Research Paper

Immune Checkpoint Inhibitor Therapy as a Novel and Effective Therapy for Aggressive Cutaneous Squamous-cell Carcinoma

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Abstract

Programmed cell death protein 1 (PD-1) blocking agents were found to have impressive and durable response rates in 18 patients with surgically unresectable or metastatic cutaneous squamous-cell carcinoma.

Background: Patients with metastatic or locally aggressive cutaneous squamous-cell carcinoma (cSCC) have historically had limited and noneffective treatment options. The mainstay treatment has been surgery, which can be disfiguring and may not be technically feasible for larger lesions. **Patients and Methods:** A retrospective review of 18 patients treated with nivolumab (n = 17) or pembrolizumab (n = 1) anti–programmed cell death protein 1 (PD-1) inhibitors for metastatic or locally advanced cSCC from March 2015 to present was performed. **Results:** Three patients had metastatic disease, 5 patients had locally aggressive plus regional nodal disease, 8 patients had locally advanced disease, and 2 had multifocal skin disease. Seventeen patients had undergone at least 1 surgery, 12 also had received radiotherapy, 8 had disease that had failed to respond to other systemic treatments, and 2 had chronic lymphocytic leukemia. Of 18 patients treated, 14 had dramatic responses with improvement in clinical symptoms and impressive tumor reduction with equally impressive duration. Objectively, 4 patients had complete response, 10 had partial response, 3 had stable disease, and 1 patient had progression of disease. Three patients died, 1 from an ischemic cerebrovascular incident possibly related to treatment, 1 likely not related to neither treatment nor disease, and 1 due to disease progression. Therapy was otherwise well tolerated, and 10 patients currently continue to receive the therapy. Thirteen patients continue to have stable or no new disease at a median time of 12 months since the start of treatment. **Conclusion:** PD-1 blocking agents may provide clinically meaningful and palliative therapy for patients with aggressive cSCC who are not surgical candidates.

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Introduction

Cutaneous squamous-cell carcinoma (cSCC) is the second most common type of skin cancer in the United States.[1] More than 1 million cases of cSCC are diagnosed in the United States each year.[2] Between 40% and 50% of Americans who live to age 65 will have either basal-cell carcinoma or squamous-cell carcinoma (SCC) at least once.[2,3] Conventional surgical excision is curative in as many as 95% of cases.[4] However, local recurrence can be as high as 12% in high-risk patients, and metastases are reported to be about 2% to 5% overall.[5,6] Effective treatment for recurrent disease, metastatic disease, or primary disease not amenable to surgery can be challenging. Radiation can control recurrent cSCC in about 50% of patients.[6] However, radiation does not affect overall mortality from recurrent disease, and it certainly would not be advocated in those with metastatic disease.[6] The presence of distant metastases is associated with dismal prognosis and median survival less than 2 years.[5-10] Systemic chemotherapies such as cisplatin result in a complete response (CR) of only about 20% and have associated toxicities.[7,8] Finally, the epidermal growth factor receptor (EGFR) inhibitor cetuximab had a response rate of only 28% when studied

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in a phase 2 trial of patients with advanced cSCC, with nearly all patients experiencing relapse within 2 months.[9] Thus, there persists a need for more effective and durable therapy.

One well-known risk factor for the development of cSCC is immunosuppression.[10] Specifically, immunosuppression after solid organ transplantation is well known to increase the risk of cSCC.[11,12] Recent data also show a higher prevalence of human papillomavirus in cSCC from immunosuppressed patients compared to immunocompetent patients.[13] Therapies blocking the immunosuppressive component of cSCC seem logical. Recently, immune checkpoint inhibitors such as ipilimumab, a CTLA-4 inhibitor, and anti–programmed cell death 1 protein 1 (PD-1) agents including nivolumab and pembrolizumab have revolutionized the treatment of metastatic melanoma by blocking tumor-induced immunosuppression.[14] Two trials of anti–PD-1 therapy in recurrent head and neck SCC of the oral cavity, pharynx, or larynx that was not amenable to curative treatment have been published with good results.[15,16] Treatment of locally recurrent and/or metastatic cSCC with PD-1 inhibitors has been tried in a few cases, but data are still extremely limited.[17-19] Here we report our use of PD-1 inhibitory therapy in patients with locally aggressive or metastatic cSCC.

Methods

We identified 18 patients with cSCC not amenable to additional surgical resection who were treated with nivolumab (n = 17), or pembrolizumab (n = 1), both PD-1 inhibitors. Data were collected about patients' demographics, previous treatments, dates of therapy, response to therapy, Foundation One results, and follow-up. The institutional review board approved this study. Foundation One is a validated comprehensive genomic profile that interrogates the entire coding sequence of 315 cancer-related genes plus select introns from 28 genes often rearranged or altered in solid tumor cancers.[20] Nivolumab was dosed at 3 mg/kg every 2 weeks, then changed to 3 mg/kg every month if a patient experienced CR or dramatic partial response (PR) with adverse effects such as fatigue. Pembrolizumab was dosed also at 2 mg/kg every 3 weeks. Patients were seen every 4 to 6 weeks to monitor toxicities with thyroid-stimulating hormone and complete blood counts checked every 3 to 4 weeks.

We utilized immune-related response criteria whereby CR is complete disappearance of all lesions (whether measurable or not, and no new lesions) with confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented.[21] PR is a decrease in tumor burden $\geq$ 50% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation. Stable disease (SD) does not meeting the criteria for CR or PR in the absence of progressive disease (PD). PD is an increase in tumor burden $\geq$ 25% relative to nadir (minimum recorded tumor burden) confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented.[21] Common Terminology Criteria for Adverse Events version 4 were used to assess toxicity.[22]

Results

At time of treatment initiation, 3 patients (17%) had metastatic disease (lung), 8 (44%) patients had locally advanced disease, 5 patients had locally advanced plus regional lymph node disease (28%), and 2 patients (11%) had multifocal squamous-cell malignancies (hands, legs, arms, and chest) not amenable to surgical resection. Patients were treated with nivolumab (n = 17) or pembrolizumab (n = 1). Patient characteristics are listed in Table 1. Seventeen patients had at least 2 prior surgeries, which comprised wide local excisions (n = 35), lymph node dissections (n = 6), parotidectomies (n = 3), left eye enucleation (n = 1), and left auriculectomy (n = 1). Twelve patients (67%) had radiotherapy, and 8 (44%) had disease that had failed to respond to other systemic therapies, including 3 whose disease failed to respond to cetuximab. Two patients also had a history of chronic lymphocytic leukemia (CLL). The median time from initial cSCC diagnosis to treatment start was 24 months (range, 2.5 months to 14 years). Foundation One profiling was performed in 6 patients. All 6 patients had a reported *TP53* mutation, 4 of 6 had a *CDKN2A* mutation, and 4 of 6 had reported *notch1* or *notch3* mutations. The median number of reported mutations per patient was 5 (range, 4-9).

In total there were 4 CRs, 10 PR, 3 SD, and 1 PD, as shown in Table 2. There appeared to be no correlation between reported mutations and response in the 6 patients with available data. The median time from treatment initiation to an observed response was 2.7 months. The median duration of response (PR + CR) was 12 months. Thirteen patients continue to have ongoing response. Overall, 10 of 18 patients continue to receive therapy, and 13 of 18 continue to experience no progression of disease at a median of 12 months since the start of treatment.

Four CRs occurred in patients with locally recurrent disease at the following sites: 2 ear, 1 scalp, and 1 temple area. Examples of 2 patients with CR are shown in Figure 1. Patient 1 in Figure 1 also had concurrent CLL. Of patients with CR, 2 patients continue to receive therapy with no disease at 10 months, 1 patient with CLL stopped therapy after 7 months as a result of toxicity occurring in combination with CLL therapy but has no new cSCC disease (patient 1), and 1 patient with a CR chose to stop therapy after 13 months and has had no recurrence.

Table 1 Characteristics of 18 Patients

Characteristic	Value
Gender	
Female	8
Male	10
Age, y, median (range)	77 (55-91)
No. of previous surgeries, median (range)	3 (0-6)
Time from initial diagnosis to treatment start, median (range)	24 months (2.5 months to 14 years)
Prior skin grafts	10 (59%)
Prior radiotherapy	12 (67%)
Prior systemic therapy	8 (44%)
History of lymph node involvement	6 (33%)
Metastatic disease	3 (17%)
Locally recurrent disease	8 (44%)
Multifocal disease	2 (12%)