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Eligibility criteria for programmed death receptor 1 inhibitors vs. real-world advice: a retrospective analysis of 69 patients with advanced cutaneous squamous cell carcinoma of the head and neck

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Dear Editor, Systemic treatment with programmed death receptor 1 (PD-1) inhibitors has been approved for patients with advanced cutaneous squamous cell carcinoma (cSCC) ineligible for curative surgery or radiation. The PD-1 inhibitors cemiplimab and pembrolizumab have shown promising response rates of 50% and 38·5%, respectively.[1,2] Experience of the use of PD-1 inhibitors in the treatment of cSCC of the head and neck region (cSCCHN) is limited. We hypothesized that PD-1 inhibitors would have a limited place in clinical practice, as a large proportion of patients with advanced disease are immunocompromised (e.g. organ transplant patients) and would have a contraindication for PD-1 inhibitors. Therefore, we analysed the proportion of our institutional cohort of patients with advanced cSCCHN who would theoretically be eligible for treatment with PD-1 inhibitors according to the eligibility criteria of the registration study and according to expected real-life eligibility criteria.

Patients with primary cSCCHN treated between 2000 and 2014 at the University Medical Center Groningen were retrospectively included. Patients diagnosed with nodal and/or distant metastatic cSCCHN or inoperable locally advanced cSCCHN (T3/T4 in the American Joint Committee on Cancer 8th edition classification system) were identified. Patients were deemed inoperable if surgery was decided against by the tumour board prior to treatment because of tumour size, expected loss of functionality or severely impaired condition of the patient. The reason for the decision not to operate was extracted from the tumour board notes in the electronic patient files.

Exclusion criteria in the registration study were categorized into absolute and relative contraindications based on clinical experience and the literature. Contraindications defined absolute were immunosuppression equalling ≥ 10 mg prednisolone, organ transplant other than kidney, and an Eastern Cooperative Oncology Group (ECOG) performance score > 2. Relative contraindications were organ failure,[3] autoimmune disease in the last 5 years,[4] brain metastases,[5] kidney transplant,[6] ECOG performance score = 2, malignancy in the past 5 years (unless treated with curative intent and no recurrence) and tumour location on eyelid or lip.[7]

Kidney transplant was considered a relative contraindication as opposed to other organ transplants, as graft rejection in kidney recipients (which may be induced by PD-1 inhibitors) does not influence overall survival.[6] Furthermore, although not preferable, kidney recipients with a failing graft could restart dialysis to replace renal function. The reason for exclusion of patients with tumours arising from the eyelid or lip is not stated in the protocol of the registration study. Furthermore, these patients may especially benefit from systemic therapy, as surgical excision will often cause a loss of functionality.

All analyses were performed at the patient level. In case of multiple tumours per patient the tumour with the highest stage was selected; in case of equal stages the tumour that developed first within the inclusion period was selected. Statistical analyses were performed using SPSS Statistics (v. 23·0; IBM, Armonk, NY, USA).

From the total of 770 patients with 1116 cSCCHNs, 164 patients had locally advanced tumours (21·3%), of whom 12 patients were deemed inoperable (1·6%). Metastatic disease occurred in 64 patients (8·3%), including 13 patients with

Table 1 Failed eligibility criteria for treatment with programmed death receptor 1 (PD-1) inhibitors in patients with inoperable locally advanced or metastatic cutaneous squamous cell carcinoma of the head and neck

Reason ineligible for PD-1 inhibitors, n (%)	Inoperable locally advanced or metastatic disease (n = 69)
Absolute exclusion criteria	
Immune suppression equalling ≥ 10 mg prednisolone	0
Organ transplant other than kidney	1 (1)
ECOG performance score > 2	3 (4)
Total absolute	4 (6)
Relative exclusion criteria[a]	
Organ failure	2 (3)
Autoimmune disease diagnosed or treated in the last 5 years	2 (3)
Brain metastases	1 (1)
Kidney transplant	3 (4)
ECOG performance score = 2	6 (9)
ECOG performance score unknown	10 (14)
Malignancy in the past 5 years (not treated locally)	3 (4)
Tumour location on eyelid or lip	16 (23)
Total relative	36 (52)

ECOG, Eastern Cooperative Oncology Group. [a]Some patients were ineligible for checkpoint inhibitors due to more than one reason, making the total number lower than when all separate criteria numbers are counted. If a criterion was unknown, the patient was considered unfit.

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distant metastasis. Seven patients had both locally advanced and inoperable, and metastatic disease, leading to a total of 69 patients [9·0%, median age 79 years (range 40–94), 50 (72%) men] with metastatic or inoperable locally advanced cSCCHN (Table 1). If only absolute contraindications were applied, 65 (94%) of these 69 patients would have been eligible for PD-1 inhibitors. Thirty-six patients (52%) were excluded due to relative contraindications, including one patient with both an absolute and a relative contraindication, leading to 30 (43%) patients fulfilling the study eligibility criteria.

The number of patients with cSCCHN rose over the years, as did the absolute number of patients who would have been eligible for PD-1 inhibitors. Further rises of incidence and numbers of eligible patients are expected in the future. Moreover, the role of PD-1 inhibitors might expand further if they can be used in the curative setting. Ongoing studies (NCT03833167 and NCT03969004) will assess the efficacy of adjuvant PD-1 inhibitors, and a study on neoadjuvant PD-1 inhibitors showed promising results.[8]

Limitations of our study are the retrospective nature, making the number of eligible patients hypothetical as patients were not actually treated with PD-1 inhibitors, and the subjective judgement of inoperability by the treating physicians, which could also have changed over time. Future research comparing real-life data on PD-1 treatment with the eligibility criteria of the registration study is necessary to confirm our results.

In conclusion, 9% of our patients with cSCCHN had advanced disease. The number of patients with advanced disease per year increased over time. A significant proportion of these patients would be eligible for treatment with PD-1 inhibitors.

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Lupus erythematosus and epidermal necrolysis: a case series of 16 patients

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Dear Editor, Epidermal necrolysis (EN), including Stevens–Johnson syndrome and toxic epidermal necrolysis (TEN), is usually induced by drugs. Prevalence of lupus erythematosus (LE) is higher in patients with EN than in the general population (1·2–2%).[1,2] Furthermore, flares of LE may present as EN (TEN-like LE).[3–5] We aimed to describe EN in patients with clinical or biological LE to better characterize the relationship between the two diseases.

We conducted a retrospective study in two departments of the French reference centre for EN. Our baseline routine investigations for all patients with EN include antinuclear antibodies (ANAs), anti-DNA antibodies and anti-ENA (extractable nuclear antigen) antibodies. Inclusion criteria were age > 18 years, EN diagnosed between 1 January 2014 and 21 December 2019, a history of LE and/or Sjögren syndrome (SS), and/or detection of autoantibodies: ANAs (titre ≥ 1 : 80), anti-DNA or anti-ENA antibodies. A culprit drug was retained with an ALDEN (algorithm of drug causality for EN) score ≥ 4.[6] Data were extracted from medical charts.

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