

Case Report

Unexpected Response to Nivolumab in a “Fast Progressor” Head and Neck Cancer Patient

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Keywords

Nivolumab · HNSCC · PD-L1 · Mixed response · Head and neck cancer

Abstract

Prior to the advent of immune checkpoint inhibitors targeting PD-1/PD-L1 axis no drug demonstrated to improve survival or quality of life in the second-line treatment of recurrent or metastatic head and neck squamous cell carcinoma (R/M-HNSCC). Nivolumab appear to have a clear clinical benefit for R/M-HNSCC, based on improved survival, good toxicity profile, reduction in symptoms and improvement in overall quality of life. This benefit seems to be greater for PD-L1 positive patients and independent of previous treatment, even being observed among heavily pre-treated patients. However, even in responding tumors acquired resistance to nivolumab usually occurred, limiting the drug's activity. We report a case of unexpected prolonged stable disease in second-line treatment with nivolumab after a rapid progression disease under first-line chemotherapy in biomarker-positive R/M-HNSCC.

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Introduction

The treatment of R/M-HNSCC is a rapidly evolving landscape. Until the publication of EXTREME trial [1], no further advances in the systemic therapy of R/M-SCCHN has been demonstrated and no established second-line treatment has never existed, up to the approval of

immune-checkpoint inhibitors. In 2016, based on CheckMate 141 trial nivolumab was approved by the FDA for patients with platinum refractory R/M-HNSCC. Nivolumab has demonstrated superiority over standard single agent systemic chemotherapy (methotrexate, docetaxel or cetuximab), with a 2 years survival rate of 16.9%, three times higher than standard therapy [2, 3]. When initiating nivolumab as a second-line therapy for patients with R/M HNSCC, testing for PD-L1 status is not required. Although this drug is approved for the second-line treatment of R/M-HNSCC regardless of tumor PD-L1 expression levels, data suggest that positive tumor PD-L1 expression predicts for greater magnitude of benefit with nivolumab, especially in association with the presence of PD-L1 expressing tumor-associated immune cells [2, 4]. We report a case of a patient with PD-L1 positive R/M-HNSCC, presenting an early tumor flare-up during treatment with platinum-based chemotherapy, and a good disease control in the next line with nivolumab.

Case Presentation

The patient was a 54-year-old-man with a previous history of an ischemic cardiomyopathy due to myocardial infarction (NYHA functional class II) and colon cancer treated with left hemicolectomy. Risk factors included smoking habit (20 pack/years). In February 2017, the patient underwent right hemimandibulectomy plus modified radical neck dissection and reconstruction with fibula flap for an infiltrative lesion of the inferior gingival, infiltrating the jaw. Histology confirmed moderately differentiated squamous cell carcinoma in pathological stage pT4a N2b (ECS-) M0 R0 (AJCC/UICC 7th edition). Multidisciplinary tumor board assessment proposed postoperative radiotherapy (PORT), while the concomitant chemotherapy was excluded due to patient comorbidities. In June 2017, the patient completed PORT receiving 66 Gy on planning target volume and 54 Gy on right level I-V and left level I-IV of the neck. In September 2017, a CT scan of the maxillofacial region and the neck showed a solid lesion of the floor of mouth. A PET scan confirmed a pathological hypermetabolism of the soft tissues of right hemimandible, the floor of mouth, and the supraclavicular, mediastinal and axillary nodes. The tumor relapse was not resectable, so a palliative approach was decided. In October 2017, patient started a modified EXTREME regimen with carboplatin AUC5 and without fluorouracil due to cardiological co-morbidity. After 3 months a cutaneous carcinosis appeared on anterior neck region and radiologic assessment confirmed progression of disease with a new lesion of soft tissue of the supraclavicular fossa and spinal bone metastases. Due to facial pain and dysphagia, patient started analgesic therapy with opioids and parenteral nutrition, required the placement of a central venous catheter and the activation of nursing home care. With the patient's consent, the tissue sample obtained during surgery was submitted for immunohistochemical testing for PD-L1, showing a high PD-L1 with both tumor proportion score (TPS) and combined positive score (CPS). A second-line treatment with nivolumab 3 mg/kg every 2 weeks was started in January 2018. Furthermore, patient underwent x-ray orthopantomography and clinical examination by maxillofacial surgeons who excluded contraindications to use of bisphosphonates, thereby he received the first infusion of zoledronic acid on January 25, 2018. After three nivolumab administrations, the patient obtained complete pain control and improvement of dysphagia with weight increase and general well-being. At first evaluation in March 2018, a stable disease was obtained. In April 2018, the patient developed G3 skin toxicity with erythematous, confluent and pruritic papules on his bilateral upper and lower extremities. Because of suspected underlying immune-induced dermatologic toxicity, treatment with nivolumab was stopped and prednisone treatment (1 mg/kg) up to

symptoms resolution was initiated. The skin reaction completely regressed in 3 weeks and nivolumab was started again in April 28, 2018. In May 2018, given the exacerbation of pain in the lumbar region, the patient underwent palliative radiotherapy receiving 30 Gy in 10 fractions in D5-D8. After six doses of radiations, due to persistent of pain in the lumbar region with debilitating irradiation to left leg, the patient was hospitalized at the emergency department where he performed X-ray of the lumbo-sacral region and the left femur without evidence of fractures or soft tissue component. Therefore, analgesic medication was optimized by increasing the dose of opioid. The restaging CT was performed in June and showed a stable disease in the soft tissue of supraclavicular fossa and a partial response of the cutaneous nodules on the neck, but a progression of single spinal metastases (L3) accompanied by pathologic fracture and initial spinal cord compression. The case was collegially discussed and given the mixed response, nivolumab was continuously administrated and a palliative radiotherapy in L3 was proposed. However, after further two doses of nivolumab, there was a worsening of clinical conditions with weight loss, increased fatigue and deteriorated performance status. CT scan documented an increase in all disease sites and the patient was hospitalized in hospice where the best supportive care was provided until the patient died in September 2018.

Discussion

We report a case of refractory disease rapidly progressed on platinum-based first-line chemotherapy in which the administration of nivolumab as second-line therapy resulted in a rapid clinical benefit and a control disease. To date, few “real life” data on nivolumab in R/M-HNSCC has been published. However, it is important to evaluate the translation of the benefit shown in the controlled clinical trials to a broader and unselected head and neck cancer population of the “real world” setting. In CheckMate 141 trial the median overall survival with nivolumab was 7.5 months and the estimated rate of PFS at 6 months was 19.7% [2]. In our clinical case, the time to progression was 6.0 months, larger than expected in second-line treatment, and the overall survival was comparable than that reported in CheckMate 141.

Although after six months clinical and radiological response on the skin and the soft tissue was maintained, our patient experienced slowly bone progression during nivolumab treatment. In the multidisciplinary tumor board, we decided to candidate patient to lumbar spine metastases radiotherapy and to continue nivolumab, considering the good performance status and the excellent response on the skin. In the cases of oligo-metastases or metastases with slow progression or few numbers, local treatments such as radiotherapy may be more suitable, especially in the presence of symptoms. Indeed, radiotherapy provides excellent palliation for localized metastatic bone pain [5] and, even if no data available in this regard, the combination of immunotherapy with local treatments should be considered in order to achieve a better clinical benefit.

Our case can be also considered an example of radiographic “mixed response”, defined as reduction in some lesions with concomitant expansion in others or appearance of new lesions. Although novel immune criteria do recognize mixed response patterns, if they accurately are able to measure them in a way that correlates to true response is unclear [6]. The management of these cases will continue to be a challenge until a standardized tool to assess true disease response is available. Until then, determination of clinical benefit will be the key in deciding when to discontinue immunotherapy. Interestingly, while checkpoint inhibitors have shown significant efficacy in visceral metastatic disease, their efficacy specifically in bone metastases is not well understood. The bone-metastatic microenvironment displays a unique immune

phenotype that could result in a distinct pattern of response to immunotherapy compared to other metastatic sites [7]. Advancing the understanding of bone immune environment is crucial to inform the development of novel treatment strategy. Combinatorial treatment strategies including targeted therapies and immunotherapies look promising in pre-clinical and clinical studies to overcome the immunosuppression in bone metastases and improve treatment of them [8].

In this case, after a total of 12 nivolumab administrations the patient presented a progression in all disease sites and worsening clinical conditions. This is not surprising since even in responding tumors acquired resistance usually occurred. Several mechanisms can elicit the resistance of head and neck tumor cells to immunotherapy and it may be hypothesized that monotherapy is not able to overcome the various mechanisms of immune escape [9]. Cabezas-Camarero et al. described an expected immune evolution of a tumor initially responding but then progressing to nivolumab, with the occurrence of a dense immune infiltrate that becomes exhausted, due to upregulation of genes related to T cell exhaustion and resistance to PD-1 blockade favoring tumor progression [10].

In this context the major challenge, that need to be addressed in order to maximize the benefits of immunotherapy, consists in the identification of strong predictive clinical factors and biomarkers to guide the patient’s selection. Indeed, only a small subset of patients benefit from immunotherapy and activity of immune-checkpoint inhibitors remains well below desired with at least 80% of subjects did not achieve any tumor size reduction.

In CheckMate 141 the magnitude of survival benefit was greater in PD-L1 \geq 1% subgroup, but no advantage was demonstrated for increasing PD-L1 level [2]. It should be noted that the assessment of PD-L1 expression in this trial was performed on tumor cells only and the benefit observed in PD-L1 negative patients could be due to PD-L1 expression in stromal cells. According to this hypothesis, an exploratory analysis from CheckMate 141 evaluating the immune profile of patients, showed that the presence of PD-L1 expressing tumor-associated immune cells was more predictive of benefit than tumor cell PD-L1 expression alone [4]. On the other hand, most of the major trials on pembrolizumab have demonstrated a positive correlation between PD-L1 positivity and clinical outcome, specially using CPS [11, 12]. Although divergent results and limited data available suggest no firm conclusion can be made in this regard, CPS seems to be more predictive than TPS in head and neck cancer. In our case, we decided to evaluate PD-L1 status using both methods obtaining a high expression level with TPS and CPS, that suggested a favorable patient immune profile.

Probably, we cannot assume PD-L1 as a perfect marker in order to identify responders, however we think that tumor PD-L1 status can be useful for decision making in some situations, such as in patients who may not be able to tolerate the chemotherapy (eg, poor performance status, old age, comorbidities); in these cases a high tumor PD-L1 expression may strongly indicate for the use of checkpoint inhibitors as an alternative option.

Moreover, the quality of life remains one of the major unmet needs in these patients who usually bear the burden of persistent treatment-related side-effects along with additional disabling symptoms attributed to the recurrent tumor. Nivolumab stabilized symptoms and functioning from baseline to different time points (9 and 15 weeks) and delayed time to deterioration of patient-reported quality-of-life outcomes, whereas chemotherapy led to clinically meaningful deterioration [13]. Overall, these findings are translating into a significant benefit for R/M-HNSCC patients.

Interestingly, our patient experienced grade 3 skin toxicity, which could effectively be treated with steroids, indicating that early detection and properly intervention are crucial to mitigate toxicity. Several reports demonstrated higher response rates and longer median

duration of response to anti-PD1 in patients with moderate or severe toxicities requiring [14, 15]. The possible relationship between the development of immune-related toxicity and the efficacy of immune-checkpoint inhibitors should be interesting, but it needs to be validated in larger series. The incidence of immune-related adverse events may reflect increased immunotherapy activity, thus leading to superior response rate. Future studies of anti-PD1 should address this association to explore the underlying biological mechanisms of efficacy.

Finally, our case is also an example of a complex management of this vulnerable patient population, who have a low baseline quality of life attributable to the persistent treatment-related effects from the initial curative-intent therapy and also to the additive effects of the recurrent tumor. All patients with R/M-HNSCC should be offered early, comprehensive palliative and supportive services to maximize benefit. Similar to what established in curative setting, the multidisciplinary team should target the assessment and management of physical and psychosocial symptoms, the establishment of goals of care (pain, bleeding, breathing and/or swallowing difficulties) and the coordination of care based on an individual patient's needs.

In conclusion unexpected prolonged stable disease in second-line and under nivolumab may be observed after a rapid progression disease under first-line chemotherapy in biomarker-positive R/M-HNSCC. However, even in responding tumors acquired resistance to nivolumab usually occurred, limiting the drug's activity. Further investigation might learn how to integrate immunotherapy with other treatments in order to overcome the numerous mechanisms of immune escape and improve benefit for these patients. Clearly, the expected improvement in survival due to immunotherapy option might not be clinically meaningful if patients do not simultaneously experience palliative benefits, including a reduction in symptoms and an improvement in their overall quality of life.

Statements of Ethics

The authors have no ethical conflicts to disclose. Written informed consent was obtained from the patient.

Disclosure Statement

The authors certify that they have no conflicts of interest to disclose in the subject matter discussed in this paper.

Author Contributions

Martina Napolitano, Lucia Trudu and Federica Bertolini: medical oncologist in charge of the patient. All authors contributed to the writing and review of the manuscript.

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