Concurrent combination of irradiation and immune checkpoint inhibitor for recurrent pleomorphic carcinoma of the lung

Ken Kodama¹ · Tomohiro Maniwa¹ · Yukio Kimura¹ · Yuriko Yagi¹ · Yoko Yamamoto¹ · Toshika Ohkawa² · Masashi Takeda³ · Hiroki Kishima⁴ · Genju Koh⁵ · Takamasa Toyofuku⁶

Received: 21 September 2017 / Accepted: 4 December 2017 / Published online: 15 December 2017
© The Japan Society of Clinical Oncology 2017

Abstract

We report the case of a 49-year-old patient who developed brain, sternal, and spine metastases almost simultaneously after the radical resection of a yp-T4N0M0 pulmonary pleomorphic carcinoma of the right upper lobe following induction chemotherapy. The left occipital brain metastasis was surgically removed and followed by radiation therapy. The sternal and vertebral metastases were treated with radiation therapy. Concurrently, the immune checkpoint inhibitor nivolumab was administered. After 12 cycles of nivolumab, the two bone metastases were well-controlled. However, the brain metastasis recurred and was surgically removed again. We were able to investigate the tumor-infiltrating lymphocytes in brain metastases resected before and after radio-immunotherapy. The results revealed the increased number of CD8- and CD68-positive cells after the combined therapy compared with before the therapy. In addition, the high-level expression of program death-ligand 1 was maintained in the brain metastasis.

Keywords Pulmonary pleomorphic carcinoma · Radiation therapy · Immune checkpoint inhibitor · Immunotherapy

Introduction

Pleomorphic carcinoma is a rare type of poorly differentiated non-small cell lung cancer (NSCLC) that belongs to sarcomatoid carcinoma. The incidence is estimated to be 0.3–1.3% of all lung malignancies. It exhibits aggressive behavior and resistance to chemotherapy and radiotherapy.

Radiotherapy in combination with immune checkpoint inhibitors, such as anti-program death-1 (PD-1),

anti-program death-ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated molecule-4 (CTLA-4) antibodies, consistently improved local tumor control, improved systemic tumor control (abscopal effect) [1], and led to the induction of specific anti-cancer immunity with a memory effect.

We report a patient who developed brain and bone metastases treated by concurrent irradiation with an anti-PD-1 immune checkpoint inhibitor. The clinical and pathological responses at each metastatic site were investigated.

✉ Ken Kodama
cfaem800@jtw.zaq.ne.jp

¹ Department of Thoracic Surgery, Yao Municipal Hospital, 1-3-1 Ryuge-cho, Yao, Osaka 581-0069, Japan

² Department of Neurosurgery, Yao Municipal Hospital, Yao, Japan

³ Department of Pathology, Yao Municipal Hospital, Yao, Japan

⁴ Department of Surgery, Kishima Hospital Main Division, Yao, Japan

⁵ Department of Clinical Oncology, Yao Tokusyukai General Hospital, Yao, Japan

⁶ Department of Radiation Oncology, Yao Municipal Hospital, Yao, Japan

Case

A 49-year-old man with a 1-month history of general fatigue and a 65 pack-year smoking history presented to the emergency department with an acute onset of shortness of breath in August 2015. Chest-computed tomography (CT) revealed a 128 × 65-mm mass lesion in the upper lobe of the right lung accompanied by chest wall invasion. He was diagnosed with clinical T4N2M0, stage IIIB lung adenocarcinoma (8th Edition of the TNM Classification for Lung Cancer) based on the results of bronchoscopy, positron emission tomography (PET), and brain magnetic resonance imaging (MRI).

Tissue staging of the mediastinum was not performed. The level of tumor markers was not elevated.

The clinical history and therapeutic interventions are shown in Fig. 1. After induction chemotherapy composed of three cycles of cisplatin, pemetrexate and bevacizumab, and one additional cycle without bevacizumab, right upper lobectomy with systematic lymph node dissection and combined chest wall resection including the third-to fifth ribs were performed, and the defect of the chest wall was reconstructed with 2-mm-thick expanded polytetrafluoroethylene (e-PTFE) dual mesh. The response to induction chemotherapy was stable disease (SD). The pathologic diagnosis was yp-T4N0M0, stage IIIA pleomorphic carcinoma. The post-operative course was uneventful, and two additional cycles of chemotherapy with carboplatin and nab-paclitaxel were administered.

The patient suffered from right homonymous hemianopsia in September 2016. Brain MRI revealed a 25-mm

mass lesion in the left occipital lobe (Fig. 1). The mass was successfully removed via craniotomy and diagnosed as recurrent brain metastasis in October 2016. One month later, he developed back and chest pain, and sternum and spine (T10) metastases were detected by PET with marked (18F)-fluoro-2-deoxy-D-glucose (FDG) uptake. Because of the high-level expression of PD-L1 in his tumor, he was treated as per the standard of care with a PD-1 inhibitor. Nivolumab was administered intravenously at a dose of 3 mg/kg of body weight every 2 weeks. A total of 12 cycles of nivolumab were administered between December 2016 and June 2017. After fully discussing the risks and benefits of concurrent radiation therapy with physicians, surgeons and radiation oncologist and obtaining informed consent from the patient, the 10th spine metastasis was treated with intensity-modulated radiotherapy (IMRT) of 45 Gy in 15 fractions (December 28, 2016 to January 23, 2017), the left occipital lobe of the brain with 3D

49 y. Male
c-T4N2M0
Pleomorphic ca.

Brain
meta.
2016/09

Recurrent
Brain meta.
2017/06

Spine (T10) meta.
sternum meta.
2016/12

2017/05

Fig. 1 Imaging and treatment throughout the disease course. CDDP cisplatin, PEM pemetrexed, BEV bevacizumab, CBDCA carboplatin, nab-PTX nab-paclitaxel, RT radiotherapy

conformal irradiation of 60 Gy in 30 fractions (January 6 to February 17, 2017) and the sternum with conventional

4-field irradiation of 45 Gy in 15 fractions (January 24 to February 13, 2017), respectively.

Although PET revealed a markedly decreased uptake of FDG at the bone metastases, brain metastasis recurred at the resection margin. We performed re-craniotomy to remove this recurrent brain metastasis (Fig. 1).

The results of immunohistochemical staining and EGFR mutation analysis are shown in Table 1. High- and low-molecular-weight cytokeratins (AE1/AE3) were positive and thyroid transcription factor 1 (TTF1) and carcinoembryonic antigen (CEA) negative in both primary lesion and brain metastasis. Morphologically, these lesions did not contain any components showing squamous or adenocarcinoma differentiation. CD8+ and CD68+ cells were significantly increased in the recurrent brain metastasis compared with the metastasis before radio-immunotherapy (Fig. 2). PD-L1 expression was assessed using clone 22C3 (Dako, Carpinteria, CA, USA). However, the proportion scores of brain metastases resected before and after radio-immunotherapy were exactly the same value (both 75%). epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) fusion protein were not detected (Table 1).

As a high proportion score for the 22C3 PD-L1 assay of the recurrent brain tumor, pembrolizumab was started after the removal of the recurrent brain metastasis.

Concurrent nivolumab and radiotherapy did not induce unexpected adverse events except for the temporary malaise of grade II (CTCAE v4.0).

Table 1 Immunohistochemistry and EGFR mutation

Antibody	Primary lesion	Brain metastasis	
		Before RI	After RI
AE1/AE3	+	+	NA
CAM5.2	+	NA	NA
TTF-1	–	–	NA
Carletinin	+	+	NA
CEA	–	–	NA
D2-40	–	NA	NA
CK7	NA	+	NA
CK20	NA	–	NA
P40	NA	–	NA
WT-1	NA	–	NA
CD4 ^a	NA	50.4 ± 9.7 cells	55.3 ± 7.4 cells
CD8 ^a	NA	98.6 ± 18.0 cells**	125.9 ± 28.3 cells**
CD68 ^a	NA	44.8 ± 3.1 cells***	60.5 ± 6.1 cells***
PD-L1 (22C3)	NA	75%	75%
ALK	–	–	NA
EGFR mutation	–	–	NA

RI radio-immunotherapy, NA not assessed

^aImmuno-reactivity was determined by the slide at low-to-intermediate power (×10, ×20 objective) to find the area of the highest immunoreactivity. A ×40 objective was then used to count positive cells. In the area with the highest activity, the number of staining cells was counted over ten consecutive high-power fields (HPF), and the mean number was compared

** $p = 0.035$, *** $p < 0.0001$

Fig. 2 Hematoxylin and eosin (HE) staining (a, e), and immunohistochemistry image for CD4 (b, f), CD8 (c, g) and CD68 (d, h) in the brain metastasis of pulmonary pleomorphic carcinoma resected before (a, b, c, d) and after (e, f, g, h) radio-immunotherapy (objective: ×20)

Discussion

Recently, Kim et al. [2] reported that pulmonary pleomorphic carcinoma very frequently expresses PD-L1 and PD-L2. Thus, targeting the PD-1/PD-L1 pathway may represent a potential therapeutic candidate for this aggressive tumor. To date, there has been one case report on the marked response of stage IV pleomorphic carcinoma after 4 cycles of therapy with nivolumab [3].

According to the result of a secondary analysis of the KEYNOTE-001 phase 1 trial [4], the previous treatment with radiotherapy in 42 patients (including 24 patients with thoracic radiotherapy) with advanced NSCLC resulted in longer progression-free survival and overall survival with pembrolizumab treatment than that seen in 55 patients who did not previously receive radiotherapy, with an acceptable safety profile. Moreover, acceptable tolerance in concurrent palliative irradiation with the anti-PD-L1 immune checkpoint inhibitor durvalumab was demonstrated in a phase 1/2 trial [5]. The optimal timing, sequencing, and dosing of these methods are a matter of intense research, but in clinical models, there has been no report on the safety of the concurrent administration of a checkpoint inhibitor and thoracic radiotherapy. When radiotherapy was applied to the tenth spine metastasis and sternum metastasis in our patient, the irradiation field was carefully determined so as not to be exposed to the lung parenchyma.

After induction chemotherapy and radical resection of the primary site, we performed concurrent radio-immunotherapy for three recurrent tumors in anticipation of improved systemic tumor control, i.e., the abscopal effect, as well as improved local tumor control. Long-term follow-up is currently ongoing, and to date (7 months after starting immunotherapy), there has been no sign of recurrence except in the brain.

Findings of recent non-randomized, open-label, phase 2 trial of pembrolizumab for patients with NSCLC and untreated or progressive brain metastases showed a brain metastasis response of 33%, and the responses were durable [6]. Despite these encouraging data, many patients did not respond to such immunotherapy in the brain or extracerebral sites. The available molecular, preclinical, and early clinical data on nivolumab and pembrolizumab support the conclusions that both drugs may well be interchangeable. However, in anticipation of the difference in affinity of antibody for ligand, we changed nivolumab to pembrolizumab. To overcome this situation, additional combination treatment will be necessary, especially in brain metastasis that might have a different disease biology than extracerebral metastasis. Recently, the PACIFIC study showed a significant increase in progression-free

survival and no new safety signals with PD-L1 antibody durvalumab in patients with stage III, unresectable NSCLC previously treated with chemoradiotherapy [7].

Radiation could also be helpful in promoting inflammation, enhancing the immunogenicity of brain tumors, disrupting the blood–brain barrier (BBB), and promoting increased antigen release [8]. The combination of radiotherapy and checkpoint inhibitors has been promising in preclinical trials, but has yet to show efficacy in humans.

In the present case, tumor margin recurrence in the brain occurred and was removed via re-craniotomy. Significant increases of cytotoxic T cells (CD8+) and macrophage/dendritic cells (CD68+) were observed in the recurrent tumor compared with the tumor removed before radio-immunotherapy. The expression of PD-L1 was maintained at the same level. As a possible explanation for the recurrence in the brain after radio-immunotherapy, we suggest that the hypoxic cells resistant to radiotherapy appeared after hemostasis at the time of the initial removal of the brain metastasis.

In conclusion, a heterogeneous response to concurrent radio-immunotherapy was observed between intra- and extracerebral metastases in a pulmonary pleomorphic carcinoma patient with higher PD-L1 expression. We histologically confirmed the significant induction of cytotoxic T cells (CD8+) and macrophage/dendritic cells (CD68+) in the brain metastasis after the concurrent therapy. This case report will help validate the use of radio-immunotherapy as a feasible option for the treatment of pleomorphic carcinoma of the lung.

Compliance with ethical standards

Ethical statement This report was approved by ethics committee of our hospital (No. 110617-13).

Conflict of interest All authors have declared no conflicts of interest.

References

1. Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kitano S et al (2012) Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med* 366:925–931
2. Kim S, Kim MY, Koh J, Go H, Lee DS, Jeon YK, Chung DH (2015) Programmed death-1 ligand 1 and 2 are highly expressed in pleomorphic carcinomas of the lung: comparison of sarcomatous and carcinomatous area. *Eur J Cancer* 51:2698–2707
3. Ito K, Hataji O, Katsuta K, Kobayashi T, Gabazza E, Yatabe Y et al (2016) “Pseudoprogression” of pulmonary pleomorphic carcinoma during nivolumab therapy. *J Thorac Oncol* 11:e117–e119
4. Shaverdian N, Lisberg AE, Bornazyan K, Veruttipong D, Goldman JW, Formenti SC et al (2017) Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. *Lancet Oncol* 18:895–903

5. Levy A, Massard C, Sonia JC, Deutsch E (2016) Concurrent irradiation with the anti-programmed cell death ligand-1 immune checkpoint blocker durvalumab: single centre subset analysis from a phase 1/2 trial. *Eur J Cancer* 68:156–162
6. Goldberg SB, Gettinger SN, Mahajan A, Chiang AC, Herbst RS, Sznol M et al (2016) Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol* 17:976–983
7. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R et al (2017) Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. <https://doi.org/10.1056/NEJMoa1709937>
8. Lakin N, Rulach R, Nowicki S, Kurian KM (2017) Current advances in checkpoint inhibitor: lessons from non-central nervous system cancers and potential for glioblastoma. *Front Oncol* 7:141. <https://doi.org/10.3389/fonc.2017.00141>