Safety Analysis of Immunochemotherapy Combined With Consolidative Thoracic Radiotherapy for Extensive-stage Small Cell Lung Cancer

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Research Article

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Abstract

Background: It has been evaluated that thoracic radiation therapy (TRT) could improve the local control and give survival benefit for the patients with extensive-stage small cell lung cancer (ES-SCLC) in the era of chemotherapy. However, there was no data to indicate the safety especially the lung toxicity of TRT during the maintenance of programmed death ligand 1(PD-L1) inhibitors after four cycles of PD-L1 inhibitors with etoposide and platinum (EP). Hence, the retrospective study aimed to investigate the risk factors of radiation pneumonitis (RP) of TRT combined with PD-L1 inhibitors.

Methods: From January 2020 through March 2021, in Shandong Cancer Hospital and Institute, patients with ES-SCLC who received TRT during the maintenance of PD-L1 inhibitors after administrating PD-L1 inhibitors with EP were enrolled in the retrospective study. RP was investigated and evaluated according to the Common Terminology Criteria for Adverse Events version 5.0(CTCAE v5.0) criteria. We used univariate and multivariate logistic regression to analyze the potential risk factors of RP.

Results: During January 2020 to March 2021, 20 patients receiving TRT during the maintenance of PD-L1 inhibitors after administrating PD-L1 inhibitors with EP were enrolled in the retrospective study. The dose fractions were 1.5Gy bid or 1.8-3Gy qd and the total dose was 30Gy to 61.4Gy. As a result, 6 patients (30%) experienced grade 2 RP, and no ≥3 grade RP occurred. At the last time of follow-up, 17 patients suffered from disease progression, 13 of them suffered from distant progression and three suffered from local failure in radiation field and one suffered from distant progression and local failure in radiation field. The median progression-free time (PFS) was 9 months.

Conclusion: The retrospective analysis showed that the lung toxicity of TRT was tolerable during the maintenance of PD-L1 inhibitors after administrating PD-L1 inhibitors with EP.

Introduction

Small-cell lung cancer (SCLC) accounts for about 15% in all lung cancers(1). The typical characteristics of SCLC are the exceptionally high proliferation rate, strong inclination for early metastasis and poor prognosis. Two-thirds of patients with SCLC usually accompany with distant metastasis at the initial diagnosis and staged as extensive disease(2).

For over three decades, the standard care in the first-line treatment for newly diagnosed metastatic SCLC has composed of a platinum agent (cisplatin or carboplatin) combing with etoposide. Using this treatment mode, the median survival time (MST) is approximately 10 months(3). In recent years, several clinical trials evaluated the role of immune checkpoint inhibitors targeting programmed cell death ligand 1 (PD-L1) or programmed cell death 1 (PD-1). It is comforted that the PD-L1 inhibitors, durvalumab and atezolizumab, have prolonged overall survival and become the standard first-line therapy in ES-SCLC from the CASPIAN and IMpower133 trial. The MST was prolonged beyond 12.0 months(4, 5). Hence, PD-L1 inhibitors combined with EP has become the standard first-line treatment of patients with ES-SCLC.

Thoracic radiotherapy (TRT) has a well establishment in the treatment of limited-disease (LD) SCLC and it was demonstrated that ChT/TRT significantly reduced the risk of intrathoracic failure to 30–60%, and the absolute long-term survival rate was increased by 5.4%(6, 7). For patients with ES-SCLC, the role of TRT was also been affirmed in Jeremics' trial and CREST trial. And our retrospective study showed that MST was improved from 9.3 months to 17 months when TRT combined with ChT. And five patients (5/60, 8.4%) suffered from grade 2 pneumonitis, and one patient (1.7%) died of it(8).

In the era of immunotherapy, there was no idea whether TRT could play a positive role for patients with ES-SCLC or not. Therefore, we conducted this retrospective study to explore the efficacy and the safety, especially the lung toxicity.

Patients And Methods

Study Population and treatment

We retrospectively reviewed ES-SCLC patients from January 2020 to March 2021 at Shandong Cancer Hospital and Institute. Patients were diagnosed with ES-SCLC according to cytology or histology and the staging system of Veterans Administration Lung Study Group and were treated by PD-L1 inhibitors and ChT for at least 4 cycles, then TRT was added to patients with partial response (PR) or stable disease (SD) after administrating PD-L1 inhibitors with EP. We selected 20 patients meeting the above requirements, in which 17 patients (85%) were PR and 3 patients were SD before TRT.

Patients received four 21-day cycles of carboplatin (area under the curve of 5 mg per milliliter per minute, administered intravenously on day 1 of each cycle) or cisplatin (25–30 mg per square meter of body-surface area, administered intravenously on days 1–3 of each cycle) and etoposide (100 mg administered intravenously on days 1–5 of each cycle) with either atezolizumab (at a dose of 1200 mg, administered intravenously on the day before chT of each cycle) or durvalumab (at a dose of 1000 mg, administered intravenously on the day before chT of each cycle). Nine patients (45%) were administrated atezolizumab and 11 (55%) were administrated durvalumab. Nine patients received TRT after 4–6 cycles of PD-L1 inhibitors combined EP, 11 patients received TRT during the maintenance of PD-L1 inhibitors after PD-L1 inhibitors combined with EP. And 10 received PD-L1 inhibitors during TRT.

TRT was administered with an intensity-modulated radiotherapy (IMRT) technique for 20 patients with ES-SCLC. The gross target volume (GTV) was composed of primary tumor and (or) the positive lymph nodes with a short-axis dimension 1 cm on CT scans. We outlined GTV and the draining area of the positive lymph nodes to be clinical targeted volume (CTV), the planning target volume (PTV) included the CTV with a 0.5 cm margin. The dose fractions were 1.5Gy bid or 1.8-3Gy qd and the total dose was 30Gy to 61.4Gy. We extracted dosimetric parameters from the treatment planning system (Eclipse system, Varian Medical Systems, Version 13.5.35) and all dosimetric parameters were lower than the dose constraints of lung.

Endpoints

1) ≥ grade 2 radiation pneumonitis: The treatment-related pneumonitis was diagnosed according to clinical symptoms, physical examinations, and chest computed tomography (CT). Toxicity was evaluated in accordance with the Common Terminology Criteria for Adverse Events version 5.0. Grade 2 RP was defined as Symptomatic; medical intervention indicated; limiting instrumental ADL.

2) PFS: Progression free survival refers to the time between the beginning of enrollment and the observation of disease progression or death from any cause.

Statistical analysis

We used univariate and multivariate logistics regression analyses to identify the risk factors of grade 2 symptomatic pneumonitis. And PFS were calculated by using the Kaplan-Meier method.

Results

1.1 Patients and treatment characteristics

Twenty patients were enrolled from January 2020 through March 2021 at Shandong Cancer Hospital and Institute, who received immunochemotherapy combined with consolidative TRT with ES-SCLC. Baseline characteristics are summarized in Table 1. Among the 20 patients, 17 were men and 3 were women. The median age was 58.5 years (range,45-74 years), all patients had good performance status (KPS scores≥80). Most patients (70%) had a history of smoking. Ten patients (50%) had 1 metastatic site and 10 patients (50%) had 2 or more metastatic sites. The most common metastatic sites were brain and liver (brain metastasis, 9 patients; liver metastasis, 7 patients). All patients received PD-L1 inhibitors, 9(45%) patients received atezolizumab and 11(55%) received durvalumab. And all patients received at least 3 cycles PD-L1 inhibitors and 4-6 cycles chemotherapy (etoposide combined platinum) before TRT. The dose fractions were detailed as follows: two patients

with 1.5Gy bid, 3Gy qd in 7 patients, 1.8-2Gy qd in 7 patients, and 2.5Gy qd in other 4 patients. The total dose was 30Gy to 61.4Gy.

1.2 The incidence rate of pneumonitis and radiation dosimetric parameters

In the entire cohort of patients, 6 patients (30%) experienced grade 2 RP, 9 patients (45%) experienced grade 1 RP, the remaining 5 patients did not experience RP. The median time of grade 2 RP onset after completion of TRT was 2.85 months (range, 1.2 - 6.2 months). The radiation dosimetric parameters for all patients are listed in Table 2. The median radiation dosimetric parameters such as V5, V20, MLD of the 6 patients with grade 2 symptomatic pneumonitis were 42.8%, 23.2% and 113.6cGy respectively. Further analysis did not find significant risk factors of grade 2 symptomatic pneumonitis.

1.3 The PFS and failure patterns

The last time of following-up was January 2022 and the median follow-up time was 16.8 months. At the time of data cutoff, 17 patients had progressive disease and MST was 9 months of all patients. Among all 20 patients, 17 patients (85%) suffered from disease progression, 10 suffered from brain metastasis, liver metastasis occurred in five of them, in which one patient suffered from brain metastasis and liver metastasis. Four suffered from local failure in radiation field and in which one patient suffered from distant progression and local failure in radiation field. Local control rate in chest was 80% and the intrathoracic PFS was 8.85 months.

Discussion

To my knowledge, this was the first retrospective study to investigate the safety of consolidative TRT after PD-L1 inhibitors with platinum and etoposide treatment. We concluded that using consolidative TRT to manage the residual lesions in chest after administrating PD-L1 inhibitors with platinum and etoposide was safe and tolerable, which was supported by the fact that the incidence of grade 2 RP was 30% and no grade 3 RP occurred. We did not identify the risk factors of grade 2 RP by using univariate and multivariate logistics regression analyses.

It has been reported that the risk of ≥ grade 2 symptomatic pneumonitis ranges from 5–30% with TRT alone or combined with platinum-based chemotherapy(9–12). Checkpoint Inhibitors-related pneumonitis is lower than 5% in patients who received PD-(L)1 inhibitors alone, in which the occurrence rate of any grade pneumonitis of PD-L1 inhibitors is 1.3%(13–17).Theoretically, PD-L1 inhibitors combing with TRT will enhance the probability of pneumonitis because radiation can increase the infiltration of inflammatory cells and inflammatory factors inside the tumor of targeted area. A retrospective study reported that the incidence rate of any grade pneumonitis was 33.9% in patients with stage III non-small cell lung cancer who received PD-L1 inhibitors after administrating concurrent chemoradiotherapy, which was considered tolerable for patients(18). Compared with the previous studies, the dosimetric parameters of our patients were all within the safe range. We considered that receiving consolidative TRT to manage the residual lesions in chest after administrating PD-L1 inhibitors with platinum and etoposide was tolerable because grade 2 RP was 30% and no grade 3 RP occurred in our study.

But there was one retrospective study showing that the occurrence rate of pneumonitis was 48.96% in patients who received consolidative TRT after PD-(L)1 inhibitors with chemotherapy, which indicated that this treatment mode was harmful to patients(19). Compared this retrospective study with our study, we found that 10 (35.7%) patients had pulmonary emphysema, and a majority of patients received PD-1 inhibitors rather than PD-L1 inhibitors in this study. Previous studies showed the occurrence rate of pneumonitis after administrating PD-1 inhibitors was 3.6%, it was higher than after administrating PD-L1 inhibitors(20–22). The potential mechanism of the higher incidence of pneumonitis induced by PD-1 inhibitors are unclear, maybe the following can explain it. As we all know, tumor cells achieve immune escape by expressing

PD-L1 and PD-L2 receptors, the immune checkpoint inhibitors can enhance anti-tumor effect by activating immune cells, and prevent the immune escape. PD-1 inhibitors not only combine with PD-L1 receptors but also combine with PD-L2 receptors, PD-L1 inhibitors only combine with PD-L1 receptors, they do not influence the PD-L2 pathway, so, PD-L1 inhibitors retain the immunomodulatory function and lower the occurrence of autoimmune diseases. Thus, the occurrence rate of RP is lower in patients who received TRT and PD-L1 inhibitors than patients who received TRT and PD-1 inhibitors.

The mPFS was 9 months for all patients in our study (Fig. 1), and respectively were 5.2 months and 5.1 months, correspondingly, in Impower133 trial and Caspian trial(4, 5). Among all 20 patients, 17 patients (85%) suffered from disease progression, the most common failure lesions were brain(50%)and liver（25%）, only four patients suffered from local failure in radiation field. Local control rate in chest was 80%, the median intrathoracic PFS was 8.85 months. The rate of isolated intrathoracic progression was 15% in our study, compared with 19.8% in CREST trial. TRT could reduce the occurrence rate of intrathoracic progression. Maybe increasing the dose in chest can decrease the recurrence rate in chest. The recurrence rate in chest was 25.8% in RTOG0937 trial, it was lower than 62.5% in CREST trial. The difference between the two trials was the total dose in chest, the former was 45Gy/15f, the latter was 30Gy/10f(23, 24).Meanwhile, one study showed that a BED(biological effective dose) > 50 Gy was beneficial to overall survival, PFS, and intrathoracic PFS at 1 year(25). We divided the 20 patients into 2 groups according to BED ≥ 50 Gy or BED < 50 Gy. But there was no statistical difference between the two groups by statistical analyses, maybe there were limited samples in our study.

In NRG LU007 (NCT04402788, https://clinicaltrials.gov) trial patients who administrating 4–6 cycles platinum and etoposide with or without atezolizumab in first line treatment were divided to 2 groups according to receiving radiation therapy (including the lesion in chest) or not. The trial was a prospective study and played an important role in confirming the function of TRT after administrating PD-L1 inhibitors combine with chemotherapy.

This study has some limitations. On the one hand, this was a retrospective study in a single medical center, short follow-up time and only 20 patients, thus we did not find the risk factors of Grade 2 RP by performing statistical analysis. But there was only 6 patients (30%) experienced Grade 2 RP, no patients experienced grade 3 or higher pneumonitis, we concluded that it was safe by using consolidative TRT after PD-L1 inhibitors with platinum and etoposide. On the other hand, the follow-up time was short, so most of patients did not achieve an overall survival outcome, so we could not analyse the OS of the 20 patients. The mPFS was 9 months of the 20 patients in our study, which was higher than 5.2m and 5.1m of IMpower133 trial and CASPAIN trial respectively. From here we can see that administrating consolidative TRT after PD-L1 inhibitors with platinum and etoposide can improve PFS.

In conclusion, administrating consolidative TRT after PD-L1 inhibitors with platinum and etoposide was safe and tolerable. Thus, we encourage more prospective studies to implement to explore the efficacy and safety of this treatment mode.

Abbreviations

ES-SCLC, extensive-stage small cell lung cancer; ICIs, immune checkpoint inhibitors; ICI/ChT, Immune checkpoint inhibitor combined with chemotherapy; ChT, chemotherapy; TRT, thoracic radiation therapy; PD-1, programmed death 1; PD-L1, programmed death ligand 1; EP, etoposide and platinum; KPS, Karnofsky performance status; Gy/f, grays/fraction; PR, partial response; SD, stable disease; RP, radiation pneumonitis; MST, median survival time; MLD, mean lung dose; IMRT, intensity-modulated radiotherapy; CT, computed tomography; GTV, gross target volume; CTV, clinical targeted volume; PTV, planning target volume; PFS, progression free survival; BED, biological effective dose.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of Shandong Cancer Hospital and Institute and was performed in accordance with the Declaration of Helsinki.

Consent for publication

Agreed.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YL and HZ conceived and drafted the manuscript. YL, JC, XJ, and JL acquired the patient data. XJ, YZ and XT analyzed these patient data. HZ edited and corrected the manuscript. All authors read and approved the final manuscript.

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Tables

Table1: Patients and treatment characteristics

Characteristic	No. of Patients (%)
Sex	
Men	17（85）
Women	3（15）
Age, y	
Range	45-74
Median	58.5
<70	17（85）
≥70	3（15）
KPS score	
80	15（75）
90	5（ 25）
Smoking status	
Yes	14（70）
No	6（30）
No. of metastatic organs	
1	10（50）
≥2	10（50）
Brain metastasis	
Yes	9（45）
No	11（55）
Liver metastasis	
Yes	7（35）
No	13（65）
PD-L1 ICIs	
Atezolizumab	9(45)
Durvalumab	11(55)

Abbreviations: KPS, Karnofsky performance status; ICIs, immune checkpoint inhibitors.

Table 2: Radiation parameters

Patients	Response to ICI/ChT before TRT	No. of ICI cycles before TRT	Dose (Gy/f)	Grade of RP	V5 (%)	V20 (%)	MLD (cGy)	GTV (ml)	PTV (ml)	The time of RP after TRT (month)
1	PR	10	45/15	2	27.53	14.49	725.8	38.59	140.24	3.9
2	PR	6	30/10	2	21.14	6.07	408	11.7	123.54	1.2
3	PR	6	54/27	2	22.43	9.11	513.9	30.95	138.57	3.6
4	PR	6	45/15	2	40.95	11.56	717.5	95.52	308.61	1.9
5	PR	9	50/20	2	22.39	11.07	576.5	22.33	114.82	6.2
6	PR	7	50/25	2	42.84	23.18	1113.6	188.42	457.31	2.1
7	PR	5	45/15	1	35.86	19.98	926.5	44.05	267.87	4.33
8	PR	4	54/30	1	39.85	19.77	1067.8	50.27	382.48	4.03
9	PR	4	50/20	1	9.15	4.36	263	5.29	31.84	4.83
10	PR	5	50/20	1	10.87	1.96	213.1	4.25	36.56	7.93
11	PR	6	46/23	1	26.92	6.56	508.9	14.8	68.53	3.27
12	SD	6	45/15	1	50.56	14.51	979.0	69.3	294.92	2.00
13	PR	5	56/28	1	30.48	16.42	890.5	163.34	347.98	2.63
14	SD	6	50/25	1	24.83	12.17	712.9	106.99	252.19	4.13
15	PR	4	45/15	1	46.74	21.24	1141.1	42.62	370.28	4.33
16	PR	7	39/26	0	28.88	12.81	630.8	47.49	298.09	
17	PR	6	30/10	0	28.35	4.74	473.6	18.61	116.28	
18	SD	3	45/30	0	37.60	10.71	659.1	100.08	377.28	
19	PR	5	1.8*23+2.0*10	0	46.3	16.96	1025.2	24.63	240.25	
20	PR	7	46.8/26	0	46.54	18.78	1003.9	339.57	576.29	

Abbreviations: TRT, thoracic radiation therapy; ChT, chemotherapy; ICI, Immune checkpoint inhibitor; ICI/ChT, Immune checkpoint inhibitor combined with chemotherapy; KPS, Karnofsky performance status; Gy/f, grays/fraction; PR, partial response; SD, stable disease; RP, radiation pneumonitis; MLD, mean lung dose

Figures

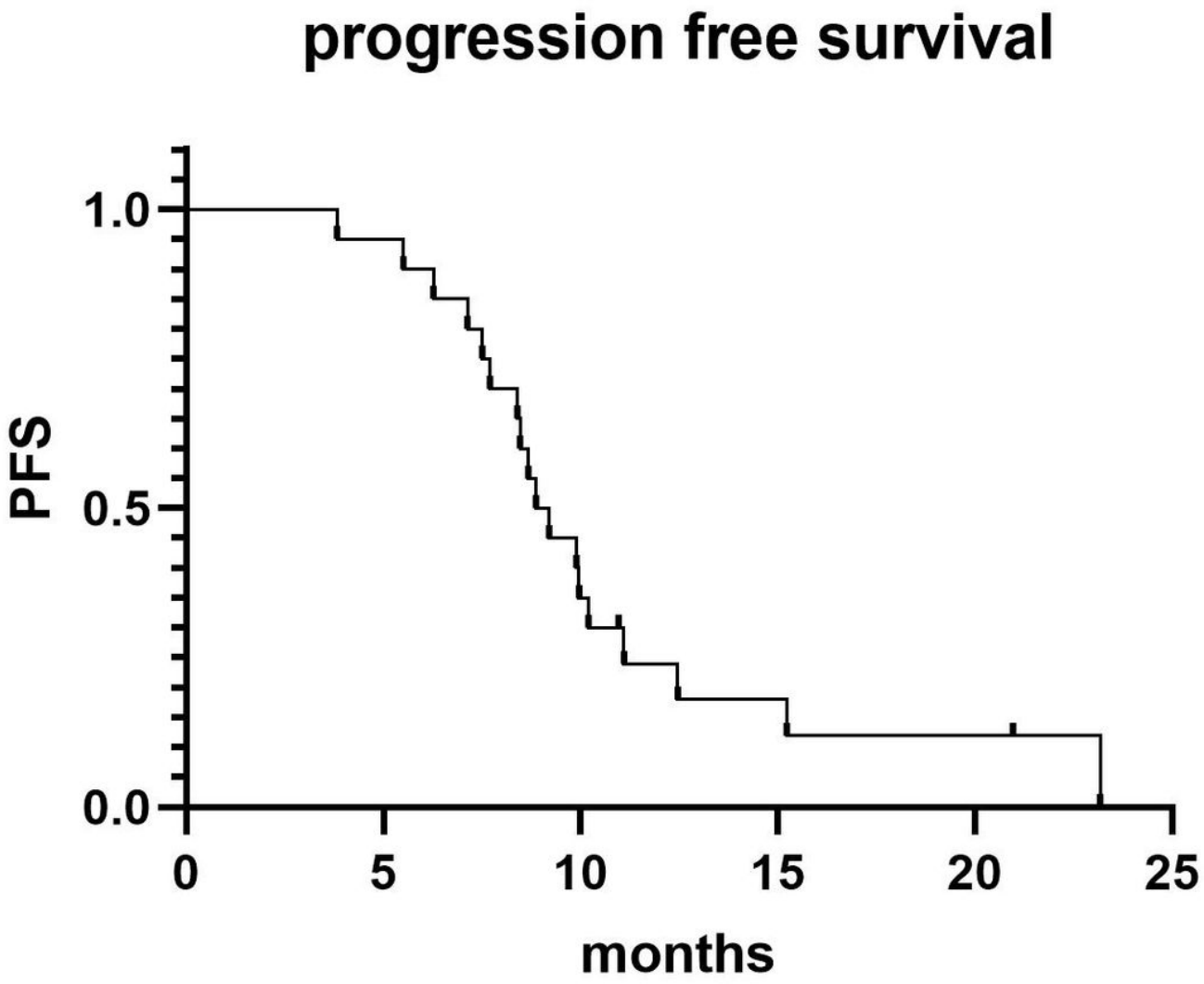

Figure 1

Legend not included with this version.