Dramatic response of refractory metastatic squamous cell carcinoma of the skin with cetuximab/pembrolizumab

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Abstract: Cutaneous squamous cell carcinoma (cSCC) accounts for 20% of skin cancers. At an advanced stage the prognosis is poor, making cSCC the second leading cause of death from skin cancer. In cases of metastatic or unresectable disease, anti-programmed cell death 1 (anti-PD1) treatment has shown promising results in a recent phase II study. Although anti-PD1 treatment now offers higher response rates, the responses remain inconsistent and may lead to therapeutic impasses. Preclinical data have suggested synergy between anti-epidermal growth factor receptor (anti-EGFR) and immunotherapy. We report the case of a patient with metastatic cSCC that proved refractory first to anti-EGFR/carboplatin and then to immunotherapy, but who showed a complete and durable response with cetuximab/pembrolizumab combination. This response could reflect synergy of the two treatments.

Keywords: anti-PD1, chemotherapy, combination immunotherapy, cutaneous squamous cell carcinoma, EGFR inhibitor

Introduction

Cutaneous squamous cell carcinoma (cSCC) accounts for 20% of skin cancers, making it the second most common skin cancer after basal cell carcinoma.[1] The annual incidence rate varies by region of the world.[2] In Europe, the reported age-standardized incidence of cSCC ranges from 15 to 77 per 100,000 individuals per year.[2] In Australia, cSCC incidence is higher (270 per 100,000 individuals per year).[3] The incidence is constantly increasing because of population ageing and sun exposure habits.[4] At an early stage, the prognosis is excellent, with a 90% 10-year survival rate, but when the disease is locally advanced or metastatic, the prognosis is poor with a median overall survival of 15.3 months from the start of first-line therapy,[5] making cSCC the second leading cause of death from skin cancer, after melanoma.

Over the last 2 years, immunotherapy has emerged as a standard of care in the management of advanced cSCC. Cemiplimab has shown promising results in a phase I and then a phase II study,

with response rates between 43.6% and 50% and median progression-free survival and median overall survival not reached after 12 months of follow-up.[6] Similarly, pembrolizumab has achieved in a recent phase II study a 38.5% response rate, with excellent tolerability.[7]

Although anti-PD1 (programmed cell death 1) treatment now offers higher response rates, the responses remain inconsistent and may lead to therapeutic impasses.

We present here the case of a patient with metastatic cSCC that proved refractory to first-line anti-EGFR (epidermal growth factor receptor)/carboplatin and then to immunotherapy, but who showed a complete response with a cetuximab/pembrolizumab combination.

Observation

In December 2016, a 65-year-old man presented with right subclavicular squamous cell carcinoma of the skin, which had been treated by surgery

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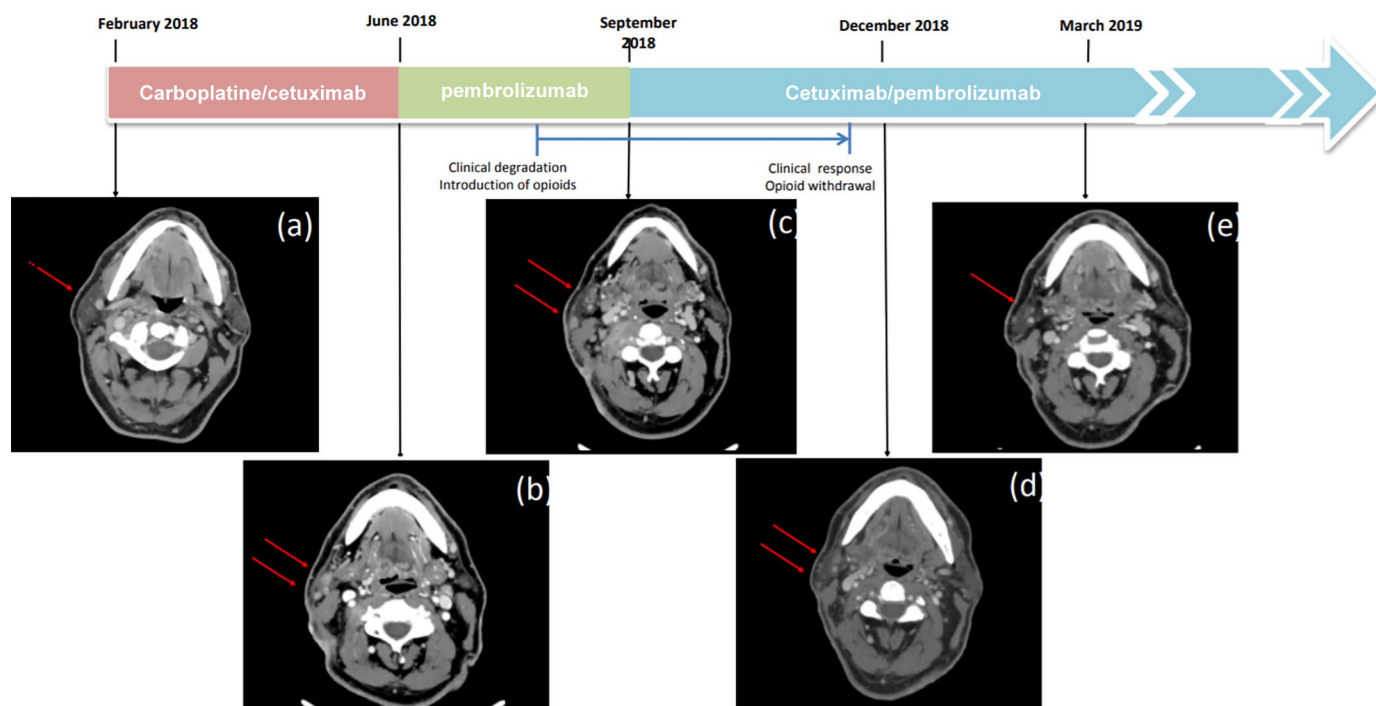CHU de Lille, Lille,
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Figure 1. Tomography scan assessments of the right parotid lesion at different time points. (a) Before starting the first course of carboplatin/cetuximab. (b) After completing five cycles of carboplatin/cetuximab and before starting the first course of pembrolizumab. (c) After completing four cycles of pembrolizumab and before starting the first course of pembrolizumab/cetuximab. (c) Three months and (d) 2 years after introduction of pembrolizumab/cetuximab.

followed by adjuvant radiotherapy. One year later, a local recurrence was observed, with infiltration of the sternocleidomastoid muscle and associated right cervical adenopathy palpable on clinical examination.

In February 2018, first-line systemic treatment was initiated with carboplatin/cetuximab. In June 2018, computed tomography (CT) scan performed after five cycles of treatment showed a mixed response, with 38% shrinkage of the right supraclavicular infiltration and emergence of a new right parotid lesion [Figure 1(a) and (b) and Figure 2(a)]. Considering tumour progression according to the RECIST 1:1 criteria, a therapeutic change with pembrolizumab was made. In July 2018, CT scan after three cycles of pembrolizumab showed a progression of cervical lymph nodes and the right parotid lesion. A new CT scan performed 2 months later (September 2018) confirmed progression 3 months after treatment initiation [Figure 1(c)]. Radiographic progression was associated with decreased performance status secondary to appearance of intense neuralgia following invasion of the brachial plexus, requiring introduction of opioids treatment [Figure 2(b)].

In September 2018, a combination treatment with cetuximab (500 mg/m²; day 1) and pembrolizumab (200 mg; day 7) every 3 weeks was initiated. Due to the lack of safety data for a combination of cetuximab and pembrolizumab, a sequential dosing regimen was chosen to monitor the occurrence of adverse events.

In December 2018, a partial radiological response was observed, associated with major clinical improvement [Figure 1(d) and Figure 2(c)]. In June 2019, a positron emission tomography scan showed no sign of metabolic activity, suggesting a complete response. After 15 cycles, cervical magnetic resonance imaging showed only a retractile fibrous laterocervical sequela with no progressive lesion. In November 2019, repeat imaging/clinical exam revealed persistence of complete response.

Because the patient developed Common Terminology Criteria for Adverse Events grade 3 folliculitis refractory to topical and systemic antibiotics, cetuximab was stopped after 19 cycles (14.3 months). In September 2020, a complete clinical and radiological response was still observed, allowing us to stop the immunotherapy [Figure 2(d)]. In January
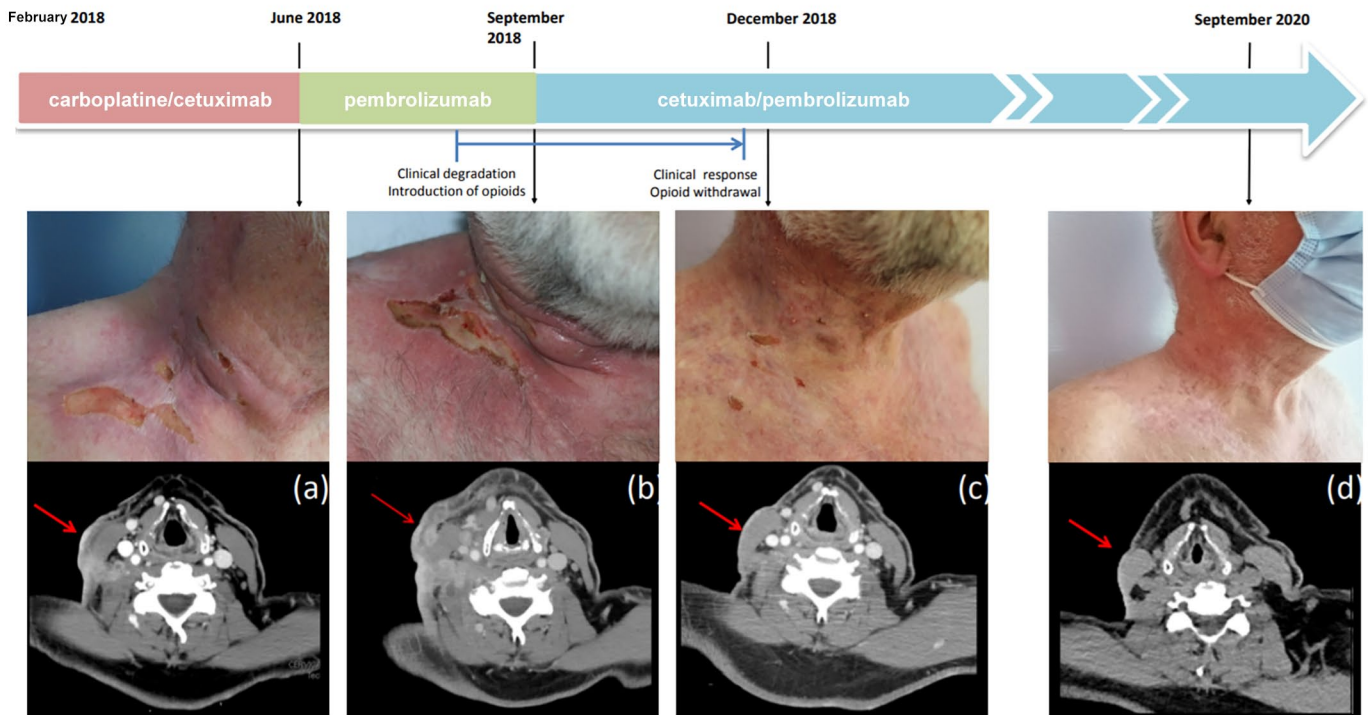
Figure 2. Clinical and computed tomography assessments of the right supraclavicular lesion at different time points. (a) Before starting the first course of pembrolizumab. (b) After completing four cycles of pembrolizumab and before starting the first course of pembrolizumab/cetuximab. (c) Three months and (d) 2 years after introduction of pembrolizumab/cetuximab.

2021, after 4 months off treatment, a complete clinical and radiological response is still observed.

Discussion

We report the observed case of a patient with metastatic cSCC who experienced a durable complete response to third-line treatment with combination anti-EGFR and anti-PD1 therapy.

There have been two previous reports concerning cSCC patients showing major responses to anti-EGFR/anti-PD1 combination therapy, but as the combination was initiated in anti-PD1 naïve patients, this could not reliably be interpreted as a potential synergistic effect.[8,9]

In our case, the successive failures of carboplatin/cetuximab combination therapy and of pembrolizumab monotherapy suggest that the response obtained with the cetuximab/pembrolizumab combination could reflect synergy of the two treatments.

The lack of response to pembrolizumab would suggest the presence of a primary resistance mechanism to PD1 therapy. Several mechanisms

of primary resistance to anti-PD1 have been described. Innate resistance may be notably related to the absence or low expression of programmed death ligand 1 (PDL1) by the tumour or stromal cells, the absence of tumour-expressed antigen, the inability of tumour-specific T cells to infiltrate the tumour microenvironment or the presence of a PD1-independent pathway suppressing anti-tumour immune responses.[10]

In our case, the addition of cetumixab appears to have overcome resistance to anti-PD1. In addition to inhibition of the EGFR receptor and downstream signalling pathways, anti-EGFR treatment can stimulate an anti-tumour immune response. By contributing to natural killer (NK) cell activation, cetuximab induces tumour cell death *via* an antibody-dependent cell-mediated cytotoxicity mechanism. Interestingly, NK cell activation by cetuximab leads to the release of tumour antigens, promoting the action of dendritic cells.[11] This stimulation, however, activates negative feedback controls *via* increased expression of PD1, PDL1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). The observed synergy might thus be due to the lifting of these controls through blocking of the PD1/PDL1 or

CTLA-4 pathway.[11] EGFR tyrosine kinase inhibitors (TKIs) have also demonstrated an ability to modulate the immune system. In a model of EGFR-mutated lung adenocarcinoma, Sugiyama *et al.*[12] found the EGFR inhibitor erlotinib to reduce infiltration of regulatory T-lymphocytes into the tumour microenvironment. In murine models, they also evidenced an association of EGFR TKI/anti-PD1 combination treatment with a better and prolonged tumour response.

What about the clinical data? A phase II trial evaluating pembrolizumab/cetuximab combination treatment in patients with recurrent or metastatic head and neck squamous cell carcinoma yielded encouraging results, with an overall response rate of 45% and a 14.9-month median duration of response (NCT03082534).[13]

We cannot completely rule out the possibility of pseudoprogression, that is, an increase in tumour burden followed by a decrease, on pembrolizumab alone, although this phenomenon is quite rare (less than 10% of cases).[14] In a retrospective multicentre study of immunotherapy applied to non-small cell lung cancer, Fujimoto *et al.*[15] observed pseudoprogression in 14 out of 542 patients (3%). Among these 14 patients, the median time between anti-PD1 initiation and confirmation of a response was 2.4 months, and in most cases a response was noted within 3 months of treatment. The median time between the first progressive disease and confirmation of a response was 1.3 months. In our case, clear progression was observed at 6 weeks and confirmed clinically and radiologically at 3 months. In addition, the worsening of clinical symptoms required the introduction of opioid therapy, and therefore we considered it inappropriate to continue anti-PD1 monotherapy.

Regarding treatment-related toxicity, our patient suffered from grade III folliculitis, which is characteristic of cetuximab; withdrawal of this drug after 6 weeks resulted in complete resolution of this toxicity. Our patient showed no adverse events related to pembrolizumab, nor did we observe any cross-toxicity between anti-EGFR and anti-PD1. Nonetheless, one case is not enough to draw conclusions from, and more studies are needed to corroborate our findings. Contrary to the combination EGFR TKI and anti-PD1, which is associated with a risk of pneumopathy, the combination cetuximab and anti-PD1 is well tolerated[13,16] The most common grade III adverse event reported was oral mucositis.[13]

Conclusion

With a likely synergistic effect on the immune system, anti-EGFR/anti-PD1 combination treatment could be a promising therapeutic option for locally advanced or metastatic cSCC.

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