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Justine LAVAUD
Astrid BLOM
Christine LONGVERT
Magali FORT
Elisa FUNCK-BRENTANO
Philippe SAIAG

Department of General and Oncologic Dermatology, Ambroise-Paré hospital, APHP & Research unit EA 4340, university of Versailles-Saint-Quentin-en-Yvelines, Paris-Saclay University, Boulogne-Billancourt France

Reprints: Philippe Saiag <philippe.saiag@uvsq.fr>

Pembrolizumab and concurrent hypo-fractionated radiotherapy for advanced non-resectable cutaneous squamous cell carcinoma

Background: Cutaneous squamous cell carcinoma (cSCC) is the second most frequent non-melanoma skin cancer. Treatment options for inoperable advanced cSCC cases are limited. The efficacy of anti-programmed cell death-1 (PD-1) monoclonal antibodies (mAb) has been reported recently in some patients with cSCC. *Objectives:* To evaluate the efficacy of anti-PD-1 mAb in a case series of inoperable advanced cSCC and to analyse the efficacy of concurrent radiotherapy. *Materials and Methods:* We retrospectively analysed the files of all patients with advanced inoperable cSCC treated with anti-PD-1 mAb and concurrent radiotherapy outside clinical trials in our skin cancer centre before December 31, 2017. *Results:* A total of four patients with locally or regionally advanced cSCC were identified. All patients received pembrolizumab at 2 mg/kg every three weeks and concurrent radiotherapy. Two patients who received pembrolizumab as first-line therapy with concurrent radiotherapy (one with skull and leptomeningeal invasion and one with rapidly progressing regional cSCC) had a complete response, allowing treatment discontinuation, without recurrence after a median of 11 months off treatment. All other patients experienced progressive disease. The median progression-free survival and overall survival were 14.4 and 15.6 months, respectively. No toxicity was observed. *Conclusion:* There appears to be a place for pembrolizumab as first-line treatment for unresectable or advanced cSCC. Further studies are needed to evaluate concomitant radiotherapy with anti-PD1 antibodies.

Key words: anti-PD-1 monoclonal antibody, cutaneous squamous cell carcinoma, pembrolizumab, radiotherapy

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Cutaneous squamous cell carcinoma (cSCC) is the second most frequent non-melanoma skin cancer. Its incidence is increasing worldwide. Main risk factors for cSCC are ultraviolet exposure and immunosuppression. The vast majority of cSCC can be cured surgically [1] but when they are locally or regionally advanced and inoperable and/or when distant metastases have occurred, treatment options and patient survival are limited. Radiotherapy, cytotoxic chemotherapy, cetuximab, alone or in combination, and panitumumab can be used [1, 2], but the level of evidence is low, and good responses are usually short-lived and infrequent.

Recently, anti-programmed cell death-1 (PD-1) monoclonal antibodies (mAb), such as nivolumab or pembrolizumab, have shown enhanced overall (OS) and progression free-survival (PFS) [3] in advanced melanoma patients, with durable tumour responses. Pembrolizumab has also been approved by the European Medicines Agency [4] for non-small cell lung cancer (NSCLC), Hodgkin lymphoma, urothelial cancer and in head and neck squamous cell cancer (HNSCC). As cSCC cells frequently express the ligand of PD-1 (PD-L1) and are characterized by a high rate of UV-induced genetic mutations [5], shown to be predictive of anti-PD-1 mAb tumour response [5], patients with advanced cSCC may be good candidates for anti-PD-1 mAb. In a preclinical mouse model, PD-1-PDL-1 activation contributed to the development of cSCC [6]. Moreover, the efficacy of anti-PD-1 mAb in patients with cSCC has been reported recently in a few case series [7-17] and in a Phase 1-2 trial with cemiplimab [18].

Herein, we report for the first time two complete responses (CR), allowing treatment discontinuation without recurrence to date, in a series of four patients with advanced cSCC treated with pembrolizumab and concurrent hypo-fractionated radiotherapy.

Patients and methods

All patients with advanced, inoperable, histologically confirmed cSCC treated in our referral skin cancer centre by

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anti-PD-1 mAb outside clinical trials before December 31, 2017 were included in this series. All received pembrolizumab at 2 mg/kg every three weeks until progressive disease (PD), unacceptable adverse effects (graded according to the Common Terminology Criteria for Adverse Events [CTCAE] version 4.0), or the clinician's decision to discontinue treatment. Therapeutic decisions were made during a multidisciplinary tumour board meeting and radiotherapy was added to anti-PD-1 mAb in case of very rapid progression or life-threatening localization.

We retrospectively analysed data which had been collected prospectively and entered into databases. Follow-up was performed according to the anti-PD-1 melanoma protocol in place in our department [19]. Before each pembrolizumab infusion, patients had physical examination and standardized blood tests. Efficacy evaluations were performed every three months with thoracic, abdominal and pelvic computed tomography (CT) scans, head CT scans or head magnetic resonance imaging, and evaluated on a weekly basis during tumour boards with radiologists with expertise in skin tumours. Response Evaluation Criteria In Solid Tumours version 1.1 (RECIST 1.1) guidelines were used (http://recist.eortc.org/recist-1-1-2/).

The primary endpoint was response to treatment. CR was defined by the absence of tumour lesions based on at least two CT scans 12 weeks apart, PD by a >20% increase in the sum of the diameters of the target lesions or occurrence of new lesions, and partial response (PR) by a > 30% decrease in the sum of the target lesions. When CR, PR, or PD were not achieved, disease was considered stable. Secondary endpoints were PFS (time from the first dose of pembrolizumab to documented progression or death) and OS. The closing date of the analysis was March 1st, 2019.

According to French Law, this study abided by standard medical practices and did not require a written informed consent. However, consent was obtained orally from all patients. The study was conducted according to the principles of the declaration of Helsinki [20].

Results

Our database extraction yielded four cases of advanced cSCCs treated with anti-PD-1 mAb and concurrent radiotherapy (*table 1*). All were located on the head and neck region and occurred in men, with a mean age of 84.6 years at the first infusion (range: 82.7-94.3). The oldest patient had a geriatric evaluation before treatment; he was in excellent condition. Two had a history of immunosuppression. At initial presentation, no patient had lymph node involvement nor distant metastases and all had surgical excision as recommended [1]. At presentation of advanced cSCC, one patient had local skull bone and lepto-meningeal invasion, and three patients had developed numerous in-transit metastases and/or important regional lymph node involvement. None had distant metastasis.

Pembrolizumab was used as first-line systemic therapy for three patients. They received concurrent hypofractionated radiotherapy (26 Gy in four fractions) because we anticipated that the three-month delay to respond, usually observed with PD-1 blockers [21], was too long. The first radiated patient had developed numerous in-transit metastases within less than two months. Patient 3 received pemprolizumab with concomitant hypofractionated radiotherapy as third-line therapy after PD with carboplatin-5fluorouracil-cetuximab, followed by paclitaxel.

Median follow-up after anti-PD-1 mAb initiation was 15.8 months (range: 4-26.5). The mean PFS and OS were 14.2 (median: 14.4) and 15.4 months (median: 15.6), respectively. We observed a CR in two patients who received first-line pembrolizumab with concomitant hypofractionated radiotherapy. The first patient, turned down by the neurosurgical team, had a CR despite initial bone and lepto-meningeal involvement (*figure 1*). A major PR was obtained at three months, and CR at six months, confirmed thereafter, allowing treatment discontinuation after 10 months. Sixteen months later, CR was maintained. The second presented a very rapid enlargement of right cervical lymph nodes (*figure 2*), six months after the initial resection of a cSCC of the right ante-tragus and was dismissed by the head/neck surgical team. A major PR was obtained at three months (*figure 2*) and CR at six months. This CR was maintained and led to pembrolizumab discontinuation after 12 months. Fourteen months after interruption, CR was maintained. No biopsy was performed to confirm CR in either case. The two remaining patients experienced PD. No adverse event of any grade was reported.

Discussion

In our series of four cases of unresectable locally or regionally advanced cSCC, pembrolizumab with concurrent radiotherapy was well tolerated, and two patients achieved CR. These two patients had received pembrolizumab as first-line treatment for cSCC in combination with concomitant hypo-fractionated radiotherapy because of very rapid local/regional progression. To the best of our knowledge, these are the first reported cases of pembrolizumab discontinuation due to CR in cSCC patients. The patients remain in CR at 16 months and 14 months after drug suspension.

Concurrent radiotherapy has not previously been used with anti-PD-1 mAb to treat advanced cSCC except in a single case of brain metastasis [10]. We cannot rule out that radiotherapy alone could explain our results. However, the association between immunotherapy (anti-CTLA-4 or anti-PD-1 mAb) and radiotherapy has proven its effectiveness in the local and distant control (abscopal effect) of melanoma, a skin cancer that, like cSCC, is characterized by a high mutational load, which is believed to be associated with anti-PD-1 mAb efficacy [5]. Radiotherapy might increase the efficacy of anti-PD-1 mAb treatment by changing the tumour microenvironment, increasing the level and activation of CD8+ T cells [20, 22], promoting homing and extravasation of effector T cells at the tumour site, up-regulating tumour-associated antigen-MHC complex expression, or enhancing antigen cross-presentation in the draining lymph nodes [22, 23].

Pembrolizumab lacked efficacy in two patients, which might be explained by its use as third-line treatment in one of them. In Phase III trials of melanoma patients, improvement of PFS and OS with anti-PD-1 mAb nivolumab or pembrolizumab was more pronounced when they were used in the first-line setting [3]. Finally, in one patient, a diagnosis of PD may have been reached too early (before three

Table 1. Characteristics and response to treatment of our series of four patients with advanced cutaneous SCC treated with pembrolizumab and concurrent hypo-fractionated radiotherapy.

Patient	Age (years)	Immuno-suppression?	SCC localization	Previous treatment(s)	Local/regional invasion or distant metastasis	Systemic treatments before Pembrolizumab	Line of previous systemic therapy	No. pembrolizumab infusions received	Concurrent radiotherapy	Best response
1	83.7	chronic lymphocytic leukaemia (multiple lines of cytotoxic chemotherapies, the last one being ibrutinib)	Vertex	Surgery	Unresectable in-transit cutaneous metastases		0	4	26 Gy, 4 fractions	PD
2	82.7	/	Right ear	Surgery	Unresectable retro-auricular mass, lymph node involvement		0	18	26 Gy, 4 fractions	CR
3	77.8	/	Vertex	Surgery	Unresectable in-transit cutaneous metastases, right basal-cervical lymph nodes	Carboplatin + 5 fluorouracil + cetuximab then paclitaxel	2nd	2	26 Gy, 4 fractions (nodes), 10 Gy electrons 1 fraction (vertex)	PD
4	94.3	Acquired haemophilia (high-dose corticosteroids and cyclophosphamide) (in remission without treatment when treated for cSCC)	Right frontoparietal region	Surgery	Unresectable local invasion: bone and meninges		0	16	26 Gy, 4 fractions	CR

SCC: squamous cell carcinoma; PD: progression disease; CR: complete response.

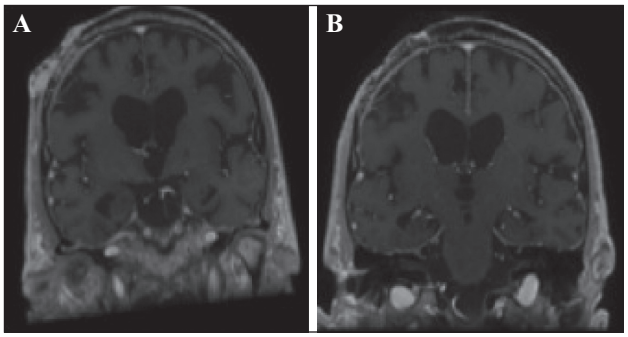

Figure 1. Magnetic resonance imaging of Patient 4 before treatment (**A**) showing bone and leptomeningeal invasion, and three months after treatment (**B**) showing an impressive partial response.

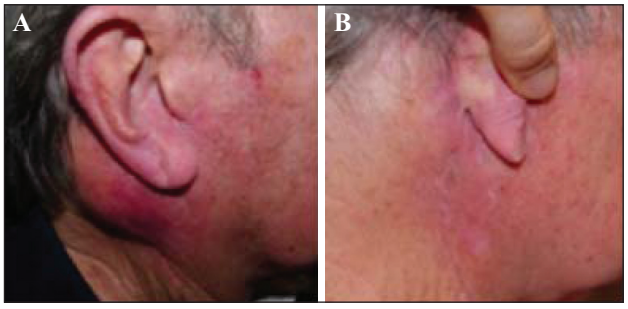

Figure 2. Patient 2 before treatment (**A**) showing an unresectable retro-auricular mass (lymph node involvement), and after three months of treatment (**B**).

months of treatment), precluding pseudo-progression, as observed in some melanoma patients.

The limitations of our study are its retrospective nature and the low number of patients. Moreover, we did not analyse PD-L1 expression in tumoral tissues. Nevertheless, we confirm that anti-PD-1 mAb is better tolerated than cytotoxic chemotherapy, which is frequently poorly tolerated in the often-fragile population of cSCC patients, with a risk of cardiac toxicity and cytopenia.

Currently, clinical trials with anti-PD-1 mAb are ongoing or planned for advanced cSCC patients, or in the adjuvant setting after complete excision of high-risk cSCC. Some of these are testing the addition of anti-PD-1 mAb to postoperative radiotherapy for cSCC of the head and neck area. Provided these further studies confirm the efficacy of anti-PD-1 mAb for cSCC, anti-PD-1 mAb will probably be a key treatment for unresectable or metastatic cSCC. Concurrent hypo-fractionated radiotherapy may enhance efficacy in some very severe patients. ■

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