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Case Report

Durable Response of Short-term Low-dose Nivolumab in a Patient with Locally Advanced Cutaneous Squamous Cell Carcinoma: A Case Report

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Abstract

Treatment for locally advanced cutaneous squamous cell carcinoma (cSCC) involves extensive and disfiguring surgery. Moreover, systemic treatments such as chemotherapy and epidermal growth factor receptor antibodies are associated with significant side effects and have short response durations. We describe a durable response to low-dose (20 mg every 2 weeks) nivolumab in an extremely elderly patient with inoperable cSCC of the right cheek. Despite the low dose, a dramatic regression of the tumor was observed. However, the patient discontinued nivolumab after seven doses due to financial concerns. The tumor exhibited a durable response for over 2 years. This case highlights the potential for a significant and lasting response to immune checkpoint inhibitors in patients with cSCC.

Keywords: Advanced cutaneous squamous cell carcinoma, durable response, immune checkpoint inhibitor, low dose, nivolumab, short term

Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most frequent type of skin cancer.[1] Although surgical excision cures 95% of patients with cSCCs, a proportion of cSCCs remains inoperable or unresectable, leading to significant morbidity, disability, and death.[2] Therefore, inoperable/unresectable cSCCs are considered an indication for systemic treatment. However, few systemic treatment options are currently available. The most commonly used chemotherapeutic agent, cisplatin, has been reported to only achieve median progression-free survival (PFS) and overall survival (OS) rates of approximately 5 and 11 months, respectively.[3] Treatment with the epidermal growth factor receptor (EGFR) inhibitor, cetuximab, resulted in an objective response rate (ORR) of 28% and mean OS of 8.1 months in one previous study.[4] Therefore,

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advanced cSCCs present a life-threatening condition in patients treated with chemotherapy or EGFR monoclonal antibodies. Moreover, the duration of response to most treatments remains limited, and toxicities can be severe. Consequently, there is an urgent need for effective therapies in this scenario.

cSCCs are characterized by a high tumor mutational burden and elevated expressions of programmed death receptor-1 (PD-1) and its ligand (PD-L1).[5] Recently, owing to compelling evidence supporting the efficacy of cemiplimab and pembrolizumab in managing advanced cSCC,[6,7] the standard of care for advanced cSCC has become immune checkpoint inhibitors (ICIs), particularly those targeting PD-1.[8] Nivolumab, a fully human, highly selective monoclonal immunoglobulin G 4-kappa antibody targeting PD-1, is presently approved for treating patients with various solid tumors. Several independent prospective studies have shown that the response rates to nivolumab vary between 15% and 40%, demonstrating its ability to prompt sustained responses.[9,10]

Given the strong evidence indicating the potential efficacy of ICI strategies in treating advanced cSCC, we report the case of a patient with cSCC who was treated with nivolumab. After treatment, the patient achieved a complete and durable response.

Case Report

In May 2021, a 92-year-old woman noticed a progressively enlarging lesion on her right cheek. It had been present for more than 1 year and had recently been growing rapidly and bleeding. She presented to the dermatology department of our hospital in July 2021 [Figure 1a]. Her facial lesion presented as an erythematous, indurated, deep fixed plaque measuring 6 cm × 7 cm, accompanied by a cutaneous ulceration with a surrounding hyperpigmented border. A skin biopsy confirmed cSCC. Computed tomography (CT) [Figure 2a and b] also revealed an enlarged lobulated right para-parotid lymph node (2.2 cm), indicative of Level II lymphadenopathy. Positron emission tomography showed right facial cancer with metastasis to one lymph node of the right neck (Level II) without distant metastasis. Ultrasound-guided fine-needle aspiration of the right Level II neck lymph node was positive for metastatic SCC. She was diagnosed with cSCC of the right cheek, with ipsilateral level II neck nodal metastasis, and the lesion was staged as cT3N1M0.

Due to her old age and multiple underlying comorbidities, including Type 2 diabetes mellitus complicated by diabetic nephropathy, chronic kidney disease stage 4, dyslipidemia, and hypertension, surgical resection of the cSCC was contraindicated. Therefore, intravenous nivolumab (20 mg biweekly) was suggested by the medical oncologist considering factors such as efficacy, toxicity, and cost. No PD-L1 staining was performed, as PD-L1 expression would not have influenced the decision to use nivolumab in this case. The treatment was started in September 2021, with the administration of 20 mg nivolumab every 2 weeks, which was lower than the standard doses of 3 mg/kg, or 240 mg every 2 weeks, or 480 mg every month (the patient weighed 69.8 kg). The treatment course lasted for 14 weeks with a total of seven doses.

After only one administration of nivolumab, a significant improvement in the lesion was observed [Figure 1b] compared to the original condition. After two administrations, the size of the tumor had reduced further and ulceration continued to heal [Figure 1c]. Despite occasional complaints of itching (Grade 2) [Figure 1d], the patient maintained an energetic demeanor. After four administrations, the ulceration was totally covered by scab [Figure 1e]. By the fifth administration [Figure 1f], the tumor had flattened, with residual pigmentation around the edge. At the conclusion

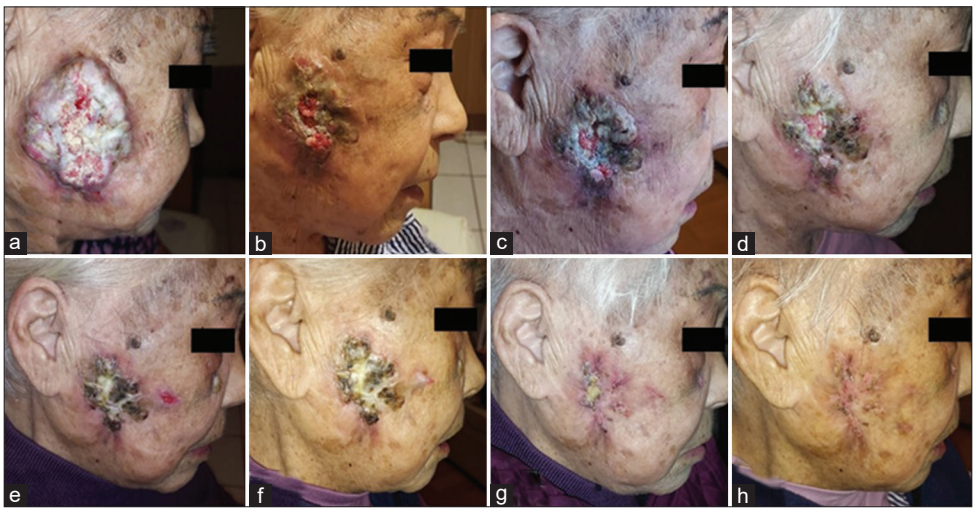

Figure 1: (a-h) The lesion in relation to treatment progression. (a) Lesion before initiation of nivolumab, (b) 2 weeks later, after 1 cycle of nivolumab, (c) 4 weeks later, after 2 cycles of nivolumab, (d) 6 weeks later, after 3 cycles of nivolumab, (e) 8 weeks later, after 4 cycles of nivolumab, (f) 10 weeks later, after 5 cycles of nivolumab, (g) 14 weeks later, after 7 cycles of nivolumab. The treatment stopped. (h) Six months after the beginning of treatment. Complete clinical remission after 7 cycles of nivolumab

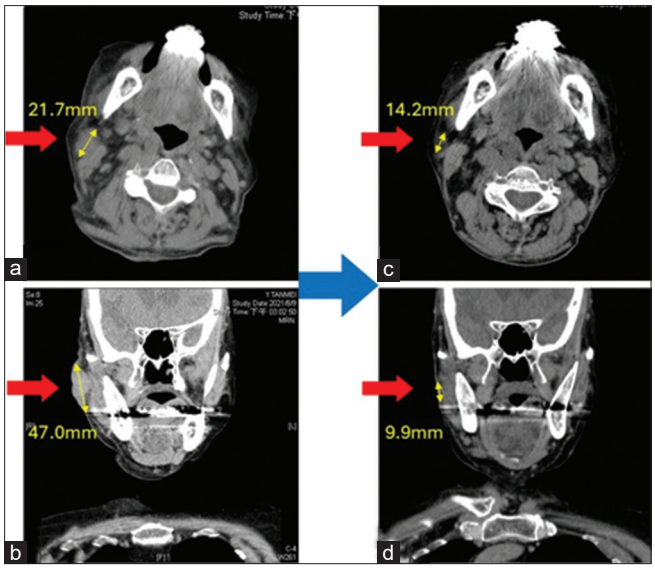

Figure 2: (a and b) Computed tomography of head and neck (H and N CT) before initiating nivolumab. A broad-based cutaneous plaque is noted on the right cheek. (c and d) H and N CT 6 months after the beginning of treatment. Partial remission is depicted by the reduction in tumor size of >75%. The arrows indicate the tumors

of the treatment (seven administrations) [Figure 1g] in December 2021, the lesion had halved in size compared to the original state. Surprisingly, 6 months later, in February 2022, the therapeutic effect of the drug remained effective. During follow-up, she achieved complete clinical remission with excellent cosmetic outcomes. The lesion had fully resolved and was covered with newly regenerated skin [Figure 1h]. Six months after the initiation of ICI therapy, a CT scan [Figure 2c and d] revealed partial remission of the right cheek SCC and the previously cytologically proven right level II metastatic node was no longer visible. She was scheduled for follow-up appointments every 3 months until August 2023, and showed a complete response with no recurrence observed after treatment. No significant adverse events, such as endocrinopathy, skin rashes, or organ dysfunction, were observed during treatment.

Discussion

Local resection has traditionally been the primary intervention for cSCC. However, in our case, local resection was contraindicated because of the patient's old age and multiple comorbidities. Treatment with low-dose nivolumab resulted in the significant achievement of a complete response, with a durable response for more than 2 years while preserving facial integrity. This case report provides evidence for the effectiveness of low-dose nivolumab in an elderly patient with locally advanced cSCC.

Similar results were observed in the MATISSE trial,[11] a phase II study focusing on patients with T1-4N0-3M0 or TxN1-3M0 cSCC who were suitable candidates for extensive and/or disfiguring surgery. After only two infusions of neoadjuvant ICIs, whether as two doses of nivolumab or nivolumab plus ipilimumab, 9 out of 50 patients demonstrated organ preservation and durable complete remission without the need for extensive or disfiguring curative surgery and/or RT. Another phase II study[12] included 24 systemic treatment-naive patients with locally advanced or metastatic cSCC who were treated with nivolumab 3 mg/kg intravenously every 2 weeks until disease progression, unacceptable toxicity, or 12 months of treatment. After a median follow-up of 17.6 months, the study demonstrated an ORR of 58.3% at 24 weeks, with a disease control rate of 79%. The median PFS was 12.7 months, and the estimated median OS was 20.7 months.

The present case demonstrates the efficacy and safety of low-dose nivolumab (20 mg) for the management of advanced cSCCs. In a randomized study[13] involving 151 patients with recurrent or newly diagnosed advanced head-and-neck SCC receiving palliative treatment, the addition of low-dose nivolumab (20 mg) to triple metronomic chemotherapy significantly improved the outcomes. Accumulating evidence suggests the effectiveness of low-dose nivolumab across certain cancer types, including nonsmall cell lung cancer (NSCLC),[14] renal cell carcinoma (RCC),[15] and advanced hepatocellular carcinoma (HCC).[16] In a cohort study focusing on low-dose nivolumab in patients with advanced HCC, 20 mg of nivolumab was found to be an independent prognostic factor for improved PFS, with all 78 patients tolerating nivolumab without grade 3–4 toxicities.[16] Yoo *et al*.[14] studied 47 patients with NSCLC who received either a low dose (20 or 100 mg) or standard dose (3 mg/kg) of nivolumab, and reported no statistical differences in ORR (13.8% vs. 16.7%), PFS (3.0 months vs. 1.0 months), and OS (12.5 months vs. 8.2 months) between the low-dose and standard-dose groups. In another study[15] focusing on RCC, no significant differences in ORR (50.0% vs. 43.8%), PFS (7.0 months vs. 7.0 months), and OS (not reached vs. 28.0 months) were observed between patients receiving a low dose (1.7 mg/kg) and standard dose (2.7 mg/kg). The findings of no significant differences in ORR, PFS, or OS in these three studies indicate the potential advantages of implementing low-dose nivolumab in clinical practice. Moreover, considering that lower doses result in reduced costs, also termed financial toxicity, low-dose nivolumab appears to be a viable treatment option, both clinically and economically.

The response of our patient to nivolumab was persistent. However, the ideal treatment duration remains unclear, and prolonged disease control beyond treatment cessation has been demonstrated in other solid tumors, particularly melanoma.[17] In two phase II trials of cemiplimab treatment in patients with advanced cSCCs, 22 of 29 responders with metastatic cSCCs[18] and 12 of 34 patients with locally advanced cSCCs had a duration of response of 12 months or more.[7] Regarding pembrolizumab, among a cohort of 36 patients with a confirmed disease response, approximately two-thirds (69%) had a durable responses for longer than 6 months.[6,19] For nivolumab, one case report[20] also described

a durable complete response of up to 6 months after cessation in a patient with oral SCC who presented with lung metastasis.

In conclusion, the management of locally advanced and metastatic cSCC continues to pose challenges. Chemotherapy and targeted agents against EGFR are hindered by their relatively short duration of response and occurrence of adverse effects, which can be particularly challenging given the frailty of many elderly patients. In contrast, ICIs, including nivolumab, can provide robust antitumor activity, prolonged response, and good tolerability in systemic treatment-naive patients with advanced cSCC. In the MATISSE study,[11] ICIs showed promising efficacy in organ preservation and durable complete response without the need for extensive or mutilating curative surgery and/or RT. Therefore, this treatment can provide a potential therapeutic option and avoid surgery and its associated complications and morbidity, even in younger patients with locally advanced cSCC.

Ethical approval

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and its amendments. This study was approved by the Institutional Review Board of Linkou Chang Gung Memorial Hospital (protocol number: IRB 202400760B0, and date of approval: May 13, 2024).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

Prof. Chiao-En Wu, the editorial board member at *Journal of Cancer Research and Practice*, had no role in the peer review process of or decision to publish this article. The other author declared no conflicts of interest in writing this paper.

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