Re-introducing the same chemotherapy after exposure to anti-PD-1 therapy

Takashi Koyama^{1,2} · Motoo Nomura¹ · Doi Keitaro¹ · Ichiro Tateya³ · Manabu Muto¹

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Abstract

Cytotoxic chemotherapy after exposure to nivolumab (nivo), an anti-programmed death-1 (PD-1) antibody, has been associated with good response compared with historical data in various cancers including head and neck squamous cell carcinoma (HNSCC). In a previous report, different chemotherapy regimens were used before and after treatment with nivo. This HNSCC case is the first report of a good response when the same cytotoxic chemotherapy regimen was used before and after nivo. In addition, the efficacy of anti-epidermal growth factor receptor antibody after nivo treatment may be better than without exposure to nivo.

Keywords Nivolumab · Chemotherapy · Head and neck cancer

Introduction

Immunotherapy targeting the programmed death 1 (PD-1) pathway is effective for various tumor types. Nivolumab (nivo), an anti-PD-1 antibody, has improved the prognosis of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) after progression or recurrence on platinum-containing chemotherapy [1]. Furthermore, cytotoxic chemotherapy after exposure to anti-PD-1 antibody was associated with a better response compared with historical data from the pre-anti-PD-1 era in HNSCC [2] and other cancers [3]. In a previous report, different chemotherapy regimens were used before and after nivo treatment. Therefore, it is possible that changing the therapy significantly contributed to the good response. So far, there have been no reports of using the same chemotherapy regimen before and after nivo.

We report that re-introducing the same regimen of cytotoxic and antibody therapy after nivo was associated with a good response.

Case report

A 68-year-old man with hepatic cirrhosis (Child-Pugh class A) received a diagnosis of a cT2N2bM0 (according to the 7th edition of the Union for International Cancer Control TNM classification of malignant tumor) right pyriform sinus squamous cell carcinoma. For organ preservation as initial treatment, the patient was treated with 5FU and cisplatin. Just after one cycle, a partial response was observed. However, a hemorrhagic gastric ulcer was also observed, so we concluded that he could not tolerate these agents. Radiation therapy alone to a total dose of 70 Gy was conducted.

Four months after chemoradiotherapy, the hypopharyngeal cancer had recurred. As neoadjuvant treatment, the patient received one cycle of docetaxel. He underwent total laryngopharyngectomy with reconstruction with a free jejunum flap and bilateral neck dissection.

Pulmonary metastasis was found at the right middle lobe 8 months after surgery. The patient received paclitaxel (80 mg/m²) and cetuximab (at first 400 mg/m², and then 250 mg/m²) therapy from that month. Dose modifications and skipping were performed for both drugs on the basis of the type and grade of the toxicity. Hand–foot syndrome without acne-like rash occurred at this treatment.

Eight months after the start of first-line chemotherapy, the pulmonary metastasis at the right middle lobe progressed, and a new metastatic lesion was detected at the right upper lobe. Nivo was introduced at 3 mg/kg every 2 weeks as second-line chemotherapy. The pulmonary metastases had progressed

✉ Motoo Nomura
excell@hkg.odn.ne.jp

¹ Department of Medical Oncology, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan

² Department of Rheumatology and Clinical Immunology, Kyoto University Hospital, Kyoto, Japan

³ Department of Otolaryngology-Head and Neck Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan

4 months after start of nivo. Because the patient had good performance status (Eastern Cooperative Oncology Group performance-status score was 0) and no specific symptoms of cancer, paclitaxel and cetuximab were re-introduced as third-line chemotherapy. The metastasis at the right upper lobe was getting smaller, and the right middle lobe metastasis was stable (Fig. 1). Interestingly, an acne-like rash without hand–foot syndrome occurred at the restarted treatment compared with the initial paclitaxel and cetuximab treatment. He was still on this therapy 1 year after start of third-line chemotherapy.

Discussion

Two conclusions can be drawn from the clinical course of this patient. First, the same cytotoxic chemotherapy being used both before and after exposure to nivo was associated with a good response. Second, the efficacy of anti-epidermal growth factor receptor (EGFR) antibody after exposure to nivo may be better than that without nivo.

The past studies changed the regimen between pre-nivo and post-nivo, which suggested that changing the therapy significantly contributed to the good response. Our case is the first report of using the same chemotherapy regimen before and after nivo. In our case, the pulmonary metastases worsened in the patient treated with paclitaxel and cetuximab before nivo. However, re-introducing the same regimen after nivo was associated with a good response for the same pulmonary metastases.

Single-agent chemotherapy regimens (docetaxel, gemcitabine, mitomycin, pemetrexed, and vinorelbine) after immunotherapy exposure have shown good response compared with historical data from the pre-anti-PD-1 era in non-small cell lung cancer (NSCLC) [3]. Other studies have also

shown that cytotoxic chemotherapy is effective for patients with NSCLC with prior anti-PD-1 antibody or anti-programmed death ligand 1 (PD-L1) antibody treatment [4, 5]. Daste et al. demonstrated two cases of a dramatic response to paclitaxel after nivo in HNSCC [2]. In ovarian cancer, Peng et al. observed that the regimen of paclitaxel and anti-PD-1 or anti-PD-L1 antibody prolonged survival [6]. Paclitaxel binds mouse toll-like receptor 4 (TLR4), and thus can activate mouse macrophages and dendritic cells (DCs) [7]. In patients with breast cancer, taxane improves T-cell and natural killer cell functions compared with a no-taxane regimen [8]. The effect of paclitaxel is potentially improved after nivo.

Moreover, a combination regimen using paclitaxel may have an impact on response. Paclitaxel stimulates TLR4 and promotes drug–drug interactions by activating the down-regulation of drug metabolizing enzymes/transporters in mice [9]. Moreover, use of a TLR4 agonist with paclitaxel may improve the effect compared with one or the other in mice [10]. TLR4 activation is probably the key for the effect of paclitaxel, and using a TLR4 stimulator in other chemotherapy regimens may have good results.

In addition, the efficacy of an anti-EGFR antibody after nivo may be better than that without nivo. Hand–foot syndrome and acne-like rash are frequently observed in patients treated with cetuximab. In our case, hand–foot syndrome without acne-like rash occurred at the initial paclitaxel and cetuximab treatment. However, acne-like rash without hand–foot syndrome occurred at the same treatment restarted after nivo. Several studies have reported an association of acne-like rash with improved response rate or survival [11–13]. A phase 2 study of the combination of cetuximab and weekly paclitaxel for HNSCC [14] has also shown the relationship between rash and response.

Fig. 1 This figure shows computed tomography images of the metastasis at the right upper lobe (on the top) and at the right middle lobe (on the bottom). **a** Two months after the re-introduction of paclitaxel and cetuximab, **b** 4 months after, **c** 6 months after

In HNSCC, using cetuximab promotes the expression of PD-1 and T-cell immunoglobulin and mucin domain 3 (TIM-3) on CD8⁺ tumor-infiltrating lymphocytes (TIL), and the numbers of PD-1⁺ CD8⁺ TILs and TIM-3⁺ CD8⁺ TILs have a negative impact on the efficacy of the cetuximab regimen [15]. Moreover, Checkmate 141 reported that previous cetuximab use impairs the effect of nivo [1]. We used cetuximab before nivo, so the effect of nivo may have similarly declined. On the other hand, nivo may have lessened the increase in PD-1⁺ CD8⁺ TILs after the initial paclitaxel and cetuximab treatment, so nivo may have contributed to the good response to re-introducing paclitaxel and cetuximab.

While we used cetuximab after nivo, it is important to note that the effect of nivo remains for several months after its discontinuation. Anti-PD-1 or anti-PD-L1 antibody combined with cetuximab may have contributed to the good response. There is an ongoing phase 1/2 study of durvalumab, a humanized monoclonal IgG1 anti-PD-L1 antibody, combined with cetuximab and radiotherapy in locally advanced HNSCC (DUCRO study) [16].

Further reports can determine whether re-introducing cytotoxic chemotherapy, especially paclitaxel, leads to a good response and whether the efficacy of anti-EGFR antibody together with or after nivo is better than without nivo.

In conclusion, re-introducing the same cytotoxic chemotherapy after exposure to nivo was associated with a good response, and the efficacy of anti-EGFR antibody after exposure to nivo may be better than no exposure to nivo. This case is the first report of using the same chemotherapy regimen before and after nivo.

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Compliance with ethical standards

Ethical approval All procedures performed in study involving human participant was in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest None of the authors have conflicts of interest to declare.

Informed consent Informed consent was obtained from a participant included in the study.

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