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Research Letter

Safety of combining thoracic radiation therapy with concurrent versus sequential immune checkpoint inhibition

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Abstract

Purpose: The objective of this study was to evaluate adverse events (AEs) in patients who received both immune checkpoint inhibitors and thoracic radiation therapy (RT). In particular, we compared the rate of toxicities of concurrent versus sequential delivery of thoracic RT and checkpoint inhibitors.

Methods and Materials: Patient and treatment characteristics were collected on all patients at our institution who were treated with programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and/or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors and underwent thoracic RT (n = 79). Receiving both treatments within 1 month was considered concurrent (n = 35; 44%), and any treatment up to 6 months apart was considered sequential (n = 44; 56%). The primary endpoint of this study was the rate of Grade ≥2 AEs from combination therapy (immunotherapy and RT), specifically those that are relevant to thoracic RT: Pneumonitis, other pulmonary events, esophagitis, dermatitis, and fatigue. Further univariate analysis was performed to compare AE rates with clinical and therapy-related variables.

Results: A total of 79 patients were identified, with lung cancer (n = 45) and melanoma (n = 15) being the most common primary histology. Sixty-two (78%) patients were treated with anti-PD-1 or anti-PD-L1 antibodies, 12 (15%) with anti-CTLA-4 antibodies, and 5 (6%) received both anti-PD-1/PD-L1 and anti-CTLA-4 antibodies. The median follow-up for survivors was 5.9 months (range,

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2.4-55.6 months). Grade ≥2 AEs included pneumonitis (n = 5; 6%), esophagitis (n = 6; 8%), and dermatitis (n = 8; 10%). No statistically significant correlation was found between these AEs when comparing concurrent versus sequential treatment. The only significant variable was a correlation of immunotherapy drug category with Grade ≥2 esophagitis ($P = .04$).

Conclusions: Overall, Grade ≥2 AE rates of thoracic RT and immunotherapy appeared as expected and acceptable. The lack of significant differences in AE rates with concurrent versus sequential treatment suggests that even concurrent immunotherapy and thoracic RT may be safe.

Introduction

Immunotherapeutic approaches have shown tremendous efficacy across many solid and hematologic tumor types. In the treatment of non-small cell lung cancer (NSCLC), anti-programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) agents are now approved by the U.S. Food and Drug Administration in the first- and second-line settings. In both responders and nonresponders, there is often still an indication for thoracic radiation therapy (RT), frequently delivered for palliative purposes. However, the interaction of immunotherapy with RT in terms of radiation-induced or immune-related adverse events (AEs) is unknown.[1] Of particular concern is the potential increased risk of pneumonitis with combined immunotherapy and thoracic RT.

Promising results from case reports and preclinical studies have led to a large number of clinical trials investigating the combination of immunotherapy and thoracic RT.[2,3] This includes 2 randomized, double-blind, phase 3 studies (ClinicalTrials.gov: NCT02125461 [PACIFIC] and NCT02768558) comparing adjuvant PD-1/PD-L1 inhibitors with placebo for patients with stage III NSCLC after concurrent platinum-based chemoradiation. The recently published PACIFIC trial demonstrated significantly longer progression-free survival with adjuvant durvalumab versus placebo and showed that AEs were overall manageable.[4] Low incidences of relevant high-grade AEs such as Grades 3 to 4 pneumonitis (3.4% vs 2.6% in the durvalumab and placebo groups, respectively) were reported and strongly indicate that the combination of definitive chemoradiation and adjuvant durvalumab delivered in a sequential setting is safe.

There are currently more than 30 studies registered on ClinicalTrials.gov that combine immunotherapy and RT for lung cancer. Although these studies will eventually provide prospectively collected data on the safety and efficacy of this approach, we currently have little data to guide us regarding the safety of combination treatment, especially in the concurrent setting.

In this study, we therefore analyzed the overall intrathoracic AE profile of combined thoracic RT and immunotherapy. We sought to elucidate whether patients who received concurrent therapy were at increased risk for pneumonitis, esophagitis, or dermatitis compared with patients receiving both treatments sequentially.

Methods and materials

Patients

In our institutional database, we identified 79 patients who received thoracic RT and immunotherapy for primary lung cancer or lung metastases between 2006 and 2015. Patient, treatment, and toxicity data were collected by review of the electronic medical records under a retrospective institutional review board waiver. Immunotherapy consisted of drugs from one of the following categories: 1) anti-PD-1 antibodies, 2) anti-PD-L1 antibodies, 3) anti-CTLA-4 antibodies, or 4) a combination of anti-PD-1/PD-L1 and anti-CTLA-4 antibodies. A total of 44 patients (56%) received the drugs as part of a prospective clinical trial and 35 patients (44%) received treatment off trial.

RT was delivered as palliative RT, stereotactic body RT, or conventionally fractionated RT. If thoracic RT and immunotherapy began within one month of each other, this was considered concurrent therapy; that within >1 month and <6 months was sequential therapy. For an additional analysis, concurrent therapy was further divided into concurrent (at the same time) and closely timed (within 1 month). Patients were followed by medical and radiation oncologists.

The primary endpoint of this study was the AE rate from combination therapy including pneumonitis, other pulmonary events, esophagitis, dermatitis, and fatigue. Only AEs that began after the initiation of the second therapy (whether immunotherapy or RT) were counted toward the primary endpoint. AEs were graded in accordance with the Common Terminology Criteria for Adverse Events version 4.03.

Data on AE attribution to RT and immunotherapy for grade >/= 2 pneumonitis, esophagitis, and dermatitis were collected from patients' study records for patients who were followed on clinical trial protocols. For patients who were treated outside of the clinical trials, we retrospectively assessed the AE attribution. We took timing after treatment, extent of toxicity in relation to RT treatment fields, and severity in relation to RT doses into account. Standard