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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 attribution categorization for RT and/or immunotherapy (ie, definitely, probably, possibly, unlikely, and unrelated) was used.

Statistics

Descriptive statistics were computed for patients and treatment characteristics as well as AE rates. Univariate analyses by Fisher's exact test and exact Wilcoxon rank-sum test were performed for categorical and continuous variables, respectively, to examine the association between pneumonitis, esophagitis, and dermatitis rates and different clinical and treatment-related variables.

Results

Patient characteristics

A total of 48 patients (61%) were male with a median age of 60 years (range, 21-93 years). Of these patients, 20 (25%) received concurrent and 15 received (19%) closely timed treatment (within 1 month). Immunotherapy was the first treatment for 43 patients (54%). Anti-PD-1 (61%) or anti-PD-L1 (18%) antibodies were most commonly used. The median thoracic RT dose was 3000 cGy (range, 1800-7400 cGy), with 46 patients (58%) receiving palliative RT. Half of the patients received RT to the right lung (n = 40; 51%), and the RT site was most commonly centrally located. The median follow-up of the whole patient cohort was 4.5 months (range, 0.2-55.6 months), and median follow-up for survivors was 5.9 months (range, 2.4-55.6 months). Additional patient characteristics are detailed in Table 1.

Adverse events

A total of 34 Grade ≥2 pulmonary AEs were reported (Table 2) including 5 patients (6%) with Grade ≥2 pneumonitis (4 Grade 2 and 1one Grade 4), pneumonia (n = 14; 18%), and upper respiratory infections (n = 5; 6%). Other common pulmonary AEs included dyspnea (n = 3), cough (n = 2), and pleural effusions (n = 3). Grade ≥2 esophagitis was seen in 6 patients (8%) (5 patients with Grade 2 and 1 patient with Grade 3). Other common Grade ≥2 AEs included dermatitis (n = 8; 10%) and fatigue (n = 13; 16%).

Table 1 Patient and treatment characteristics

Factor		No. (79)	%
Sex	Male	48	61
	Female	31	39
Median age, years (range)		60 (21-93)	
Cancer type	Lung cancer	45	57
	Melanoma	15	19
	Other	19	24
Treatment timing	Within 1 month (concurrent)	35	44
	1-6 months (sequential)	44	56
First treatment	Radiation therapy	36	46
	Immunotherapy	43	54
Immunotherapy category	Anti-PD-1	48	61
	Anti-PD-L1	14	18
	Anti-CTLA-4	12	15
	Anti-PD-1/PD-L1+anti-CTLA-4	5	6
Laterality irradiated lesion	Right lung	40	51
	Left lung	27	34
	Mediastinum	12	15
Site irradiated lesion	Mediastinum	32	41
	Hilum	19	24
	Upper lobe	14	18
	Lower lobe	14	18
Fractionation	Palliative	46	58
	Stereotactic body radiation therapy	18	23
	Other	15	19
Median radiation therapy dose, cGy (range)		3000 (1800-7400)	
Median follow-up time, months (range)		4.5 (0.2-55.6)	
Median follow-up time for survivors, months (range)		5.9 (2.4-55.6)	

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Table 2 Adverse events Grade ≥2 after thoracic radiation therapy and immunotherapy

Adverse events (Grade ≥2)		Grade 2 (n)	Grade 3 (n)	Grade 4 (n)	Grade 5 (n)	Grade ≥2 (n)	Grade ≥2 (%)
Pneumonitis		4	0	1	0	5	6.3
Esophagitis		5	1	0	0	6	7.6
Dermatitis		8	0	0	0	8	10.1
Other pulmonary	Pneumonia	6	7	1	0	14	17.7
	Upper respiratory infection	5	0	0	0	5	6.3
	Dyspnea	3	0	0	0	3	3.8
	Cough	1	1	0	0	2	2.5
	Pleural effusion	0	3	0	0	3	3.8
	Pulmonary embolism	0	1	0	0	1	1.3
	Bronchopulmonary aspergillosis	0	1	0	0	1	1.3
Fatigue		8	5	0	0	13	16.5

AE attributions to RT and immunotherapy for Grade ≥2 pneumonitis, esophagitis, and dermatitis are shown in Table 3. The majority of Grade ≥2 pneumonitis (4 of 5 cases) and esophagitis (5 of 6 cases) developed due to thoracic RT, whereas dermatitis (4 of 7 cases) was more likely caused by immunotherapy. The median time to diagnosis for pneumonitis was 119 days (range, 33-152 days) after the start of the second treatment, 14 days for esophagitis (range, 6-20 days), and 19 days for dermatitis (range, 1-177 days).

Univariate analysis

No statistically significant correlation was seen between treatment timing (concurrent vs sequential treatment) and Grade ≥2 pneumonitis, esophagitis, or dermatitis rates (Tables 4–6). When analyzed as concurrent versus closely timed (within 1 month) versus sequential treatment, no significant correlation with toxicities was identified either (data not shown). The only significant variable for any Grade ≥2 AE was the immunotherapy drug category, which correlated with the rate of Grade ≥2 esophagitis ($P = .04$; Table 5). Of the 6 patients with Grade ≥2 esophagitis, 3 (50% of cases) developed esophagitis after receiving anti-PD-L1 antibodies, 2 (33%) after anti-CTLA-4 antibodies, and 1 (17%) after anti-PD-1 antibodies. None of the patients who were treated with a combination of anti-PD-1/anti-PD-L1+anti-CTLA-4 antibodies developed esophagitis.

No significant association was found with sex, age, cancer type, first therapy (RT vs immunotherapy), RT laterality, RT technique, or median RT dose. Multivariate analysis was not possible given the absence of multiple significant variables on univariate analysis.

Table 3 Adverse event attributions to radiation therapy and immunotherapy

Patient no.	Adverse event Grade	Attribution to radiation therapy	Attribution to immunotherapy
Pneumonitis			
P1	2	probably	possibly
P2	2	probably	possibly
P3	2	probably	unlikely
P4	2	probably	unlikely
P5	4	unlikely	probably
Esophagitis			
E1	2	probably	possibly
E2	2	probably	unrelated
E3	2	probably	unlikely
E4	2	definitely	unrelated
E5	2	unknown	unknown
E6	3	definitely	possibly
Dermatitis			
D1	2	unrelated	unrelated
D2	2	unrelated	probably
D3	2	unrelated	probably
D4	2	unrelated	probably
D5	2	unrelated	probably
D6	2	unlikely	unlikely
D7	2	probably	unlikely
D8	2	probably	unlikely

Discussion

To our knowledge, this is the largest study to date to systematically compare AEs in a patient cohort specifically treated with immune checkpoint inhibitors and thoracic RT in a concurrent versus sequential fashion. Similar studies have been published for other disease sites and histologies (eg, investigating the safety of combining checkpoint inhibitors and [cranial] irradiation in patients with melanoma)[5-7] and showed that there were no increased AE rates after combination therapy compared with monotherapy. Due to the limited published clinical data on immunotherapy and thoracic RT-related toxicity available to date, the herein observed toxicity rates should be viewed in context with known toxicities of thoracic RT or immunotherapy alone.

Pneumonitis is seen in 1% to 8% of patients who were treated with checkpoint inhibitors alone in the absence of thoracic RT.[8,9] Pneumonitis rates after definitive concurrent chemoradiation typically range from 5% to 20%, but palliative RT doses and newer radiation techniques that more

Table 4 Univariate analysis of clinical and treatment characteristics and Grade ≥2 pneumonitis by Fisher's exact test or exact Wilcoxon rank-sum test

	Pneumonitis Grade ≥ 2				*P*-value
	No (n = 74)		Yes (n = 5)		
	n	%	n	%	
Sex					.07
Female	27	36.5	4	80.0	
Male	47	63.5	1	20.0	
Median age, years (range)	60 (21-93)		69 (47-75)		.28
Cancer type					1.00
Lung	42	56.8	3	60.0	
Melanoma	14	18.9	1	20.0	
Other	18	24.3	1	20.0	
Treatment timing					1.00
Concurrent	33	44.6	2	40.0	
Sequential	41	55.4	3	60.0	
First therapy					.37
Radiation therapy	35	47.3	1	20.0	
Immunotherapy	39	52.7	4	80.0	
Immunotherapy category					1.00
Anti-PD-1	45	60.8	3	60.0	
Anti-PD-L1	13	17.6	1	20.0	
Anti-CTLA-4	11	14.9	1	20.0	
Anti-PD-1/PD-L1+anti-CTLA-4	5	6.8	0	0	
Radiation therapy laterality					.45
Right lung	38	51.4	2	40.0	
Left lung	24	32.4	3	60.0	
Mediastinum	12	16.2	0	0	
Radiation therapy technique					.37
Palliative	44	59.5	2	40.0	
Stereotactic body radiation therapy	17	23.0	1	20.0	
Other	13	17.6	2	40.0	
Median radiation therapy dose, cGy (range)	3000 (1800-7400)		3000 (2400-6600)		.62

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

effectively spare healthy tissue are associated with lower incidences.[10,11] Because of its potential severity and common association with both therapies, the risk for overlapping toxicities, especially pneumonitis, is particularly relevant when combining the 2 treatment modalities. In a subanalysis of Keynote 001 (97 patients), patients with NSCLC who were treated with pembrolizumab developed pneumonitis at non-significantly higher rates if they had previously received thoracic RT compared with no prior RT (8% vs 1%; $P = .15$).[12] In our study, we observed 5 cases (6%) of symptomatic (Grade ≥2) pneumonitis. This rate is within the expected incidence range of either RT alone or immunotherapy alone. It thus appears reassuring that thoracic RT can be delivered safely in patients treated with immunotherapy, even when administered concurrently.

Esophagitis is typically the most significant acute toxicity of thoracic RT. The observed rate of Grade ≥2 esophagitis (8%) and the absence of any significant differences between concurrent and sequential treatments indicates that there is no strong additive esophagitis risk with combination therapy.[10] We found a significant association between Grade ≥2 esophagitis and the immunotherapy drug category, with anti-PD-L1 treatment resulting in the most esophagitis cases (n = 3; 50%), followed by anti-CTLA-4 (n = 2; 33%), and anti-PD-1 (n = 1; 17%). This result should be interpreted with caution given the small number of AE cases per category. Furthermore, the development of esophagitis is most likely more strongly linked to the esophageal dose from thoracic RT rather than the type of checkpoint inhibitor therapy (Table 3). To our knowledge, there is no other literature to date that shows a difference in esophagitis rates with various checkpoint inhibitors given the limited data available on combining immunotherapy and thoracic RT.

Grade ≥2 dermatitis was seen in 8 patients (10%). Dermatitis is a common toxicity of immunotherapy, with 30% to 60% of patients experiencing some form of skin or mucosal irritation.[1,13] This is also the case in 70% to 90% of patients who undergo radiation. However, no unusually high rates of Grades 2 to 3 and no Grades 4 to 5

Table 5 Univariate analysis of clinical and treatment characteristics and Grade ≥2 esophagitis by Fisher's exact test or exact Wilcoxon rank-sum test

	Esophagitis Grade ≥2				*P*-value
	No (n = 73)		Yes (n = 6)		
	n	%	n	%	
Sex					1.00
Female	29	39.7	2	33.3	
Male	44	60.3	4	66.7	
Median age, years (range)	61 (21,93)		57 (32,81)		.74
Cancer type					.07
Lung	44	60.3	1	16.7	
Melanoma	13	17.8	2	33.3	
Other	16	21.9	3	50.0	
Treatment timing					1.00
Concurrent	32	43.8	3	50.0	
Sequential	41	56.2	3	50.0	
First therapy					.21
Radiation therapy	35	47.9	1	16.7	
Immunotherapy	38	52.1	5	83.3	
Immunotherapy category					.04
Anti-PD-1	47	64.4	1	16.7	
Anti-PD-L1	11	15.1	3	50.0	
Anti-CTLA-4	10	13.7	2	33.3	
Anti-PD-1/PD-L1+anti-CTLA-4	5	6.8	0	0	
Radiation therapy laterality					1.00
Right lung	37	50.7	3	50.0	
Left lung	25	34.2	2	33.3	
Mediastinum	11	15.1	1	16.7	
Radiation therapy technique					.61
Palliative	42	57.5	4	66.7	
Stereotactic body radiation therapy	16	21.9	2	33.3	
Other	15	20.5	0	0	
Median radiation therapy dose, cGy (range)	3000 (1800-7400)		3375 (2700-4500)		.78

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

dermatitis were observed with combination immunotherapy and RT.

Treatment timing (concurrent/sequential) may have an impact on toxicity rates. Bang et al. reported a trend toward increased rates of immune-related AEs when immune checkpoint inhibitors were administered within 14 days of palliative RT to any site in patients with NSCLC, melanoma, or renal cell cancer.[14] However, only 34 patients were treated to the lungs. Pneumonitis was reported in 3 patients (9%) who received RT to the thoracic spine, chest wall, and lungs. Although this study included a relatively small number of thoracic RT sites, our findings in a larger patient population of 79 patients who were treated exclusively to intrathoracic sites confirm these findings of pneumonitis rates <10% with combination therapy.

In a retrospective study (presented in abstract form) of 29 patients who received thoracic RT and immune checkpoint inhibitors, 3 patients developed Grade ≥3 pneumonitis after RT. In all 3 cases, RT was received 1 to 2 months after immunotherapy.[15] Given the very limited number of patients and events it is difficult to conclude from this study whether the timing of RT and immune checkpoint inhibitors had a significant impact on the risk of developing pneumonitis.

Similarly, in a study of patients with metastatic lung cancer who received immune checkpoint inhibitors with or without thoracic RT, immune-related AE rates including pneumonitis were not higher when patients were treated with both therapies.[16] However, the interval between both therapies in that study covered a wide range between 0.1 and 69 months (median: 8.6 months) and did not examine whether there were differences in pneumonitis risk on the basis of the interval. In our study, we did not find statistically significant higher rates of pneumonitis, esophagitis, or dermatitis with concurrent or closely timed immunotherapy and thoracic RT. This may be partially due to the overall small number of AEs that were observed despite our larger patient population. However, it is reassuring that we did not observe any trends toward increased toxicity with concurrent treatment.

Table 6 Univariate analysis of clinical and treatment characteristics and Grade ≥2 dermatitis by Fisher's exact test or exact Wilcoxon rank-sum test

	Dermatitis Grade ≥2				*P*-value
	No (n = 71)		Yes (n = 8)		
	n	%	n	%	
Sex					.47
Female	29	40.8	2	25.0	
Male	42	59.2	6	75.0	
Median age, years (range)	60 (21-93)		66 (44-77)		.63
Cancer type					.12
Lung	40	56.3	5	62.5	
Melanoma	12	16.9	3	37.5	
Other	19	26.8	0	0	
Treatment timing					.46
Concurrent	30	42.3	5	62.5	
Sequential	41	57.7	3	37.5	
First therapy					.72
Radiation therapy	33	46.5	3	37.5	
Immunotherapy	38	53.5	5	62.5	
Immunotherapy category					.17
Anti-PD-1	45	63.4	3	37.5	
Anti-PD-L1	12	16.9	2	25.0	
Anti-CTLA-4	9	12.7	3	37.5	
Anti-PD-1/PD-L1+anti-CTLA-4	5	7.0	0	0	
Radiation therapy laterality					1.00
Right lung	36	50.7	4	50.0	
Left lung	24	33.8	3	37.5	
Mediastinum	11	15.5	1	12.5	
Radiation therapy technique					.58
Palliative	42	59.2	4	50.0	
Stereotactic body radiation therapy	15	21.1	3	37.5	
Other	14	19.7	1	12.5	
Median radiation therapy dose, cGy (range)	3000 (1800-7400)		3000 (2000-5000)		.43

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

The interpretation of our data is limited by the retrospective nature of this analysis, the heterogeneity with regard to tumor histology, thoracic RT field and doses, lines of prior systemic therapy, immunotherapy type, duration and interval to thoracic RT, and relatively short follow-up. However, this study is homogenous because we included only patients who received thoracic RT. The follow-up was relatively short because many patients were treated after multiple lines of prior therapy at advanced stages of their disease. However, the follow-up should be sufficient to capture acute toxicities from thoracic RT such as dermatitis and esophagitis, which occur during and within the first month after RT completion. This follow-up time should also capture the majority of radiation pneumonitis from thoracic RT, which occurs within the first 3 to 4 months after thoracic RT and thus is acceptable for the specific endpoints in this study.

Conclusions

This is a more focused analysis of intrathoracic toxicities of combination therapy than prior published series because we limited this study to thoracic RT only and the 3 most common types of immunotherapy. The low incidence of each AE limits the power of correlation with treatment. However, from a patient and practitioner perspective, these findings are encouraging in that no excess toxicities were observed that should prevent future studies from investigating the combination of thoracic RT with immunotherapy. Further studies are needed to assess the impact of treatment timing and sequence as well as the type of inhibitor and RT doses on toxicity rates.

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