Thoracic Cancer

Open Access

Thoracic Cancer ISSN 1759-7706

CASE REPORT

Anti-PD-1 therapy plus chemotherapy showed superior and durable survival benefit in a patient with small cell esophageal cancer: A case report

Wei Ren[1†], Puyuan Wu[1†], Jing Tian[2], Dongsheng Chen[2], Si Li[2] & Baorui Liu[1]

1 The Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China

2 The State Key Laboratory of Translational Medicine and Innovative Drug Development, Jiangsu Simcere Diagnostics Co., Ltd, Nanjing, China

Keywords
Chemotherapy; immunotherapy; small cell esophageal cancer.

Correspondence
Baorui Liu, The Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, 210008, China.
Tel: +86 139 1598 1834
Fax: +86 25 8310 6666
Email: baoruiliu@nju.edu.cn

†These authors contributed equally to this work.

Received: 18 September 2020;
Accepted: 20 October 2020.

doi: 10.1111/1759-7714.13735

Thoracic Cancer **12** (2021) 264–267

Abstract

The prognosis of the small cell esophageal cancer (SCEC) patient in our study was poor due to lack of treatment options which were limited to surgery and chemotherapies, with a median overall survival (OS) of only 11.1 months according to previous studies. Herein, we adopted the regimen of immunotherapy plus chemotherapy, which exerted superior and durable benefit (OS > 19 months) in the patient in our study. Immunotherapy plus chemotherapy might therefore be a reasonable option for selected SCEC patients. In addition, well-designed trials for better evidence are required to verify the findings in this study.

Introduction

Small cell esophageal cancer (SCEC) is a rare clinical disease, accounting for 0.05%–4% of all esophageal malignancies.[1] The five-year survival rate is poor due to the lack of treatment options which are limited to surgical resection and chemotherapy.[2] New therapies are urgently needed. Herein, we report a patient with SCEC who achieved a remarkable benefit from immunotherapy plus chemotherapy.

Case report

A 73-year-old male was admitted to the hospital in February 2019 with a history of a recurrent headache and retrosternal pain. Gastroscopy showed erosion and bulging of the esophageal mucosa, and pathological findings from biopsy specimens confirmed a diagnosis of small cell carcinoma. Immunohistochemical (IHC) staining showed CK (+), CgA (−), Syn (+), CD56 (+), P40 (−), CD20 (−), CD3 (−), Ki67 (80%+). Computed tomography (CT) scan revealed metastases in the liver, lung, and multiple lymph nodes. The disease was diagnosed as extensive-stage small cell carcinoma of the esophagus and cardia.

Biopsy samples were subjected to whole-exome sequencing and IHC analysis. MDM2 amplification and positive PD-L1 expression (1.83%) were revealed and tumor mutation burden was 2.99 Muts/Mb. Subsequently, six cycles of toripalimab (a PD-1 monoclonal antibody) (day 5, 240 mg) plus etoposide (day 1–5, 100 mg)/carboplatin (day 1, 450 mg) were administered from February to July 2019. Enhanced CT revealed no obvious enhancement of liver metastases, and the lymph nodes in mediastinal 4R area and lung metastases had completely disappeared.

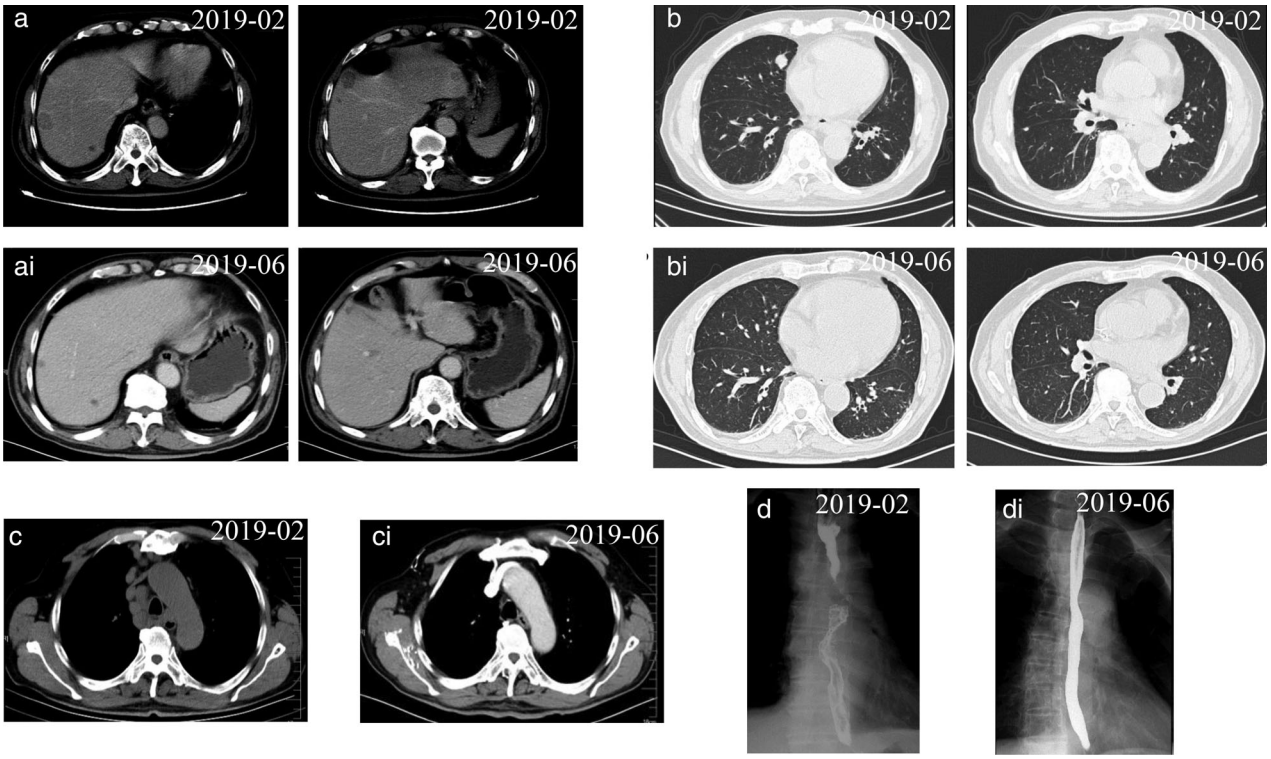

Figure 1 (**a**) Computed tomography (CT) scan showing liver metastases in February 2019; (**ai**) CT scan showing liver lesions which achieved a near complete response (nCR) after therapy; (**b**) CT scan showing lung metastases in February 2019; (**bi**) CT scan showing lung lesions which achieved a complete response (CR) after therapy; (**c**) CT scan showing lymph node metastases in February 2019; (**ci**) CT scan showing lymph node lesions which achieved aCR after therapy. (**d**) Barium meal imaging in February 2019. (**di**) Barium meal imaging after therapy.

Barium meal imaging revealed a smooth esophageal wall. Re-examination of the gastroscope indicated that the esophageal lesions were completely eliminated, showing scar-like changes. The patient obtained a near complete response (nCR) (Fig 1). Toripalimab (day 4, 240 mg) plus etoposide (day 1–4, 100 mg) was thereafter administered as maintenance treatment. Unfortunately, intracranial metastasis was subsequently detected in October 2019. Thus, four cycles of toripalimab (day 2, 240 mg) plus irinotecan (day 1, 300 mg), and one course of radiotherapy for brain metastasis were administered immediately. Intracranial lesions achieved complete response (CR) and extracranial lesions achieved nCR in June 2020. Toripalimab (240 mg) was administered thereafter. So far, the overall survival (OS) of this patient has exceeded 19 months (Fig 2), and he remains in a stable condition, without any serious adverse effects.

Discussion

In this case report, we first report a SCEC patient who achieved a remarkable and sustained response from toripalimab plus chemotherapy. Immune checkpoint inhibitors (ICIs) are the first agents in the last decade to determine an improvement in the outcomes of small cell lung cancer (SCLC) patients. In the IMpower 133 and CASPIAN studies, patients with SCLC showed a significant improvement in OS with an acceptable safety profile, leading to a new standard of care for the first-line therapy of patients. In addition, there is now a trend to use immunotherapy plus chemotherapy in the treatment of digestive tract tumors. While median OS with pembrolizumab versus chemotherapy (7.1 vs. 7.1 months) was similar in the treated population in the KEYNOTE-181 study, pembrolizumab plus chemotherapy versus chemotherapy alone successfully improved median OS (12.4 vs. 9.8 months) and progression-free survival (PFS) in the first-line treatment of advanced esophageal cancer patients in KEYNOTE-590, and even patients with a low percentage of PD-L1 expression were shown to benefit from combination therapy.[3,4] Similarly, nivolumab was associated with a significant improvement in median OS (10.9 vs. 8.4 months) compared with chemotherapy alone in the ATTRACTION-3 study, and survival benefit occurred regardless of tumor PD-L1 expression.[5] In our case, the patient had low PD-L1 expression but obtained OS of more than 19 months, which far exceeded the median OS of SCEC (11.1 months according to

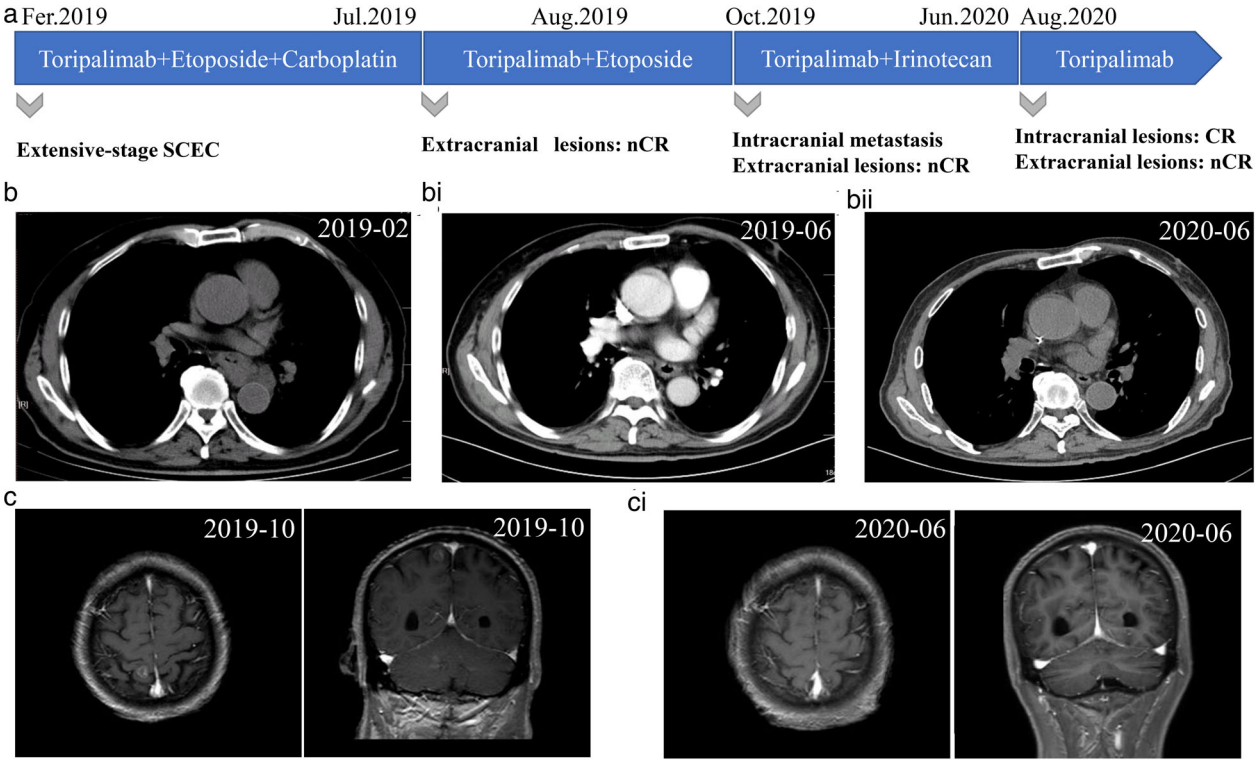

Figure 2 (**a**) Timeline of treatment; (**b**) Computed tomography (CT) scan before therapy; (**bi**) CT scan showing a near complete response (nCR) after six cycles of treatment; (**bii**) CT scan showing the patient was in a stable condition after 16 months of treatment; (**c**) Magnetic resonance imaging (MRI) showing intracranial metastasis in October 2019; (**ci**) MRI showing the intracranial lesions achieved a complete response (CR) after treatment.

a study which included 1176 SCEC cases).[2] This response might be sporadic but still indicated that immunotherapy plus chemotherapy is a potential option for SCEC patients.

For the treatment of brain metastasis, irinotecan instead of etoposide was administered for its better permeability of the blood-brain barrier and the intracranial lesions soon obtained CR.[6] It is suggested that selection of chemotherapy is critical once brain metastasis is revealed. In addition, no hyperprogression was observed in this case, although the patient had *MDM2* amplification, which was considered as a risk factor of hyperprogression.[7] We speculated that either simultaneous chemotherapy could lower the incidence of hyperprogression or *MDM2* was not associated with hyperprogression in SCEC.

In conclusion, immunotherapy plus chemotherapy might be a reasonable option for SCEC patients. Well designed trials for better evidence are required to verify the findings in our report.

Acknowledgment

We thank Dr Mingzhe Xiao, and Dr Chuang Qi from Simceredx for their kind assistance. This work was supported by the National Natural Science Foundation of China (No. 81602077), and the Nanjing Medical Science and Technology Development Foundation (No. YKK16103).

Disclosure

The authors have declared no conflicts of interest.

References

1 Kukar M, Groman A, Malhotra U *et al.* Small cell carcinoma of the esophagus: A SEER database analysis. *Ann Surg Oncol* 2013; **20**: 4239–44. https://doi.org/10.1245/s10434-013-3167-3.

2 Lu X, Luo J-D, Ling Y *et al.* Management of small cell carcinoma of esophagus in China. *J Gastrointest Surg* 2013; **17**: 1181–7. https://doi.org/10.1007/s11605-013-2204-7.

3 Kojima T, Shah MA, Muro K *et al.* Randomized phase III KEYNOTE-181 study of pembrolizumab versus chemotherapy in advanced esophageal cancer. *J Clin Oncol* 2020; Jco2001888. https://doi.org/10.1200/jco.20.01888. [Online ahead of print].

4 Kato K, Shah MA, Enzinger P *et al.* KEYNOTE-590: Phase III study of first-line chemotherapy with or without pembrolizumab for advanced esophageal cancer. *Future Oncol* 2019; **15**: 1057–66. https://doi.org/10.2217/fon-2018-0609.

5 Kato K, Chul Cho B, Takahashi M *et al*. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): A multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2019; **20**: 1506–17. https://doi.org/10.1016/s1470-2045(19)30626-6.

6 Chen G, Huynh M, Chen A, Fehrenbacher L, Gandara D, Lau D. Chemotherapy for brain metastases in small-cell lung cancer. *Clin Lung Cancer* 2008; **9**: 35–8. https://doi.org/10.3816/CLC.2008.n.006.

7 Adashek JJ, Subbiah IM, Matos I *et al*. Hyperprogression and immunotherapy: Fact, fiction, or alternative fact? *Trends Cancer* 2020; **6**: 181–91. https://doi.org/10.1016/j.trecan.2020.01.005.

