Efficacy of anti-programmed cell death-1 immunotherapy for skin carcinomas and melanoma metastases in a patient with xeroderma pigmentosum

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Summary

Xeroderma pigmentosum (XP) is an orphan disease of poor prognosis. We report one case of parallel efficacy with anti-programmed cell death-1 (PD-1) antibody on both melanoma and skin carcinoma in a patient with XP. A 17-year-old patient presented with metastatic melanoma and multiple nonmelanoma skin cancers. He was treated with pembrolizumab, a monoclonal anti-PD-1 antibody, at a dose of 2 mg kg⁻¹ every 3 weeks. Parallel therapeutic efficacy of anti-PD-1 was observed in metastatic melanoma and skin carcinomas, and maintained at week 24. This observation suggests anti-PD-1 may be considered in patients with XP and metastatic melanoma in addition to advanced nonmelanoma skin cancer.

What’s already known about this topic?

• Xeroderma pigmentosum (XP) is a rare disease with a poor outcome.
• XP affects nucleotide excision repair, with cutaneous, ocular and neurological manifestations. Management of patients with XP currently includes highly efficient ultraviolet protection and close dermatological follow-up for early detection and treatment of skin carcinomas.

What does this study add?

• We report the efficacy of anti-programmed cell death-1 (PD-1) antibody immunotherapy for skin carcinoma in a patient with XP.
• Anti-PD-1 antibody may improve the prognosis of this rare skin condition.
significant mutational load, which increases the amount of tumour neoantigens.\textsuperscript{10} We report here the parallel therapeutic efficacy of pembrolizumab, an anti-PD-1 monoclonal antibody in metastatic melanoma and skin carcinomas in a patient with XP.

**Case report**

A 17-year-old patient was diagnosed with XP at the age of 2 years. He was born in the French Department of Mayotte off the coast of Southeast Africa and had been followed in our...
national reference centre for rare dermatological diseases for 10 years. UV-protection measures during the first years of life were not fully implemented. The patient, with skin Fitzpatrick phototype VI, presented with solar lentigines, hypopigmented macules and early-onset skin carcinomas. XP type C (XP-C) diagnosis was confirmed by molecular analysis showing homozygous mutations of NM_004628: c2251-1G>C in the XPC gene. This founder mutation is common in Africa.11

In the past 10 years, the patient had been repeatedly treated for multiple skin carcinomas with surgery and/or photodynamic therapy and/or topical chemotherapy with fluorouracil cream. The patient underwent enucleation of the left eye at the age of 12 for squamous cell carcinoma infiltrating the inner canthus and the eye. In 2012, the patient presented with a nodular and ulcerated melanoma of the scalp, Breslow thickness 3.3 mm, mitotic rate 8 mm². A 2-cm-wide enlarged excision was performed. The sentinel lymph node biopsy was free of tumour cells. A follow-up, including abdominal and lymph node ultrasound monitoring, was performed every 6 months.

In January 2016, at the age of 17 years, hepatic metastases were identified and a whole body computed tomography scan showed multiple pulmonary metastases (Fig. 1). The BRAFV600 mutation was not detected in liver tumour cells. The melanoma was staged T4bN0M1c, American Joint Committee on Cancer stage IV with normal lactate dehydrogenase. Physical examination showed numerous actinic keratoses, basal cell and squamous cell carcinomas mostly on the face and limbs (Fig. 1). Pembrolizumab treatment at the dose of 2 mg kg⁻¹ every 3 weeks was initiated according to the decision taken by the multidisciplinary dermato-oncology team.

After four cycles of treatment, a partial response with a decrease in size of metastases was observed (Fig. 1). Physical examination showed vitiligo depigmentation occurring preferentially on UV-exposed areas, regression of cutaneous carcinomas and disappearance of many pre-existing actinic keratoses.

After eight cycles of treatment, therapeutic efficacy on melanoma and skin carcinomas was maintained (Fig. 1). Pembrolizumab treatment was continued every 3 weeks. Metastases continued to decrease after 12 cycles. In June 2017, the patient was still under treatment and metastases have been stable in size for 6 months. The patient did not have any of the known adverse side-effects of anti-PD-1 therapy such as pneumonitis, colitis, hepatitis, nephritis, rash, hypophysitis, thyroiditis, diabetes or infusion reaction. Immunohistochemistry was used in the melanoma and three different squamous cell carcinomas to analyse lymphocyte expression of CD3 and PD-L1 (Fig. 2).

Discussion

Here we report a parallel therapeutic response of metastatic melanoma and primary cutaneous carcinomas in a patient with XP treated with anti PD-1. A similar case of regression of melanoma lung metastases, multiple basal cell carcinomas and Bowen disease in a patient with XP type E using pembrolizumab has recently been reported by Hauschild et al.4 Recent publications have reported the efficacy of anti-PD-1 immunotherapy in nonmelanoma skin cancers (Table 1). The effect of anti-PD-1 immunotherapy has been reported for squamous cell carcinoma of the head and neck12 and anti-PD-1...
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immunotherapy has become a major treatment for squamous cell lung cancer.13

Eight XP complementation groups have been described [XP-A to XP-G and XP variant (POLH)] that correspond to the affected DNA repair gene. Seven of these genes, XPA to XPG, are involved in nucleotide excision repair, repairing UV-induced damage from DNA. The eighth gene, POLH, codes for DNA polymerase η, which is required for the replication of DNA containing unrepaired UV-induced damage.14

XP mutations cause DNA repair disorders that promote skin carcinoma, resulting in multiple early skin carcinomas (including melanoma and nonmelanoma skin cancers) with a high mutational load.13 A high mutational load is currently suggested as a predictive factor of tumour response to immune checkpoint inhibitors, tumours carrying a high mutational load being probably more inclined to express tumour neoantigens that are specifically recognized by T cells.10

In our patient, parallel regression of melanoma metastases and skin carcinomas were observed. We hypothesize that the XP may have been the field of skin carcinomas and melanoma carrying a high mutational load, which could participate in the therapeutic response of both the melanoma and skin carcinomas. Interestingly, we also observed that pembrolizumab-induced vitiligo pigmentation was preferentially observed on UV-exposed areas of the skin, once again suggesting a role of UV-induced mutations in the therapeutic response that was observed in this patient.

UV exposure not only induces DNA damage, but also skin immunosuppression.15 To our knowledge, no data have been reported on the role of UV-induced immune suppression in the development of skin carcinoma in patients with XP. In our patient, UV-induced immune suppression does not seem to be the major pathophysiological mechanism to explain the efficacy of the anti-PD-1 antibody.

In conclusion, we report the parallel therapeutic response of metastatic melanoma and multiple nonmelanoma skin cancers in a patient with XP treated with the anti-PD-1 antibody pembrolizumab. This observation suggests anti-PD-1 may be considered in patients with XP and metastatic melanoma in addition to advanced nonmelanoma skin cancer.

References


Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Appendix S1 References for Table 1.