Complete response to cetuximab plus paclitaxel therapy in nivolumab-refractory patients in distant metastasis of squamous cell carcinoma of the tongue: a report of two cases

Hidetake Tachinami[1], Kei Tomihara[2], Danki Takatsuka[3], Atsushi Ikeda[1], Shin-ichi Yamada[3], and Makoto Noguchi[3]

[1]University of Toyama Faculty of Medicine Graduate School of Medicine and Pharmaceutical Science for Education
[2]Niigata University Faculty of Medicine Graduate School of Medical and Dental Science
[3]University of Toyama

March 29, 2023

Abstract

Herein, we report two cases of patients diagnosed with nivolumab-refractory distant metastatic squamous cell carcinoma of the tongue who were successfully treated with a combination of paclitaxel and cetuximab, thus demonstrating that some nivolumab-refractory patients with recurrent or distant metastatic oral squamous cell carcinoma may benefit from subsequent salvage chemotherapy.

Complete response to cetuximab plus paclitaxel therapy in nivolumab-refractory patients in distant metastasis of squamous cell carcinoma of the tongue: a report of two cases

Authors

Hidetake Tachinami[1], Kei Tomihara[1,2*], Danki Takatsuka[1], Atsushi Ikeda[1],Shinichi Yamada[1], Makoto Noguchi[1]

Affiliations

[1] Department of Oral and Maxillofacial Surgery, Faculty of Medicine, Academic Assembly, University of Toyama, Toyama, Japan

[2] Divisions of Oral and Maxillofacial Surgery, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

[*] These authors contributed equally to this work.

Corresponding author

Hidetake Tachinami

Department of Oral and Maxillofacial Surgery

Faculty of Medicine, University of Toyama

2630 Sugitani, Toyama city, Toyama 930-0194, Japan

Tel: +81-76 434-7383(extn. 7383)

Fax: +81-76 434-5041

E-mail: hidetake@med.u-toyama.ac.jp

Declarations

Data availability statement: Data sharing is not applicable to this article as no datasets were generated or analyzed during the study.

Funding statement

No funding was received for this work.

Conflicts of interest disclosure

The authors declare that they have no conflict of interest.

Ethics approval statement

This study was approved by the Institutional Review Board for Human Studies at the University of Toyama Hospital (R2020023).

Patient consent statement

Written patient consent was obtained.

Permission to reproduce material from other sources :

not applicable

Abstract

Herein, we report two cases of patients diagnosed with nivolumab-refractory distant metastatic squamous cell carcinoma of the tongue who were successfully treated with a combination of paclitaxel and cetuximab, thus demonstrating that some nivolumab-refractory patients with recurrent or distant metastatic oral squamous cell carcinoma may benefit from subsequent salvage chemotherapy.

Key Clinical Message

We report on two patients diagnosed with nivolumab-refractory distant metastatic squamous cell carcinoma of the tongue who were successfully treated with a combination of paclitaxel and cetuximab, thus demonstrating that some nivolumab-refractory patients with recurrent or distant metastatic oral squamous cell carcinoma may benefit from subsequent salvage chemotherapy.

Introduction

Nivolumab, an immune checkpoint inhibitor (ICI), has revolutionized the treatment of recurrent and metastatic oral cancer.[1]Few patients respond to nivolumab solely; thus, additional chemotherapy is required to improve the prognosis in refractory cases. Though it has been well-documented in the literature that conventional chemotherapy is highly effective for patients with advanced lung cancer in conjunction with nivolumab administration,[2] only a few reports of its use in head and neck cancer are available. In this study, we report two cases of patients with tongue cancer who presented with progressive disease after nivolumab administration and subsequently responded to salvage chemotherapy. Although there is prolonged overall survival with salvage chemotherapy, complete response is rare. We report a complete response to cetuximab plus paclitaxel after chemotherapy in two patients with distant metastases to the liver and bone.

Case reports

Case 1

A 43-year-old male with unremarkable medical and family histories presented with pain on the left side of his tongue, which he had delayed seeking treatment for. Hematological findings of the initial examination

were not available. The patient appeared to be well nourished. While there were no significant extraoral findings, intraoral examination revealed a raised, ulcerated lesion measuring 40 × 30 mm that extended from the left lateral margin to the ventral surface of the tongue.

The histological diagnosis of the biopsy specimen was squamous cell carcinoma; the patient was diagnosed with squamous cell carcinoma of the tongue (T3N0M0, Stage III). After induction chemotherapy, the patient underwent neck dissection, partial left-sided tongue resection, and anterolateral thigh flap reconstruction. Eight months later, computed tomography (CT) images revealed a swelling in the left submandibular region, pale ring-shaped nodular shadows in both lung fields, and osteolytic changes in the left iliac bone (Figure 1a). Fluorodeoxyglucose (FDG)-positron emission tomography (PET) revealed an abnormal accumulation in the left iliac bone (Figure 1a). In view of these findings, nivolumab (3 mg/kg) was administered every two weeks. After completion of 10 cycles, contrast-enhanced CT and FDG-PET revealed enlargement of each target lesion, indicating progressive disease (Figure 1b). The patient was started on paclitaxel and cetuximab (PC) therapy (paclitaxel: 80 mg/m^2, cetuximab: 400 mg/m^2). After 16 courses of PC therapy, all target lesions had decreased in size, indicating a partial response. After 46 courses of PC therapy, all target lesions had almost disappeared, indicating a complete response (Figure 1c). There was no recurrence after 36 months.

Grade 1 hypothyroidism, which occurred as a secondary immune-related adverse event, was treated with levothyroxine sodium hydrate (Tirazin®) at the Endocrinology Department of our hospital. After PC therapy, the patient developed grade 2 interstitial pneumonia; thus, steroid therapy was initiated, which required hospitalization for approximately 1 week. In addition, he developed grade 2 dermatitis. However, no secondary symptoms of grade 3 or higher levels of dermatitis were observed.

Case 2

A 67-year-old female with diabetes mellitus and hypertension presented with pain on the right side of her tongue, which she had delayed seeking treatment for. The patient appeared to be well nourished. Hematological findings at the initial examination revealed a hemoglobin Alc level of 6.0%. Extraoral examination revealed no significant findings; however, intraoral examination revealed a raised, ulcerated lesion 30 × 30 mm in size extending from the right lateral margin to the ventral surface of the tongue.

The histological diagnosis of the biopsy specimen was squamous cell carcinoma; the patient was diagnosed with squamous cell carcinoma of the tongue (T3N0M0, Stage III). The patient refused surgery and received chemoradiation therapy. Three months later, the primary tumor was under control; however, CT and FDG-PET revealed multiple cavernous nodules in the right lung field (Figure 2a). The patient was started on nivolumab (3 mg/kg, administered every two weeks) for multiple lung metastases. After nine courses of nivolumab, contrast-enhanced CT revealed an increase in the size of the target lesion and a new low-density nodule in the left lateral lobe of the liver, which was diagnosed as liver metastasis (Figure 2b). The patient was started on PC therapy (paclitaxel: 80 mg/m^2, cetuximab: 400 mg/m^2). After 19 courses of PC therapy, all target lesions had almost disappeared, which indicated a complete response (Figure 2c). No recurrence was observed at the 36-month follow-up.

Grade 1 hypothyroidism, which occurred as a secondary immune-related adverse event, was treated with levothyroxine sodium hydrate (Tirazin®) at the Endocrinology Department of our hospital. Following PC therapy, the patient developed grade 2 liver function abnormality and grade 2 dermatitis, which were treated with ursodeoxycholic acid (Urso®[?]) at the Department of Gastroenterology. However, no severe secondary symptoms of grade 3 or higher levels of dermatitis were observed.

Discussion

Nivolumab, an ICI that blocks programmed death-1 (PD-1; an immune checkpoint molecule), was approved in 2017 in Japan as a treatment option for recurrent or distant metastatic advanced oral cancer. Nivolumab has brought about a revolution in the treatment of oral cancer by significantly improving patients' prognoses. However, its efficacy is limited. The overall response rate is low, and additional salvage therapy and

subsequent chemotherapy are required for refractory patients. Although there is prolonged overall survival with salvage chemotherapy, complete response is rare. We report a complete response to cetuximab plus paclitaxel after chemotherapy in two patients with distant metastases in the liver and bone.

Following the advent of ICIs in recent years, salvage chemotherapy has been found to be effective for several solid tumors, including those in patients with head and neck cancer.[2-5] Because ICIs targeting PD-1 occupy T cells for over two months, the effects of salvage chemotherapy may overlap those of prior nivolumab therapy. Nivolumab reportedly inhibits the binding of programmed death ligand-1 (PD-L1; expressed on cancer cells) to the PD-$1^{+}$$CD8^{+}$ T cells in the tumor microenvironment, thereby inhibiting PD-1/PD-L1 signaling.[6] However, in the actual tumor microenvironment, immunosuppressive cells, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), prevent the nivolumab-mediated antitumor immune response.[7] Control of these immunosuppressive cells is expected to improve the antitumor effects of nivolumab. It has long been reported that some chemotherapeutic agents specifically modulate the activities of immunosuppressive cells.[8] For example, cisplatin increases the expression of tumor antigens and activates cytotoxic T cells, while 5-fluorouracil (5-FU) and docetaxel reportedly inhibit the activity of Tregs and MDSCs.[8] Paclitaxel has been shown to upregulate the expression of class I major histocompatibility complex proteins in cancer cells, thereby increasing their antigenicity. It also increases the antigen-presenting ability of dendritic cells.[8] Cetuximab, an epidermal growth factor receptor inhibitor, activates cytotoxic T cells by increasing tumor antigens through antibody-dependent cytotoxicity.[9] Therefore, based on these mechanisms, chemotherapeutic agents administered after ICIs may cause immunosuppression in the tumor-bearing host, thereby enhancing the ICI-driven antitumor immune responses.[9] Compared to other chemotherapeutic regimens, PC therapy has been reported to have a significantly higher response rate for head and neck cancer.[9]

There are multiple first-line treatment options for recurrent and distant metastatic advanced oral cancer. However, studies have noted that a course of checkpoint inhibitors and subsequent chemotherapy activates an antitumor immune response.[9] Furthermore, the KEYNOTE-040 study on head and neck cancer revealed a decreased response rate to checkpoint inhibitors in patients previously treated with cetuximab; thus, checkpoint inhibitors may be preferable if the disease is mild.[10]

Studies on combination immunotherapy have shown that the administration of an ICI alters the immune environment of the host, which is maintained even after switching to other therapies. Based on the findings of the KEYNOTE-048 study,[9] the combination of pembrolizumab, an ICI, with platinum and 5-FU, a chemotherapeutic, may be an effective treatment strategy for such cancers.

Our findings from these two cases of tongue cancer demonstrate that some nivolumab-refractory patients with recurrent or distant metastatic oral squamous cell carcinoma may benefit from subsequent salvage chemotherapy.

Author Contributions

Data collection was performed by Hidetake Tachinami. The first draft of the manuscript was written by Danki Takatsuka, Hidetake Tachinami, Kei Tomihara, Shinichi Yamada, and Makoto Noguchi.

Acknowledgments: We would like to express our sincere gratitude to Professor Ryuji Hayashi of the Department of Clinical Oncology, University of Toyama Hospital, and Dr. Narusuke Okazawa of the First Department of Internal Medicine for their cooperation and guidance in completing this article.

References

1. Ferris, R. L., Blumenschein, G., Fayette, J., et al. 2018. Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of Check Mate 141 with analyses by tumor PD-L1 expression. Oral Oncology 81:45-51.
2. Schvartsman, G., Peng, S. A., Bis, G., et al. 2017. Response rates to single-agent chemotherapy after exposure to immune checkpoint inhibitors in advanced non-small cell lung cancer. Lung Cancer 112:90-95.

3. Park, S. E., Lee, S. H., Ahn, J. S., et al. 2018. Increased response rates to salvage chemotherapy administered after PD-1/PD-L1 inhibitors in patients with non–small cell lung cancer. Journal of Thoracic Oncology 13(1):106-111.
4. Daste, A., De-Mones, E., Cochin, V., et al. 2018. Progression beyond nivolumab: Stop or repeat? Dramatic responses with salvage chemotherapy. Oral Oncology 81:116-118.
5. Ogawara, D., Soda, H., Iwasaki, K., et al. 2018. Remarkable response of nivolumab-refractory lung cancer to salvage chemotherapy. Thoracic Cancer 9(1):175-180.
6. Chen, D. S., and Mellman, I. 2013. Oncology meets immunology: The cancer-immunity cycle. Immunity 39(1):1-10.
7. Tomihara, K., Fuse, H., Heshiki, W., et al. 2014. Gemcitabine chemotherapy induces phenotypic alterations of tumor cells that facilitate antitumor T cell responses in a mouse model of oral cancer. Oral Oncology 50(5):457-467.
8. Saleh, K., Daste, A., Martin, N., et al. 2018. Response to salvage chemotherapy after progression on immune checkpoint inhibitors in patients with squamous cell carcinoma of the head and neck. Journal of Clinical Oncology 36(15_suppl):6015.
9. Burtness, B., Harrington, K. J., Greil, R., et al. 2019. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): A randomised, open-label, phase 3 study. Lancet 394(10212):1915-1928.
10. Cohen, E. E. W., Soulieres, D., Le Tourneau, C., et al. 2019. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): A randomised, open-label, phase 3 study. Lancet 393(10167):156-167.

Figure captions

Figure 1 Radiological findings of the tumor in Case 1. (a) Findings before nivolumab administration; (b, c) Findings after salvage chemotherapy

Figure 2 Radiological findings of the tumor in Case 2. (a, b) Findings before nivolumab administration; (c) Findings after salvage chemotherapy