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Real-World Experience With Cemiplimab in Advanced Cutaneous Squamous Cell Carcinoma

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Abstract

Background: Cutaneous squamous cell carcinoma (cSCC) is the second most common nonmelanoma skin cancer in Canada. However, few real-world reports exist on the treatment of refractory locally advanced (LA) and metastatic cSCC with cemiplimab to date.

Objectives: The objective of this study was to characterize the demographic and clinical outcomes of advanced cSCC patients on cemiplimab in a real-world setting.

Methods: Retrospective analysis of adult patients with refractory LA and metastatic cSCC treated with cemiplimab at the London Regional Cancer Program in Canada. Patient demographics and treatment characteristics were reported, as well as Kaplan-Meier estimates of progression-free survival (PFS) and overall survival (OS).

Results: Forty patients were included in this study. Sixteen (40%) had LA disease and 24 (60%) had metastatic disease. Median treatment duration was 3.5 months (range: 0.6-29.4 months). Kaplan-Meier analyses of the entire study population revealed that the median OS was not reached [NR; 95% confidence interval (CI) 9.1 months-NR], but median PFS was 11.5 months (95% CI 7.0 months-NR). A total of 25% of patients experienced at least one adverse event from cemiplimab. Reasons for treatment discontinuation were death from any cause (25%), disease progression (15%), cemiplimab adverse events (5%), and other causes (15%).

Discussion: The 12 month estimates of OS and PFS were lower than pivotal phase I and II clinical trials. However, toxicity was tolerable. Cemiplimab remains a safe and effective therapy in patients with refractory LA and metastatic cSCC disease.

Keywords

cancer, immunotherapy, squamous cell carcinoma

Introduction

In Canada, over 75,000 Canadians are diagnosed with non-melanoma skin cancer (NMSC) annually.[1] Of the NMSC subtypes, cutaneous squamous cell carcinoma (cSCC) is the second most common after basal cell carcinoma.[1,2] About 1 in 20 Canadians will be affected by cSCC in their lifetime,[1,2] and risk factors include older age, smoking, exposure to ultraviolet light, immunosuppressive treatments, photosensitizing drugs, radiation, and other industrial carcinogens. Most important, evidence suggests that the incidence rates of cSCC are increasing rapidly worldwide, especially in light-skinned populations.[3] Although localized cSCC is the most common presentation of the disease and is often highly curable, locoregional or distant metastases develop in approximately 1% to 5% of cases.[4] For those in whom metastatic disease occurs, prognosis remains poor with a 5 year mortality of approximately 80% to 90%.[5-8]

Historically, systemic treatment of incurable locally advanced (LA) and metastatic cSCC has been limited to chemotherapy or EGFR-targeted treatments (eg, cetuximab), alone or in combination with radiation therapy or surgery where appropriate.[8,9] However, these systemic therapies have been only modestly effective, warranting exploration of

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other arms of disease management in this setting. cSCC has a high tumor mutational burden relative to other solid tumors,[10] which has been associated with higher rates of response to immune checkpoint inhibitors, presumed due to their increased neoantigen load.[11,12] Cemiplimab is a high-affinity, human immunoglobulin G4 (IgG4) monoclonal antibody to the programmed cell death-1 (PD-1) receptor that blocks interactions of PD-1 with programmed death-ligand 1 and 2 (PD-L1 and PD-L2).[13] It has shown efficacy in cornerstone phase 1/2 clinical trials, with response rates of approximately 50%.[14] In the metastatic cohort of the phase 2 study, estimated 12 month PFS was 53% [95% confidence interval (CI) 37-66], and estimated 12 month OS was 81%.[14] By contrast, in the paired phase 2 trial with LA patients, estimated at 12 month PFS was 58% (95% CI 44-70), and estimated 12 month OS was 93% (95% CI 84-97).[15]

Cemiplimab has since been approved by Health Canada for the treatment of refractory LA or metastatic cSCC unfit for curative-intent surgery or radiotherapy, and is currently the only immune checkpoint inhibitor approved in Canada for this indication. However, despite the evidence for cemiplimab in this patient population and the exploration of efficacy of other immune checkpoint inhibitors in this setting,[16,17] real-world data regarding response rates and survival outcomes remain limited. We herein report a retrospective single-centre analysis of patient outcomes with unresectable and metastatic cSCC. This objective of this study was to describe our local experience with cemiplimab in the treatment of cSCC over a 12 year period with a focus on demographic characterization, treatment outcomes, and adverse events. The goal of this report is to provide data supporting continued research on this deadly disease.[5-8]

Methods

We performed a retrospective observational cohort study of adult patients with LA or metastatic cutaneous SCC at the London Regional Cancer Program. Inclusion criteria were the presence of histologically confirmed cSCC, treatment with cemiplimab between January 1, 2011, and October 15, 2022, and having an age of at least 18 years at the time of systemic treatment. Cemiplimab was initially provided by a pharma-sponsored patient support program (Sanofi Canada), and subsequently by the Ontario Health New Drug Funding Program. This study was approved by the Western Research Ethics Board. All methods were reported in keeping with STROBE criteria.[18]

The following data were collected for each patient: age; sex; height, weight, and disease staging at treatment initiation; past medical history including the presence/absence of immunosuppression; date, histologic characteristics, and anatomic location of biopsy confirming cSCC preceding cemiplimab treatment; date(s) of cemiplimab initiation and discontinuation; date(s) of any surgery or radiation performed after cemiplimab initiation; adverse events; date of last follow-up; and last known survival status including cause of death if known. For disease staging at treatment initiation, the AJCC eighth edition staging system[19] for squamous cell carcinoma was used as a template to characterize the extent of disease. Localized disease was defined as T1-4N0M0, regional disease as TXN1-3MX, and metastatic disease as TXNXM1. LA patients were considered as those with local or regional disease unsuitable for and/or incurable with further surgical and/or radiation therapy.

Adverse events documented in clinical notes were graded in accordance with CTCAE v5.0. Statistical analyses were completed in Excel, and corresponding Kaplan-Meier analyses were completed using R.[20] All data were stored in a secure electronic database (REDCap[21]). All background literature searches were completed using a building-block search strategy in PubMed across all years up to and including January 23, 2023, primarily to identify existing real-world studies of immune checkpoint inhibitor therapies in advanced cSCC.

Results

Patient Demographics

Between January 1, 2011 and October 15, 2022, 40 patients were treated with cemiplimab. 16 patients (40%) had incurable LA disease (stages I-III), and 24 (60%) had metastatic disease (stage IV) at the initiation of cemiplimab therapy. The median age was 74.3 years (range: 33-92 years). A total of 29 patients were male (72.5%) and 11 (27.5%) were female. A total of 9 patients (22.5%) were immunosuppressed. Of them, 5 had rheumatoid arthritis and were all on iatrogenic immunosuppression (12.5%), 3 had received prior solid organ transplants and were iatrogenically immunosuppressed (7.5%), and 1 had CLL and was intrinsically immunosuppressed (2.5%). One patient (2.5%) had inflammatory bowel disease (IBD), but was not immunosuppressed. At the cutoff date of analysis, median duration of treatment with cemiplimab was 3.5 months (range: 0.6 -29.4 months). During or after the completion of cemiplimab immunotherapy, 6 patients (15%) underwent radiotherapy and 4 patients (10%) received surgery. Additional demographic and treatment metrics have been summarized in Supplemental Tables S1 and S2.

Progression-Free Survival and Overall Survival

In the entire study population, the median OS was not reached (NR; 95% CI 9.1 months-NR); the median PFS was 11.5 months (95% CI 7.0 months-NR). The estimated probability of OS at 12 months for all patients was 63.8% (95% CI 48.4%-84.3%), and estimated probability of PFS at 12 months was 46.1% (95% CI 30.4%-69.9%; Figure 1B and D). When the populations were stratified by stage, the median OS was NR (95% CI 17.3 months-NR) for LA patients, and NR (95%

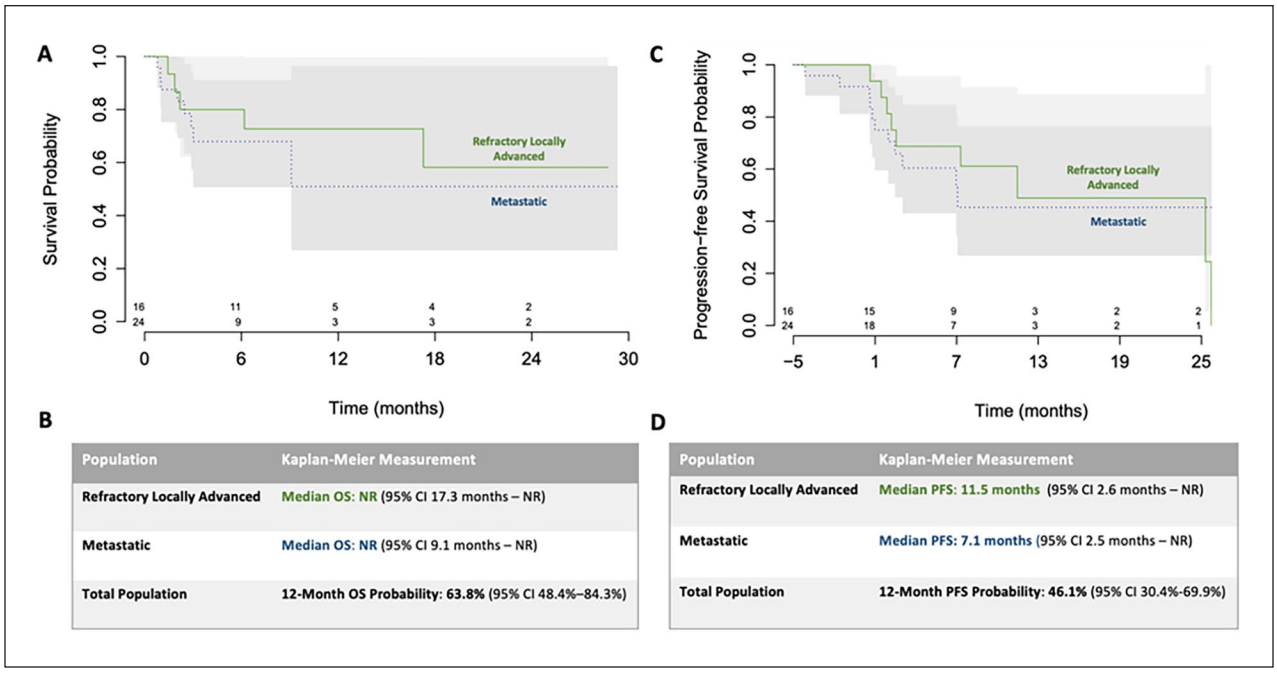

Figure 1. (A) Kaplan-Meier analyses of OS, stratified by refractory LA versus metastatic disease at the time of treatment initiation. (B) Kaplan-Meier median OS for refractory LA and metastatic disease, as well as estimated 12 month probability of OS in the total population. (C) Kaplan-Meier analyses of PFS, stratified by refractory LA versus metastatic disease. (D) Kaplan-Meier median PFS stratified by stage, as well as estimated 12 month PFS probability in the total population. OS, overall survival; LA, locally advanced; PFS, progression-free survival.

CI 9.1 months-NR) for metastatic patients (Figure 1A). Median PFS was 11.5 months (95% CI 2.6 months-NR) and 7.1 months (95% CI 2.5 months-NR), respectively (Figure 1C). At the time of study cutoff, 15 patients (37.5%) had died from any cause.

Safety and Treatment Discontinuation

Therapy with cemiplimab was generally very well tolerated, with 75% of patients (n = 30) experiencing no reported adverse events related to cemiplimab. Ten patients (25%) experienced at least one adverse event from cemiplimab, for which their worst adverse event outcome was distributed as 4 grade I patients (10%), 5 grade II patients (12.5%), and 1 grade III patient (2.5%). Of these 10 patients, 9 were alive or censored at the time of study cutoff. Distribution of adverse events in these patients were 4 (10%) experiencing a rash, 4 with arthritis (10%), 1 had pruritis (2.5%), 1 had diarrhea (2.5%), 1 had weakness (2.5%), and 1 had hypothyroidism (2.5%). Of the patients with an underlying autoimmune condition, 4 out of the 5 of the patients with rheumatoid arthritis (80%) experienced a flare of arthritis on therapy, whereas the single patient with IBD did not experience a flare of their disease (0%). Among the 3 solid organ transplant patients, none experienced a rejection of their transplant due to cemiplimab. No patient deaths were directly attributable to cemiplimab therapy.

Patients were considered to have discontinued treatment if they stopped or suspended therapy for any reason. The most common reason for treatment discontinuation was death from any cause, which occurred in 10 patients (25%). Six patients (15%) stopped treatment due to disease progression. Two patients (5%) stopped treatment due to side effects; both of these patients had underlying rheumatoid arthritis. Six patients (15%) had to stop treatment for other reasons, such as a new or worsening existing comorbidity or a treatment break due to radiographic and observational clinical complete response.

Discussion

A small minority of patient with cSCC develop incurable local recurrence or metastatic disease.[1,2,22] Cemiplimab has demonstrated benefits for disease control in these patients and is Health Canada approved for this indication. However, benefits seen in clinical trials may not always generalize well to real-world practice. Our retrospective cohort study aims to help interrogate real-world outcomes in this patient population from the London Regional Cancer Program in Ontario, Canada.

Overall and PFS were lower in our patient cohort than reported in cemiplimab phase I/II clinical trials.[14,15] The estimated 12 month OS and PFS probabilities were 63.8% (95% CI 48.4%-84.3%) and 46.1% (95% CI 30.4%-69.9%),

respectively. Migden et al[14] reported estimated 12 month OS 81% (95% CI 68-89),[14] and estimated 12 month PFS was 53% (95% CI 37-66)[14] for the metastatic cohort of their phase II study. The 12 month OS and PFS estimates for LA patients in the subsequent phase II study were even higher.[15] It is not surprising that outcomes were somewhat better than we observed in our real-world cohort. Clinical trials typically represent a highly selected population skewed toward better overall health, and patients with immunosuppression, concurrent malignancies, or lower performance status are usually excluded. In our study, the median age was similar to the phase I/II studies, but the age range of our patients was broader, almost a quarter of patients were immunosuppressed, fewer patients had well-differentiated histology, and more had a lower performance status; lower estimated 12 month PFS and OS outcomes were not unexpected.

However, toxicity was similar to that observed in the pivotal phase I/II trials,[14,15] with only 2 patients (5%) requiring treatment discontinuation due to side effects; both of these patients had underlying rheumatoid arthritis. By comparison, Migden et al in 2020[15] reported a treatment discontinuation rate of 8% due to adverse events from therapy. Discontinuation rates due to adverse events from cemiplimab or similar PD-1 inhibitors in advanced cSCC patients range from 6.6%[23] to 40.9%.[24] No deaths were directly attributable to cemiplimab in our cohort, which was lower than the 3% rate of treatment-emergent death in the study of Migden et al in 2020,[15] and a 3% to 5% treatment-related death rate in the study of Migden et al in 2018.[14] We recognize that our toxicity data are limited by retrospective collection, and may under estimate adverse effects of cemiplimab in our study population.

To date, 3 other published real-world studies have reported the efficacy and/or safety cemiplimab in patients with advanced cSCC.[23-25] Of these, only one has analyzed survival outcomes[23]; in this study, the median PFS was 16 months and median OS was 18 months.[23] This could be partly accounted for by the fact that 83% of the patients had LA cSCC,[23] a higher proportion than both our cohort (60%) and the phase I/II trials.[14,15] However, our report is among the first reporting Canadian patients, and is one of only a few published real-world studies to date. As cSCC is usually cured with local therapy, more data are needed to improve our understanding of treatment of this uncommon population with cemiplimab immunotherapy.

Limitations of our study include its small sample size and retrospective nature. We have also not reported objective response rates. Although some definitions of disease response have been proposed, such as the composite response criteria used by Migden et al in 2018,[14] there remains no formal consensus at this time. Furthermore, radiographic and clinical reporting in patient charts in this study collected retrospectively was widely variable. Efforts to standardize the definition of response in this disease site would undoubtedly afford improved accuracy in cross-trials comparisons of outcomes. Notwithstanding these limitations, the work presented herein offers crucial insights into the application of cemiplimab in a real-world setting.

A prospective collection of real-world data for this patient population is actively underway at our centre. This is anticipated to generate a more comprehensive and precise dataset that will expand the demographic and clinical metrics collected, helping to address some of the limitations inherent to this retrospective study. Collaboration with other centres to generate larger sets of real-world data would offer even more robust insights into the efficacy, safety, and accessibility of cemiplimab in cSCC patients in Canada. Indications for the use of cemiplimab for cSCC may expand as benefits or cemiplimab neoadjuvant therapy in LA surgically resectable cSCC have recently been reported.[26] Last, expanding the scope to include other immunotherapies that have been validated in this setting such as pembrolizumab[27] and nivolumab[28] would be of value. In conclusion, cemiplimab remains a safe and effective systemic treatment in patients with refractory LA and metastatic cSCC disease, and should be considered as a standard of care option in this population.

Declaration of Conflicting Interests

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Research Data

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Supplemental Material

Supplemental material for this article is available online.

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