1 and another simultaneous immunotherapy were administered, such as concurrent CTLA-4 therapies. Pneumonitis is a toxicity of variable onset clinically, and in the aforementioned study, it ranged from 9 days to 19.2 months (45). Concern for a pneumonitis requires urgent evaluation with imaging and often rapid

initiation of steroids to avoid severe and potentially life-threatening respiratory compromise.

Another complication that can occur with both RT and immunotherapy is myocarditis. Unlike pericarditis that can occur in the acute or subacute setting, radiotherapeutic injury to the myocardium is thought to be a delayed effect with long-term toxicities such as coronary artery disease and valvular injury. In contrast, fulminant cases of myocarditis from immunotherapy have been described, particularly with the combination of nivolumab and ipilimumab. The incidence of fatal myocarditis with nivolumab alone is <0.01% and with dual nivolumab and ipilimumab is 0.17%. The incidence of any myocarditis with single-agent nivolumab is 0.06% compared to 0.27% with dual agent therapy. In post-mortem examination of the cardiac tissue of immune checkpoint mediated myocarditis, increased expression of PD-L1 was found in the injured myocardium of patients, consistent with the upregulation of myocardial PD-L1 studies in mice. Investigators have hypothesized that PD-L1 upregulation in the myocardium is a cytokine-induced cardioprotective mechanism that is abrogated by immune checkpoint blockade (46).

Therefore, combinatorial therapy of CRT and immunotherapy must be approached with caution and careful clinical evaluation in prospective clinical trials.

Acknowledgements

Footnote

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