Successful rechallenge with cetuximab after progression with nivolumab for recurrent cervical lymph node metastasis from carcinoma of the tongue

Yasuyuki Asada[1], Chitoshi Teramura[2], Takuma Wada[2], Yoshisato Machida[1], Shinya Koshinuma[1], and Gaku Yamamoto[1]

[1]Shiga University of Medical Science
[2]Otsu City Hospital

April 2, 2021

Abstract

We demonstrate the effectiveness of readministering cetuximab as a salvage chemotherapeutic agent after nivolumab administration to a patient with a recurrence of cervical lymph node metastasis after tongue cancer surgery. We can infer that the immunostimulatory effect of nivolumab and reactivation of cetuximab enhance the antitumor effect of the therapy.

Successful rechallenge with cetuximab after progression with nivolumab for recurrent cervical lymph node metastasis from carcinoma of the tongue

Yasuyuki Asada[1)], Chitoshi Teramura[2)], Takuma Wada[2)], Yoshisato Machida[1)], Shinya Koshinuma[1)], Gaku Yamamoto[1)]

Department of Oral and Maxillofacial Surgery, Shiga University of Medical Science, Seta-Tsukinowa-cho, Otsu, Shiga 520-2192, Japan

Department of Oral and Maxillofacial Surgery, Otsu City Hospital, 2-9-9, Motomiya, Otsu, Shiga 520-0804, Japan

Corresponding Author:

Yasuyuki Asada

Department of Oral and Maxillofacial Surgery in Shiga University of Medical Science, Seta-Tsukinowa-cho, Otsu, Shiga 520-2192, Japan

Phone No: (+81)-80-5361-1016

Email Address: yasuyuki0505@gmail.com

Abstract

We demonstrate the effectiveness of readministering cetuximab as a salvage chemotherapeutic agent after nivolumab administration to a patient with a recurrence of cervical lymph node metastasis after tongue cancer surgery. We can infer that the immunostimulatory effect of nivolumab and reactivation of cetuximab enhance the antitumor effect of the therapy.

Key Clinical Message

We can infer that the immunostimulatory effect of nivolumab and reactivation of cetuximab enhance the antitumor effect of the therapy.

Keywords: carcinoma of the tongue, nivolumab, cetuximab, rechallenge, metastasis

1. Introduction

In March 2017, nivolumab, an immune checkpoint inhibitor, was approved for use in the treatment of squamous cell carcinomas of the head and neck with recurrence or metastasis in Japan. Nivolumab differs from conventional chemotherapeutic drugs, in that, it is known to show a reaction and has been reported to be highly effective for lung cancer, when given after immunotherapy; however, few reports of its use for head and neck cancer treatment are available. Here, we present our experience with a patient who had recurrent cervical lymph node metastasis caused by tongue cancer. Administration of cetuximab and nivolumab led to increased metastasis, but readministration of cetuximab resulted in a remarkable response.

2. Case report

A 55-year-old patient (height, 160 cm; weight, 52 kg; in good nutritional status) presented to our hospital because of an ulcer on the right tongue margin in June 2015. The patient had been previously diagnosed with endometrial atypical growth by the obstetrics and gynecology department of a nearby hospital in December 2012. The patient was neither a drinker nor a smoker and had no family history of cancer. An extraoral examination revealed no abnormal findings in the cervical lymph nodes, whereas intraoral examination using magnetic resonance imaging (MRI) showed an ulcerative lesion with a diameter of 22 mm on the right tongue margin (Fig. 1A). Infiltrative lesions showing a contrast effect with gadolinium were also observed in the area (Fig. 1B,C). Positron emission tomography (PET) showed high accumulation of fluorodeoxyglucose in the right tongue margin but not in other organs (Fig. 1D). Based on these findings and pathological evaluation of an intraoral biopsy specimen, we diagnosed the patient with stage II (T2N0M0) squamous cell carcinoma of the tongue [1].

In July 2015, the patient underwent partial right tongue resection under general anesthesia. Postoperative adjuvant therapy was not administered because the surgical margin was negative. Although no recurrence was found locally or in the neck, swelling of the right cervical region was observed in December 2015 and the patient was followed up by monthly MRI thereafter. The MRI performed in February 2016 showed that the right upper-internal jugular vein lymph node had a minor axis of 12 mm. The patient was then diagnosed with late cervical lymph node metastasis of tongue cancer because the MR image showed a region with moderate signal intensity that included a part of the low-signal region (Fig. 2A). In the same month, the patient underwent right total neck dissection under general anesthesia. Postoperative adjuvant therapy was administered this time because histopathological diagnosis did not detect extracapsular invasion in the right superior-internal jugular vein lymph node.

Follow-up was continued, and swelling was observed in the lower part of the patient's right jaw in May 2016. Computed tomography (CT) showed that the right submandibular lymph node had become swollen with a minor axis of 15 mm and that the boundary with the surrounding area was unclear (Fig. 2B). Recurrence was confirmed after the patient was diagnosed with late cervical lymph node metastasis of tongue cancer, and chemoradiotherapy (cisplatin [cis-diamminedichloroplatinum II] total dose, 300 mg/m^2; radiotherapy total dose, 66 Gy) was performed from the same month onward. The treatment resulted in a stable disease (Fig. 2C).

Chemotherapy with cetuximab began in September 2016. Cetuximab was initially administered at a dose of 400 mg/m^2 and subsequently at 250 mg/m^2 once weekly. Cisplatin was administered at 80 mg/m^2 on Day 1, and fluorouracil was administered at 800 mg/m^2 on Days 1–4. A CT scan was performed in December 2016, at the end of the three courses of cetuximab combination chemotherapy. The recurrent lymph node had disappeared and a complete response (CR) was hence recorded (Fig. 3A). Serious complications, including bone marrow suppression, and side effects were not detected. In addition, paronychia of the limbs was observed. Although it was considered to be a skin reaction triggered by cetuximab, it only caused mild pain

and improved with the application of a moisturizer. Cetuximab alone was maintained from the same month onward at a dose of 250 mg/m^2 administered once a week.

Another CT scan was performed in March 2017, three months after the maintenance administration of cetuximab alone was initiated, and it revealed that the right submandibular lymph node was swollen. Therefore, the treatment response was classified as progressive (Fig. 3B). Nivolumab therapy was then started at a dose of 3 mg/kg once every two weeks. Immune-related adverse events due to nivolumab were not observed. A CT scan was performed again in July 2017, after six doses of nivolumab had been administered, and it revealed a shrinkage of the right submandibular lymph node (Fig. 3C). The treatment response was categorized as partial, and nivolumab administration was continued.

However, in October 2017, after 14 courses with nivolumab, we observed swelling of the right submandibular gland and CT images showed a marked increase in the right submandibular lymph node (Fig. 3D). The patient was thus considered to have a progressive disease, and cetuximab combination chemotherapy was recontinued from the same month onward. The dose and dosing interval were the same as previously implemented. The next CT scan was performed in February 2018, after three courses with the readministration of cetuximab combination chemotherapy, and showed that the right submandibular recurrent lymph node was markedly reduced (Fig. 3E). From the same month onward, the patient received maintenance administration of cetuximab alone. The final CT scan was performed in March 2019, after 52 doses of cetuximab. The submandibular lymph node had disappeared, and CR was achieved (Fig. 3F). Cetuximab alone was still being administered as maintenance therapy 20 months later. PET has not detected any recurrence or metastasis, and the course has been uncomplicated (Fig. 4A, B).

3. Discussion

With recent advances in drug therapies, such as molecular-targeted therapies and immune checkpoint inhibitors, the role of drug therapy in the treatment of head and neck cancers is rapidly expanding and its scope is becoming more complex[2]. In Japan, the antiepidermal growth factor receptor antibody cetuximab was approved as a molecular targeted drug for head and neck cancers in December 2012. On the other hand, a 2017 subanalysis of the CheckMate 141 trial found that the antiprogrammed death 1 (PD-1) antibody nivolumab had favorable effects in the treatment of recurrent and metastatic squamous cell carcinomas of the head and neck [3]. Nivolumab is now being used as one of the standard treatments for head and neck cancers[3].

Nivolumab has been shown to have responses and therapeutic effects distinct from those of conventional anticancer and molecular targeted drugs. It has been reported to have long-lasting effects in successful cases and suppress the exacerbation of tumors for long periods in unchanged ones[4]. Studies have suggested that salvage chemotherapy after the administration of previously approved immune checkpoint inhibitors is highly effective for the treatment of nonsmall cell lung cancer [5–7].

In this study, recurrent lymph nodes disappeared after chemotherapy with cetuximab but increased after the treatment was switched to cetuximab alone. Nivolumab was subsequently administered; however, as recurrent lymph nodes continued to increase, chemotherapy with cetuximab was performed again. The patient has shown a marked reduction of recurrent lymph nodes and continues to be in a CR at present. These outcomes may be related to the reactivation of cetuximab and the immunostimulatory effect of nivolumab.

Regarding the reactivation of cetuximab, Santini et al.[8] found tumor growth after cetuximab was administered and readministered as an adjuvant therapy in 21 of 39 patients with colorectal cancer, 53.8% of whom reported a response. Regarding the mechanism by which readministration of cetuximab is effective, Aparicio and Caldas[9] reported that there was a heterogeneous presence of cells sensitive to cetuximab and low cells in the tumor. They found that the administration of cetuximab (1) initially led to a reduction in the number of sensitive cells, an increase in that of insensitive cells, and tumor growth but (2) subsequently resulted in an increase in the number of sensitive cells. These findings suggest that readministration of cetuximab causes tumors to shrink.

Regarding its immunostimulatory effect, nivolumab is a human immunoglobulin G4 anti–PD-1 antibody [10]. PD-1, which is a receptor from the CD28 family [10], is expressed in such immune cells as differentiated effector T cells and B cells after activation. The binding of antigen-presenting cells to PD-L1 and PD-L2 ligands in lymphocytes and that of PD-L1 expressed in tumor cells and PD-1 expressed in T cells, which transmits a negative signal to T cells, suppress activation[10].

Nivolumab restores the cancer immune response by inhibiting the binding of PD-1 to PD-L1 and PD-L2 and diminishing inhibitory signals to T cells[10]. In addition, research has considered that conventional chemotherapy is brought about by the suppression of cell growth of cancer cells and cytotoxicity [4]. However, in recent years, it has become clear that immune cells represented by T cells are involved in long-term clinical effects [4]. Chemotherapeutic agents have been shown to act directly on immunocompetent and immunosuppressive cells as well as cancer cells, thereby affecting their antitumor effects [4].

Cisplatin has been reported to increase the expression of tumor-specific antigens and promote the induction of cytotoxic T cells associated with them [11]. Paclitaxel is known to improve not only antigenicity by enhancing the expression of major histocompatibility complex class I molecules in cancer cells but also the ability of dendritic cells to present antigens to T cells by acting directly on the dendritic cells[12]. Fluorouracil has also been shown to selectively induce apoptosis in myeloid-derived suppressor cells and increase their antitumor effect [13].

The change in the cancer immune microenvironment caused by the administration of nivolumab influences the effects of succeeding chemotherapeutic agents used on immunocompetent and immunosuppressive cells, with said influence being enhanced by its interaction with the original cell-killing effect. The limited data on successful cases of rescue chemotherapy after administration of such immune checkpoint inhibitors in oral cancer highlight the need for more cases to be reported.

4. Conclusion

Our case has demonstrated the effectiveness of readministering cetuximab as a salvage chemotherapeutic agent after administering nivolumab to a patient diagnosed as having a progressive disease for the recurrence of cervical lymph node metastasis after tongue cancer surgery. Our findings suggest that the immunostimulatory effect of nivolumab and reactivation of cetuximab enhance the antitumor effect of the therapy and highlight the need to accumulate more cases similar to ours to further validate the data.

Ethical approval

Written informed consent was obtained from the patient prior to the inclusion of laboratory data and accompanying clinical images in the manuscript. Any investigation on subjects has been in accordance with the Declaration of Helsinki.

Author Contributions:

Yasuyuki Asada: Conception and design of study, acquisition of data, analysis and/or interpretation of data, Drafting the manuscript

Chitoshi Teramura: Conception and design of study, acquisition of data, analysis and/or interpretation of data, Drafting the manuscript

Takuma Wada: acquisition of data

Yoshisato Machida: analysis and/or interpretation of data

Shinya Koshinuma: revising the manuscript critically for important intellectual content

Gaku Yamamoto: Conception and design of study, revising the manuscript critically for important intellectual content

All authors critically revised the report, commented on drafts of the manuscript, and approved the final report.

Acknowledgments

No.

Conflict of Interest

The authors declare that they have no competing interests.

ORCID

https://orcid.org/0000-0002-5540-2213

References

1. Sobin, L. H.; Gospodarowicz, M. K.; Wittekind, C. H.. TNM classification of malignant tumors. 7th ed. West Sussex, UK: John Wiley & Sons; 2009.

2. Tanaka, K. 2020. IV. Treatment of unresectable cases-immune checkpoint inhibitor. Gan To Kagaku Ryoho Cancer & Chemotherapy 47:1050-54.

3. Kiyota, N., Hasegawa, Y., Takahashi, S., Yokota, T., Yen, C.J., Iwae, S., et al. 2017. A randomized, open-label, Phase III clinical trial of nivolumab vs. therapy of investigator's choice in recurrent squamous cell carcinoma of the head and neck: A subanalysis of Asian patients versus the global population in checkmate 141. Oral Oncology 73:138-146.

4. Hanamure, Y., Hayashi, T., Takaki, M., Ito, K. 2019. Response to salvage chemotherapy after progression on nivolumab in patients with recurrent/metastatic head and neck squamous cell carcinoma. Japanese Journal of Head and Neck Cancer 45:41-45.

5. Park, S.E., Lee, S.H., Ahn, J.S., Ahn, M.J., Park, K., Sun, J.M. 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 13:106-111.

6. Schvartsman, G., Peng, S.A., Bis, G., Lee, J.J., Benveniste, M.F.K., Zhang, J., 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.

7. Ogawara, D., Soda, H., Iwasaki, K., Suyama, T., Taniguchi, H., Fukuda, Y., et al. 2018. Remarkable response of nivolumab-refractory lung cancer to salvage chemotherapy. Thoracic Cancer 9:175-180.

8. Santini, D., Vincenzi, B., Addeo, R., Garufi, C., Masi, G., Scartozzi, M., et al. 2012. Cetuximab rechallenge in metastatic colorectal cancer patients: how to come away from acquired resistance? Annals of Oncology 23:2313-2318.

9. Aparicio, S., Caldas, C. 2013. The implications of clonal genome evolution for cancer medicine. New England Journal of Medicine 368:842-851.

10. Ueda, M., Rin, S., Niiyama, T., Hata, H., Imamachi, K. 2018. Collaboration in medical treatment to use Nivorumab against oral cancer, Clinical Oncologist and Oral and Maxillofacial surgeon. Journal of Japanese Society of Oral Oncology 30:135-143.

11. Jackaman, C., Majewski, D., Fox, S.A., Nowak, A.K., Nelson, D.J. 2012. Chemotherapy broadens the range of tumor antigens seen by cytotoxic CD8(+) T cells in vivo. Cancer Immunology, Immunotherapy 61:2343-2356.

12. Shurin, G.V., Tourkova, I.L., Kaneno, R., Shurin, M,R. 2009. Chemotherapeutic agents in noncytotoxic concentrations increase antigen presentation by dendritic cells via an IL-12-dependent mechanism. Journal of Immunology 183:137-144.

13. Vincent, J., Mignot, G., Chalmin, F., Ladoire, S., Bruchard, M., Chevriaux, A., et al. 2010. 5-Fluorouracil selectively kills tumor-associated myeloid-derived suppressor cells resulting in enhanced T cell-dependent antitumor immunity. Cancer Reserach 70:3052-3061.

Figure legends

Fig. 1. (A) Photograph taken during the patient's initial visit, showing an ulcerative lesion measuring 22 mm in diameter on the right tongue margin. (B) MR image showing frontal disconnection. (C) MR image in the horizontal view. An invasive lesion showing a contrast effect with gadolinium was observed on the right tongue margin. (D) A PET scan image showing high accumulation of fluorodeoxyglucose in the right tongue margin.

Fig. 2. (A) MR image taken seven months after tongue cancer surgery. The right upper internal jugular vein lymph node had become swollen with a minor axis of 12 mm, and the T2-emphasized image shows a region with moderate signal intensity that included a part of the low-signal region. (B) A CT scan image taken three months after right neck dissection. The right submandibular lymph node had become swollen with a minor axis of 15 mm, and the boundary with the surrounding area was unclear. (C) A CT scan image taken after chemoradiotherapy. No change in the size of the right submandibular lymph node was observed, and the boundary with the surrounding area was unclear.

Fig. 3. (A) A CT scan image taken after three courses of cetuximab combination chemotherapy. The right submandibular recurrent lymph node had disappeared. (B) A CT scan image taken three months after maintenance administration of cetuximab alone was initiated. Swelling of the right submandibular lymph node was observed. (C) A CT scan image taken after six doses of nivolumab. Shrinkage of the right submandibular lymph node was observed. (D) ACT scan image taken after 14 doses of nivolumab. Significant enlargement of the right submandibular lymph node was observed. (E) A CT scan image taken after three courses of chemotherapy with cetuximab. Significant reduction of the right submandibular recurrent lymph node was observed. (F) A CT scan image taken after 52 doses of cetuximab alone. The right submandibular lymph node had disappeared.

Fig. 4. (A, B) PET scan images taken 20 months after CR was achieved. No recurrence or metastasis was observed.