Preface

Harnessing the potential synergy of combining radiation therapy and immunotherapy for thoracic malignancies

Thoracic malignancies are among the most lethal group of tumors. The most common thoracic malignancy, lung cancer, is histologically grouped as non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Nearly three-fifths of NSCLC patients and two-thirds of SCLC patients present with stage IV disease, and the median survival of both of these groups approximates one year (1,2). Malignant pleural mesothelioma is a malignancy of the mesothelial lining of the pleura and is associated with a median survival of 12–18 months (3,4). While thymic malignancies often present at an early stage, only approximately half of patients with stage III–IV thymoma will achieve a 5-year survival, and that percentage falls to approximately 30% for patients with stage III–IV thymic carcinoma (5,6).

Driven by the high propensity for distant metastatic spread of lung cancer despite standard cytotoxic chemotherapy, a common pattern of progression and the greatest driver of survival for patients with thoracic malignancies is extrathoracic metastases. With only a modest incremental survival benefit achieved with newer cytotoxic chemotherapy agents or chemotherapy combinations, there has been great interest over the past decade to identify more effective systemic agents.

With increasing recognition that the immune system plays a critical role in cancer surveillance and tumor rejection (7), interest in immunotherapy for thoracic malignancies has flourished. Gene therapy and vaccine therapy have been trialed across thoracic malignancies with limited success. Interest in immunotherapy has more recently heightened with the success of checkpoint inhibitors across numerous malignancies. The earliest successes of immune checkpoint inhibitors were demonstrated for melanoma, where evidence emerged demonstrated a survival benefit of immune checkpoint blockade targeting CTLA-4 (8) and then later programmed cell death protein 1 (PD-1) (9). Immune checkpoint inhibitors shortly thereafter were shown to be efficacious for thoracic malignancies, with those with a high neoantigen burden showing the greatest benefit.

A human IgG anti-PD-1 monoclonal antibody was approved by the United States Food and Drug Administration in 2015 for patients with locally advanced or metastatic NSCLC that have progressed on chemotherapy (10,11). More recently, immune checkpoint inhibitors have emerged as a standard first line option for patients with newly diagnosed, untreated NSCLC with metastatic PD-L1 positive disease (12). Based on this success in metastatic patients, immunotherapy is beginning to be incorporated into curative treatment regimens for non-metastatic NSCLC (13). Early reports suggesting a potential for improved clinical outcomes with immune checkpoint inhibitors are beginning to emerge for other thoracic malignancies, including SCLC (14), malignant pleural mesothelioma (15), and thymic malignancies (16).

Advances in thoracic radiotherapy, including stereotactic body radiation therapy (17), intensity-modulated radiation therapy (18), proton therapy (19,20), and image-guided photon (21) and proton (22) radiation therapy, have also shown the potential to improve treatment delivery, reduce toxicities, and even improve outcomes for patients with thoracic malignancies. These advances may allow for safer implementation of multi-modality therapy (23) and offer new potential to combine radiation therapy with immunotherapy. While immunotherapy in the non-metastatic setting is being tested to determine if the addition of immunotherapy to radiation therapy can improve clinical outcomes (24), and while the addition of radiation therapy to systemic therapy in the oligometastatic or oligoprogressive setting has been shown to improve clinical outcomes (25), very little data to date exist combining these two modalities. As such, the safety and efficacy of combining immunotherapy and radiation therapy currently are not well defined.

Radiation therapy, however, may itself be immunomodulatory. Radiotherapy can upregulate tumor-infiltrating lymphocytes, activate CD8 T-cells, and enhance MHC class I expression to allow the immune system to react to tumor neoantigens (26,27). Radiation therapy can also generate a stimulatory signal to the immune system from its localized anti-tumor effects that can, in select cases, lead to out-of-field tumor responses, termed an "abscopal" effect (28). Such abscopal effects may be achieved from radiotherapy with or without immunotherapy. The combination of radiation therapy and immunotherapy may allow for a synergistic therapeutic response (29) since irradiation can increase tumor antigen production and presentation, upregulate cytotoxic T-lymphocyte activity, and downregulate myeloid-derived suppressor cells (30,31).

This focused issue of *Translational Lung Cancer Research* details the current pre-clinical and clinical evidence supporting the use of immunotherapy for the treatment of thoracic malignancies, including for NSCLC, SCLC, thymic malignancies, and malignant pleural mesothelioma, as well as for unique disease considerations such as oligometastases, recurrent tumors being treated with reirradiation, and patients receiving palliative radiotherapy. Advances in thoracic radiation therapy are described, and the rationale for combining radiation therapy with immunotherapy is highlighted, including a discussion of the potential synergistic response that can be achieved when combining these modalities and how this treatment combination could potentiate the antitumor effects of the systemic immune response to treatment. Radiotherapy dose, fractionation, timing relative to immunotherapy and modality sequencing, and toxicity consideration are discussed in detail. Ultimately, much work is still needed to optimize the combination of radiotherapy and immunotherapy across thoracic malignancies, but readers of this focused issue will readily be able to appreciate why there is a state of great excitement for immunotherapy in thoracic malignancies and understand how the addition of radiation therapy may facilitate the next level of success of these increasingly important systemic therapies.

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