Journal of Geriatric Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

journal homepage: www.elsevier.com/locate/jgo

Research Letter to Editor

Early discontinuation of cemiplimab in patients with advanced cutaneous squamous cell carcinoma

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ARTICLE INFO

Keywords:
Non-melanoma skin cancer
Skin cancer
Anti-PD-1
Cemiplimab
Cutaneous squamous cell carcinoma
CSCC
Immune-checkpoint inhibitor

1. Introduction

Cutaneous squamous cell carcinoma (CSCC) is the second most common malignancy [1]. The main risk factors are chronic sun exposure, age, fair skin phototype, and immunosuppression (immunosuppressive therapy for autoimmune disease, hematologic malignancy, solid organ transplantation and HIV infection) [1].

In most cases the prognosis is good [2], however, especially in immunocompromised patients with multiple concomitant diseases and unfavourable social conditions, CSCC may present in an advanced form, requiring systemic therapy [1,2].

Three phase 2 studies demonstrated the efficacy of anti-PD-1 agents in the treatment of advanced CSCC [2]. The EMPOWER-CSCC-1 trial demonstrated the safety and activity of cemiplimab in over 200 patients with an overall response rate (ORR) of more than 50%, with a significant improvement in patient-reported outcomes (PROs) [3–5]. In the phase 2 CARSKIN and KEYNOTE-629 trials, a total of 57 and 105 patients received pembrolizumab, respectively, with disease control rates (DCR) of about 50% in both studies [6,7]. The planned protocol duration of these treatments was up to 24 months [3,6,7].

Patients presenting with advanced CSCC are likely to be older adults with many comorbidities and often lacking financial, social, and family-supporting resources, and therefore unlikely to adhere to treatment [2]. Therefore, there is a need to understand whether treatment with anti-PD-1 for advanced CSCC can be discontinued earlier in real-life clinical practice, when the best response is obtained.

We conducted a retrospective analysis of patients with advanced CSCC treated at the IRCCS Ospedale Policlinico San Martino (Genoa, Italy) to evaluate the occurrence of progressive disease (PD) after discontinuation of cemiplimab upon achieving a response. The aim of our study was to better understand whether a shorter exposure time to cemiplimab therapy could be still associated with a long-term maintenance of response.

2. Methods

We retrospectively reviewed data of all patients with histologically confirmed locally advanced or metastatic CSCC treated with cemiplimab at our Institution from August 19, 2019, to August 8, 2022. The cut-off date of follow-up was December 31, 2022. Ethical approval by our Local Ethics Committee was obtained.

Patients treated with cemiplimab were those who were ineligible for

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https://doi.org/10.1016/j.jgo.2023.101640
Received 23 March 2023; Received in revised form 29 August 2023; Accepted 27 September 2023

radical surgery or radiotherapy after a multidisciplinary decision. The clinical response was assessed radiologically according to the RECIST 1.1 criteria [8], or clinically according to the WHO criteria [9]. Patients underwent individualised reassessment according to the site of the tumour, its superficial extension on the skin, or deep extension in the surrounding tissues, according to the feasibility of undergoing an iodinated contrast scan or according to the compliance of each patient. Based on these characteristics, patients were monitored via CT scan, MRI, or clinical photography. Clinical lesions were considered measurable if their superficial extension on the skin (as nodules and/or palpable lymph nodes) was at least 10 mm in diameter. Patients were clinically examined at each cycle of cemiplimab. Patients received follow-up clinical visits and radiological assessments as per clinical practice, according to patients' characteristics and to their compliance, every four to six months, even after discontinuation of cemiplimab.

3. Results

3.1. Patients' Characteristics

A total of 48 patients were treated with cemiplimab starting on August 19, 2019. Patients' characteristics are summarized in Table 1. The median age was 82 years, most patients had a good Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 1 (only one patient had ECOG performance status of 2). The patients included in our case series were in overall good physical condition, according to the geriatric assessment domains, with a median modified Katz Activities of Daily Living (ADL) Scale of 5 (out of a maximum score of 6) [10]. However, a total of 12 patients (25%) had social, economic, or psychological characteristics of frailty. About 25% of the patients had a remarkable medical history of immunosuppression due to haematological malignancy ($n = 7$), solid organ transplantation ($n = 1$), history of chronic immunosuppressive therapy secondary to autoimmune disease ($n = 2$), or HIV infection (n = 1).

About 80% of patients had locally advanced CSCC ($n = 38$), while 20% had metastatic CSCC ($n = 10$). The body areas involved were mainly the head and neck region ($n = 41$), trunk (n = 4), perineal region ($n = 2$), and lower limbs (n = 1).

About 40% of patients had received previous treatment with surgery ($n = 21$), 15% with radiotherapy ($n = 6$), and a total of four patients had undergone both surgery and radiotherapy. Two patients were pretreated with capecitabine: in one case the patient had also undergone surgery, and in the other the patient had also received prior radiotherapy.

Table 1
Patients' characteristics.

Characteristics	No. of patients (% or range)
No. of patients	48
Patient	
Median age	82 (53–98)
Male sex	33 (69)
ECOG PS 0	22 (46)
ECOG PS 1–2	26 (54) PS ECOG 2 = 1 patient
Chemotherapy history	2 (4)
Radiotherapy history	6 (13)
Previous surgery	21/22 (95); 26 unknown
Treatment naive	41 (85)
Immunosuppression	12 (25)
Hematologic malignancies	7 (15)
Immunosuppression for solid organ transplant	1 (2)
Immunosuppression for autoimmune disease	2 (4)
Chronic kidney disease	1 (2)
HIV infection	1 (2)
Tumour	
Locally advanced	38 (79)
Metastatic	10 (21)
Anatomic region	
Head & neck	41 (86)
Trunk	4 (8)
Upper/lower limbs	1 (2)
Perineal/genital region	2 (4)

Table 1. Baseline characteristics of the included patients.
ECOG PS: Eastern Cooperative Oncology Group Performance Status.

3.2. Treatment with Cemiplimab

Details on treatment with cemiplimab are summarised in Supplementary Table 2. Fig. 1 shows the patients' profiles. At the cut-off date, nine patients were still on treatment, 17 patients were alive without treatment, and 22 patients had died.

Median time of treatment with cemiplimab was 6.2 (0–31.6) months, with an ORR of 68% and a DCR of 78%. Median time to partial response (PR) was 2.8 (0.6–19.1) months.

Three patients discontinued treatment due to an adverse event. All of them achieved a response, but in one patient, the adverse event was fatal.

Among patients who did not have a PD ($n = 28$), nine were continuing treatment with cemiplimab at the cut-off date, while therapy was discontinued permanently in 19 cases, as shown in the swimmer plot (Supplementary Fig. 2). The reasons for treatment discontinuation were adverse events ($n = 3$), patient's or physician's choice after achieving a stable disease, or partial or complete response ($n = 16$). At a median follow-up of 9.2 (1.1–41) months, no patients with early discontinuation experienced a disease relapse.

4. Discussion

To our knowledge, these are the first real-life data focusing on the impact of early discontinuation of cemiplimab in patients with advanced CSCC.

Our results show that when treatment was permanently discontinued for reasons other than PD, no patient had disease progression at a median follow-up of 9.2 months after treatment discontinuation.

Treatment stopping was allowed in the clinical trials of cemiplimab and pembrolizumab for advanced CSCC under certain conditions [3,6,7]. In the EMPOWER-CSCC-1 trial, an early discontinuation of cemiplimab was possible after a minimum of 24 weeks of treatment in patients in complete response (CR) or in patients with stable disease (SD) or PR for three subsequent disease assessments [3]. In the CARSKIN and KEYNOTE-629 trials, early discontinuation of pembrolizumab was possible in patients with confirmed CR after at least 24 weeks of treatment and at least two doses of treatment after the first evidence of CR [6,7]. However, in both studies, treatment was stopped earlier for reasons other than PD or unacceptable toxicity in a very small number of patients; only the CARSKIN study reported the results of these patients showing that clinical response was maintained in two of eight patients with CRs and in one patient with SD [3,5–7]. This observation underscores the complexity of treatment decisions in real-world clinical practice and emphasizes the need for a more nuanced understanding of factors influencing treatment duration and response. In fact, our results show that at a median follow-up of approximately nine months, none of the patients who responded to cemiplimab experienced disease relapse after early treatment discontinuation.

Early discontinuation of anti-PD-1 is still a burning question in the treatment with immune-checkpoint inhibitors (ICIs) across different malignancies. In the treatment of advanced melanoma, hypotheses have been made about the possibility of safely discontinuing anti-PD-1 when CR/PR is reached, with a good response rate in case of relapse. In the KEYNOTE-006 trial, patients with advanced melanoma achieving PR/CR after 24 months of treatment could safely stop treatment with anti-PD-1, maintaining their response in 75% of cases [11]. The 23 patients with CR who stopped pembrolizumab (after at least six months of treatment) had a two-year progression-free survival (PFS) of 86%, similar to what observed in patients with CR who completed 24 months

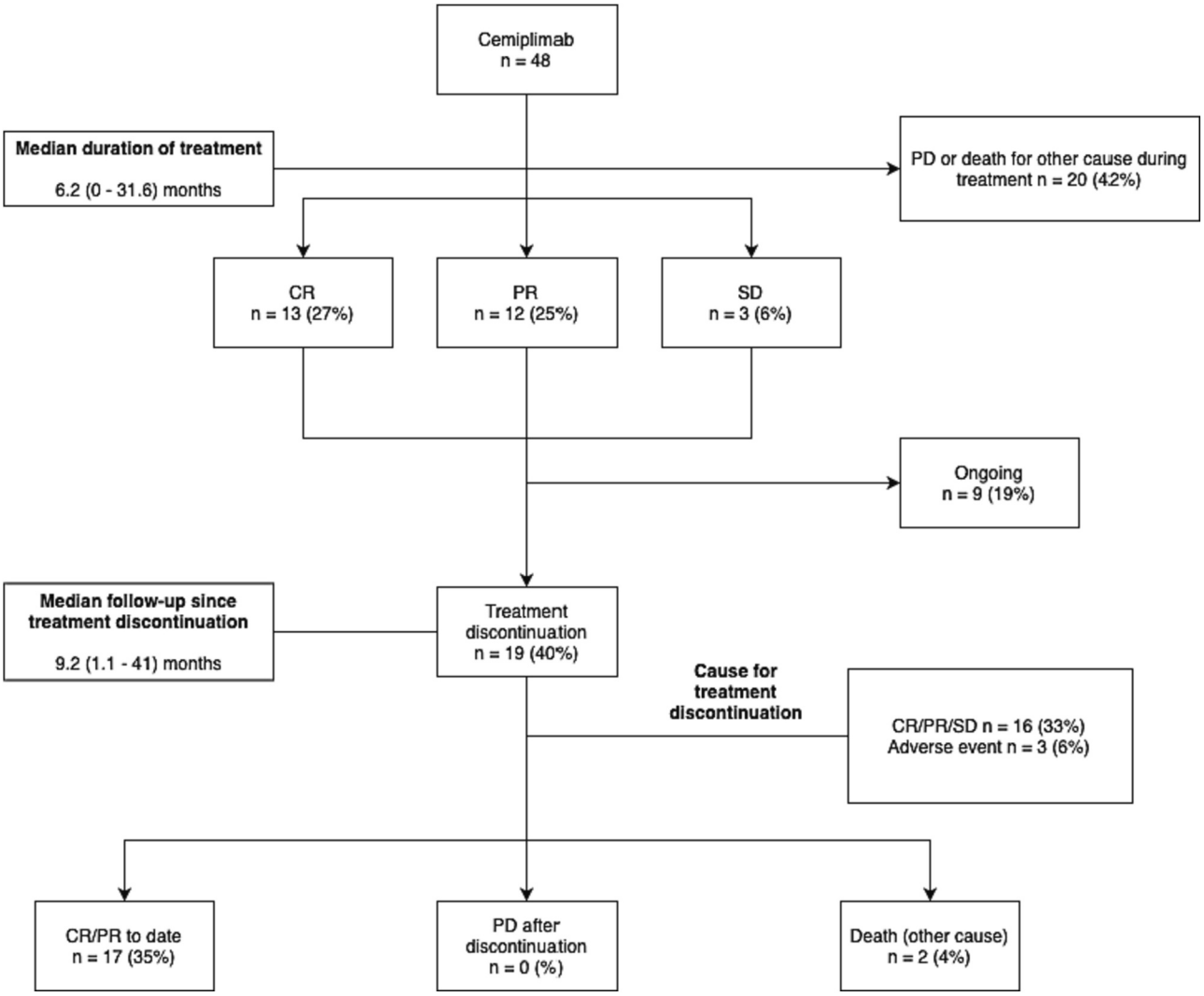

Fig. 1. Patient distribution.
CR: complete response; PR: partial response; PD: progressive disease; SD: stable disease.

of treatment [11]. Treatment discontinuation was not as safe in patients with SD, leading to a PD in 50% of patients [11]. Based on these findings, a European Society of Medical Oncology (ESMO) Consensus recommended to consider stopping treatment after at least six months in case of CR, and after 24 months of treatment in case of PR or SD [12].

However, the same attempt has been conducted in patients with non-small cell lung cancer (NSCLC) but with different outcomes compared to what was observed in melanoma [13]. In the CheckMate 153 trial, a total of 252 patients with previously treated NSCLC were randomized to receive one-year fixed duration or continuous treatment with nivolumab. Of these, 85 and 89 patients respectively had not progressed after one year of treatment. Median PFS was longer with continuous versus one-year fixed-duration treatment (25 versus 9 months) [13], suggesting that in this group of patients continuing nivolumab beyond one year improved outcomes.

In our study, we noted an ORR of 68%, which surpasses the ORRs observed in the main prospective trials (ranging between 40 and 50%) [3,6]. This variance can likely be attributed to the fact that, among our total population of 48 patients, eight individuals had died due to non-tumour-related factors prior to the first response evaluation, potentially introducing an imbalance in favor of responders. Moreover, the lack of confirmatory biopsy of CR may have overestimated the number of patients with CR in our population. On the other hand, the median time to response was consistent with what observed in the clinical trials of cemiplimab and pembrolizumab, but with a shorter median treatment exposure time (about 6 months compared to 8–11 months in the EMPOWER-CSCC-1 and CARSKIN trials) [3,6]. The patients included in our study had an older median age (82 years) and have mostly been treated with an anti-PD-1 as first-line treatment.

Our real-life population had a high proportion of older adults and with more comorbidities, physical, social, and financial frailty. This is consistent with what has been observed in an Italian real-life study including 131 patients with a median age of 79 years, of whom only 20% had an ECOG PS 0 [14]. For these reasons, early discontinuation of treatment was preferred, with the possibility of a retreatment in case of recurrence.

The retrospective nature is the main limitation of our single-centre study. Furthermore, a confirmatory biopsy of clinically assessed responses was not performed in our patients.

Our study provides real-life findings that may potentially support an early discontinuation of treatment with cemiplimab in patients with advanced CSCC upon achieving a tumour response. Potential benefits include prevention of overtreatment, improvement in quality of life, reduction of potential immune-related adverse events that may potentially contribute to a clinical deterioration in older adults and frail patients, reduction of hospital visits, and optimization of healthcare costs. Further prospective studies are necessary to confirm our findings. Furthermore, the integration of translational research, including

molecular assays such as circulating tumour DNA (ctDNA) analysis, is instrumental in providing a comprehensive assessment of treatment response. Confirming complete response at the molecular level not only validates clinical and pathological observations but also offers insights into the underlying mechanisms of response or resistance. This multifaceted approach enhances the clinical relevance of trial outcomes and brings us closer to tailoring treatment approaches that maximize therapeutic benefit while minimizing unnecessary exposure to immunotherapeutic agents.

Ethics Statement

Approval was obtained from the local ethics committee. The patients in this manuscript have given informed consent to publication of their case details. Patient privacy and confidentiality have been diligently protected throughout the study, in strict adherence to recognized ethical guidelines, according to the current EU General Data Protection Regulation (GDPR).

CRediT authorship contribution statement

Andrea Boutros: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Elena Croce:** Data curation, Visualization, Writing – review & editing. **Enrica Teresa Tanda:** Visualization, Validation. **Federica Cecchi:** Visualization, Validation. **Luca Arecco:** Visualization, Validation. **Carlo Genova:** Visualization, Validation. **Ilaria Baldelli:** Visualization, Validation. **Matteo Lambertini:** Visualization, Writing – review & editing, Validation, Supervision. **Edoardo Raposio:** Visualization, Validation. **Lucia Del Mastro:** Visualization, Validation, Supervision. **Francesco Spagnolo:** Conceptualization, Data curation, Methodology, Visualization, Writing – review & editing, Validation, Supervision.

Declaration of Competing Interest

CG has received grants from Italian Ministry of Health and BMS and Honoraria for presentations or lectures from AstraZeneca, BMS, Lilly, MSD, Roche, Sanofi, Takeda, Thermo Fisher; ML has received personal fees (advisory role and/or speaker honoraria) from Roche, Takeda, Sandoz, Eli Lilly, Pfizer, AstraZeneca, Novartis Exact Sciences and Ipsen; LDM has reported consulting fees from Roche, Novartis, MSD, Pfizer, Ipsen, AstraZeneca, Genomic Health, Eli Lilly, Seattle Genetics, Eisai, Pierre Fabre, and Daiichi Sankyo, speaker Honoraria from Roche, Novartis, Eli Lilly and MSD, travel grants from Roche, Pfizer and Celgene; FS has reported Honoraria for presentations or lectures from Sanofi Genzyme, Roche, BMS, Novartis, Merk, Sun Pharma, MSD, Pierre Fabre and for advisory board for Novartis, Philogen, SunPharma, MSD.

Data Availability

The data that support the findings of this study are available on request from the corresponding author, AB.

Acknowledgements

Italian Ministry of Health (Ricerca Corrente) and Italian Association of Medical Oncology (AIOM) Liguria ‘Gardin Young Oncologist Award 2021’ supported this work.

Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2023.101640.

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