Advanced Cutaneous Squamous Cell Carcinoma: Italian Multicentric Retrospective Analysis of Patient Profiles and Therapeutic Approaches

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Keywords
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Abstract
Background: Advanced cutaneous squamous cell carcinoma (aCSCC) represents an area of unmet clinical need, with no standardized treatments until the recent approval of immune checkpoint inhibitors (ICIs). ***Objectives:*** The aim of the study was to describe clinical characteristics and therapeutic strategies of a real-life Italian cohort of aCSCC patients managed at the beginning of cemiplimab approval as compassionate use in Italy. ***Methods:*** A multicenter retrospective study was performed by 10 Italian centers in the period January 1, 2018–May 31, 2020. Patients aged ≥18 years and diagnosed with aCSCC (locally aCSCC and metastatic CSCC) were eligible for the study. Analysis of patients' characteristics and treatment strategies was performed. ***Results:*** 239 patients were initially recruited in the study: 19 patients were excluded due to incomplete data collection, yielding a final cohort of 220 patients, of which 191 and 220 were included for patients' clinical characteristics and therapeutic intervention analysis, respectively. Median age at the time of diagnosis was 81 years (range: 72–86);

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nodal metastases were detected in 64/220 (29%) patients, and distant metastatic spread was reported in 33/220 (15%) patients. Most of our patients referred chronic occupational and/or recreational sun exposure, experienced ≥1 sunburn during their lifetime, never wore hats or used photoprotective filters, and presented with signs of cumulative sun damage (solar lentigines and/or actinic keratosis). Majority of our cohort received at least one intervention directed to the primary tumor (*n* = 212, 96.3%); surgery and radiotherapy were the most common therapeutic choices. Immunotherapy was administered to a small number of patients as compassionate use, especially in the metastatic setting. ***Conclusions:*** Our study outlines the complex and heterogeneous clinical and therapeutic landscape of aCSCC patients at the beginning of ICI era, highlighting the need of a standardized care for this fragile and high-need patient population.

Introduction

Cutaneous squamous cell carcinoma (CSCC) is the second most common type of non-melanoma skin cancer, accounting for 20% of keratinocyte tumors [1]. It is usually diagnosed in a localized early stage, which is successfully managed by surgery or radiotherapy, with excellent treatment outcomes [2]. In 5–20% of cases, CSCC may present in an advanced stage, displaying infiltrating behavior and/or locoregional involvement and possible metastatic spread, thereby causing significant morbidity and mortality [3, 4]. The term advanced CSCC (aCSCC) encompasses two different clinical entities: locally aCSCC (laCSCC) and metastatic CSCC [5]. LaCSCC is defined as a non-metastatic CSCC for which curative surgery and/or curative radiation therapy is not possible because of multiple tumor recurrences, large extension, deep infiltration of the surrounding tissues, or unacceptable rate of complications resulting from therapeutic interventions. Metastatic CSCC is characterized by involvement of lymph nodes and/or internal organs.

No standardized treatment options were available for aCSCC, until recent anti-PD-1 immunotherapy introduction [6]. The approval of immune checkpoint inhibitors (ICIs) represented a breakthrough in the management of this tumor, leading to remarkable clinical benefits with an acceptable safety profile in this high-need fragile population [7]. Cemiplimab is an anti-PD-1 monoclonal antibody approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for treatment of aCSCC patients who are not candidates for curative surgery or radiotherapy, while pembrolizumab is currently approved by FDA only. Patients' profile, disease characteristics, and clinical course of aCSCC need to be better characterized to provide a framework for clinical data interpretation and to serve as a proxy for upcoming real-life studies following ICI approval. Here, we describe clinical characteristics and therapeutic strategies of a real-life Italian cohort of patients diagnosed with aCSCC at the beginning of ICI approval as compassionate use in Italy.

Materials and Methods

A multicenter retrospective observational study was conducted at the Dermatology Clinic of Catholic University of Rome - Fondazione Policlinico A. Gemelli, IRCCS, Rome, Italy, along with other nine Italian centers, in the period from January 1, 2018, to May 31, 2020. The study protocol was approved by the Ethical Committee of Fondazione Policlinico A. Gemelli, IRCCS, Rome. Patients aged ≥18 years and diagnosed with aCSCC (laCSCC and metastatic CSCC) who attended, either upon first visit or on follow-up, the outpatient clinics of the involved centers were eligible for the study. Patients had to read, understand, and sign an informed consent (in case of patient's death, authorization of a relative was needed). LaCSCC included tumors which could not be cured or were unlikely to be cured by surgery, radiotherapy, or both (based on decision of the local multidisciplinary tumor board), and multiple relapsing, multifocal, and neglected lesions. Metastatic CSCC encompassed locoregional (lymph nodes) and/or distant (visceral organs) metastasis.

Study procedures included patients' data collection based on an anonymous questionnaire. The questionnaire was divided into 4 main sections comprising (1) information on patients' age, sex, education, and occupational history; (2) patients' phenotype (hair color at the age of 18, eye color; skin type according to Fitzpatrick classification) and habits, such as occupational and/or recreational sun exposure, history of sunburns, use of photoprotection, tanning beds, and smoking; (3) patients' family and personal medical history and clinical examination (nevus count, solar lentigines, actinic keratoses [AKs]); (4) patients' vital status and tumor characteristics (patient's age and date at time of diagnosis, tumor location, presence of lymph nodes and/or visceral metastasis, treatments of primary tumor and/or metastasis, treatment response, disease progression, and time to progression).

The STATA software (version 13.1) was used for statistical analysis. For continuous numerical variables, we calculated mean and standard deviation, median and interquartile range; for categorical variables, we worked out absolute and percentage frequencies. The non-parametric Mann-Whitney test was used to compare numerical variables between 2 groups; the χ^2 test or Fisher's exact test was applied to compare the frequencies between two categorical variables. A p value <0.05 was chosen as a threshold level of statistical significance. Results are reported also for p values <0.1.

Table 1. Patients' clinical characteristics

Age at diagnosis, years	
Median (range)	81 (72–86)
Sex, *N* (%)	
Male	142 (74.4)
Female	49 (25.6)
Fitzpatrick skin type, *N* (%)	
I	29 (15.2)
II	119 (62.3)
III	41 (21.5)
IV	1 (0.5)
Personal history of non-cutaneous neoplasms, *N* (%)	
Yes	52 (27.2)
No	139 (72.8)
Cardiovascular comorbidities, *N* (%)	
Yes	125 (65.5)
No	66 (34.5)
Immunosuppression, *N* (%)	
Yes	34 (17.8)
No	157 (82.2)
Chronic occupational/recreational sun exposure, *N* (%)	
Yes	139 (72.7)
No	52 (27.3)
History of sunburns, *N* (%)	
Yes	116 (60.7)
No	75 (39.3)
Solar lentigines, *N* (%)	
Yes	153 (80.1)
No	38 (19.9)
Actinic keratosis, *N* (%)	
Yes	168 (88)
No	23 (22)

Table 2. Tumor localization

Chronic photo-exposed area, *N* (%)	
Yes	180 (81.8)
No	40 (18.2)
Head-neck region, *N* (%)	169 (76.8)
Trunk, *N* (%)	6 (2.7)
Upper and lower limbs, *N* (%)	36 (16.3)
Anogenital area, *N* (%)	9 (4)
Patients with lymph node metastasis, *N* (%)	
Yes	64 (29)
No	156 (71)
Patients with visceral organ metastasis, *N* (%)	
Yes	33 (15)
No	187 (85)
Visceral organ metastasis localization, *N* (%)	
Lung	21 (53.8)
Parotid gland	7 (17.9)
Skin	6 (15.3)
Liver	2 (5.1)
Bone	2 (5.1)
Brain	1 (2.5)

Results

239 patients were initially recruited in our study: 19 patients have been excluded from further analysis due to incomplete data collection, yielding a final sample size of 220 patients. We collected comprehensive information on patients' clinical characteristics for 191 patients (shown in Table 1), and on tumor features (shown in Table 2) and therapeutic intervention (shown in Table 3) for 220 patients.

Most subjects were males (n = 142, 74.4%), and median age was 81 years [IQR = (72; 86)]. At the time of diagnosis of the aCSCC, nodal metastases were detected in 64 (29%) patients, and visceral organ metastatic spread was reported in 33 (15%) patients, with lung (n = 21) and parotid gland (n = 7) being the most frequently affected sites. Fitzpatrick skin types I, II, III, and IV were observed in 30 (15.2%), 119 (62.3%), 41 (21.5%), and 1 (0.5%) patient, respectively. 125 (65.5%) patients had cardiovascular comorbidities, 34 (17.8%) patients were immunosuppressed, and 52 (27.2%) patients reported personal history of non-cutaneous neoplasms. Majority of our cohort (n = 108, 56.5%) had a previous diagnosis of CSCC, and 58 of these tumors were located at the same site of the aCSCC. Advanced CSCC arising on sun-exposed areas as the head-neck region, dorsum of the hands, forearms, and décolleté accounted for 81.8% (n = 180) of the whole tumor diagnosis. The most common primary tumor localization was the head-neck region (n = 169, 76.8%), with 75/169 (44.3%) affecting the scalp, followed by cheek (n = 27, 15.9%) and ear (n = 22, 13%).

Concerning sun exposure habits, 60.7% (n = 116) of patients experienced at least one sunburn during their lifetime and, among these, 77.6% (n = 90) reported ≥1 sunburn at the same site of CSCC. Most of our patients (n = 134, 70.1%) denied use of sunscreens, never wore hats (n = 76, 39.8%), or used them for less than half of the sun exposure time (n = 66, 34.5%). Also, 72.7% (n = 139 patients) reported chronic occupational and/or recreational sun exposure.

Regarding clinical examination, most patients (n = 153, 80.1%) showed solar lentigines, and among them, 107 (69.9%) displayed these cutaneous lesions at the same site of aCSCC, yielding a strong correlation between these two variables (p value <0.001). Similarly, 88% (n = 168) of patients presented with AKs, which were mostly located on the face (n = 81, 48.2%) and on the scalp (n = 66, 39.3%). Assessment of the correlation between AKs and the occurrence of aCSCC on the same site yielded a highly significant figure (p value <0.0001).

Table 3. Local and systemic first-line treatments of primary tumor, lymph node, and/or visceral organ metastases

Primary tumor-directed therapy, *N* (%)	
Surgery	161 (75.9)
Radiotherapy	39 (18.4)
Electrochemotherapy	5 (2.3)
Chemotherapy/anti-EGFR	3 (1.4)
Immunotherapy	4 (1.9)
Lymph node metastasis-directed therapy, *N* (%)	
Surgery	22 (41.5)
Radiotherapy	13 (24.5)
Electrochemotherapy	1 (1.8)
Chemotherapy/anti-EGFR	4 (7.5)
Immunotherapy	13 (24.5)
Visceral organ metastasis-directed therapy, *N* (%)	
Surgery	6 (26)
Radiotherapy	2 (8.7)
Chemotherapy/anti-EGFR	5 (21.7)
Immunotherapy	10 (43.5)

EGFR, epidermal growth factor receptor.

Concerning treatment of the primary tumor, 212 (96.3%) patients received at least one therapeutic intervention: 42.5% (n = 90) received one line of treatment only, and 32.3% (n = 71), 13.6% (n = 30), 4.1% (n = 9), and 5.4% (n = 12) underwent two, three, four, and five different therapeutic modalities, respectively. Surgery was the most common first-line treatment option (n = 161, 75.9%), radiotherapy accounted for 18.4% (n = 39), electrochemotherapy for 2.3% (n = 5), immunotherapy for 1.9% (n = 4), and chemotherapy for 1.4% (n = 3) (shown in Table 3). A similar trend was observed for second-line treatments, with surgery and radiotherapy being the most frequent treatment choices. Taking into account all lines of therapy, surgery was the most common primary tumor-directed intervention (n = 167, 50.3%), followed by radiotherapy (n = 92, 27.7%), immunotherapy (n = 45, 13.5%), consisting of cemiplimab as compassionate use (n = 43) and off-label pembrolizumab (n = 2), electrochemotherapy (n = 15, 4.5%), and chemotherapy (mainly platinum-based) and methotrexate/anti-epidermal growth factor receptor (EGFR) (cetuximab) (n = 13, 3.9%).

Regarding therapeutic management of nodal metastasis, 53/64 (82.8%) patients received at least one therapeutic option. The most common first-line treatment modality was surgery (n = 22, 41.5%), followed by radiotherapy (n = 13, 24.5%), immunotherapy (n = 13, 24.5%), chemotherapy with platinum agents or anti-EGFR (n = 4, 7.5%), and electrochemotherapy (n = 1, 1.8%) (shown in Table 3). Overall, surgery accounted for approximately one-third (n = 22, 33.8%) of the total lymph node metastasis-directed therapies, followed by immunotherapy (n = 19, 29.2%), radiotherapy (n = 17, 26.1%), chemotherapy (n = 5, 8%), and electrochemotherapy (n = 2, 3%).

As for distant metastasis, 23 of 33 (69.7%) patients received at least one therapeutic intervention. First-line treatment choice was as follows (shown in Table 3): 10 patients (43.5%) received immunotherapy, 6 patients (26%) underwent surgery, 5 patients (21.7%) were managed by platinum compounds chemotherapy or anti-EGFR, and 2 patients (8.7%) were treated with radiotherapy. Looking at data for all lines of treatment, it appears that immunotherapy was the most common choice in the distant metastatic setting (n = 14, 51.8%), followed by surgery (n = 6, 22.2%), platinum-based chemotherapy or anti-EGFR (n = 5, 2%), and radiotherapy (n = 2, 7%).

Discussion

In the present retrospective study, we investigated the clinical characteristics of an Italian cohort of patients diagnosed with aCSCC, as well as the local and systemic treatments they underwent at the very beginning of ICI approval as compassionate use in Italy. Advanced CSCC is a tumor of the elderly, with ≥80% of cases occurring in patients aged >60 years [8–10]. In our series, median age at the time of diagnosis was 81 years, which is higher compared to previous studies by Hillen et al. [10] and Amaral et al. [3] reporting 76 and 78 years, respectively. As a result of such an advanced patients' age, more than half of our cohort was affected by cardiovascular comorbidities, and non-cutaneous neoplasia and immunosuppression were reported at a rate of 27.2% and 17.8%, respectively. These findings are comparable to a French retrospective study investigating aCSCC patients' characteristics and revealing similar figures [11].

UV radiation exposure is the most important environmental risk factor for CSCC development [12, 13]; this evidence is further confirmed by analyzing the sun exposure patterns of our patients' cohort, their clinical characteristics, and site of occurrence of aCSCC. Majority of the aCSCC developed on chronically sun-exposed areas (n = 180, 81.8%), and the head-neck region was the most frequently affected site. In our series, the scalp accounted for one-third of all aCSCCs; these findings are in line with literature data, where the head-neck region and in particular the scalp represent the most common localization of CSCC [3, 10, 14]. Concerning patients' phenotypic

characteristics, 15.2% and 62.3% of our cohort displayed type I and type II skin types, respectively. These phenotypic traits represent a well-known intrinsic risk factor for CSCC development [15], especially if coupled to actinic damage [16]. More than half of our cohort experienced ≥1 sunburn during their lifetime, and 77.6% (n = 90) of these referred at least one sunburn on the same site of CSCC. Also, majority of our patients presented with solar lentigines and AKs colocalizing with aCSCC, yielding a strong correlation between these cutaneous lesions and the occurrence of aCSCC on the same site. Both solar lentigines and AKs are signs of cumulative sun damage [17, 18], and their association with CSCC strengthens the causative role of sun exposure in CSCC development.

In our study, we detected lymph node metastasis at a rate of 29% (n = 64); this figure is lower compared to previous studies by Hillen et al. [10], who reported metastatic lymph node involvement in 40% of his cohort, and Amaral et al. [3], who considered stage III and stage IV aCSCC patients only, reporting a figure of 65.6%. Conversely, we registered visceral organ metastatic spread in 15% (n = 33) of our patients, and this number is similar to previous literature data [3, 14]. It is evident that these rates are considerably higher compared to the cumulative metastatic risk of CSCC, which ranges between 1.2% and 4%, according to different series [9, 19–21]. Our numbers reflect the focus on the specific high-risk population of aCSCC.

Concerning therapeutic interventions, it appears that 96.3% of our patients underwent at least one primary tumor-directed therapy, and 57.5% of them were managed by ≥2 therapeutic options. The high number of treatments recorded in our study implies frequent patients' accesses to the hospitals, as well as to the primary care physicians, and results in extensive health-related expenditures for the National Health System (NHS). An observational study assessing aCSCC health-related costs estimated an expenditure of € 10.281 per patient, with therapeutic interventions accounting for 33.7% of the whole expenses [22]. Similarly, a recent Italian study investigating the total annual NHS costs for the management of CSCC revealed an average annual expenditure of € 4.490 for a single patient diagnosed with aCSCC, versus € 2.236 for a surgically resectable CSCC patient [23]. These elevated costs are partially related to the lack of an appropriate standard of care and reflect the unmet therapeutic need for this fragile patient population. In our series, patients have been exposed to heterogeneous therapeutic interventions. Considering all primary tumor-directed therapies, half of our cohort underwent surgery, followed by radiotherapy, immunotherapy, electrochemotherapy, and chemotherapy. These data provide an outline of the current therapeutic options for aCSCC, where surgery and radiotherapy represent the most common treatment choices, although they do not always result in a curative outcome. Our figures are confirmed by previous retrospective studies reporting a similar clinical scenario, with a very heterogeneous and unsatisfactory landscape of therapeutic interventions, claiming an urgent need for appropriate treatment modalities [3, 10, 14, 24].

In our cohort, anti-PD-1 immunotherapy was employed in a small number of patients as compassionate (cemiplimab) or off-label (pembrolizumab) use. This small number stems from the drug unavailability for some of the involved centers, as we were at the beginning of the cemiplimab era as compassionate use in Italy, and also from the decision of the local multidisciplinary tumor board which considered patient and tumor's characteristics, and patient's preferences for anti-PD-1 immunotherapy eligibility. The excellent response rates and the favorable safety profile, also in elderly and fragile patients, make it a very appealing treatment choice, unveiling a new range of opportunities and filling the therapeutic gaps for aCSCC patients [7, 25].

In conclusion, this retrospective study provides an outline of the clinical characteristics and the treatment strategies of an Italian cohort of patients diagnosed with aCSCC at the very beginning of ICI era. Our data contribute to clinically characterize this high-need and fragile patient population. The broad and heterogeneous landscape of therapeutic interventions reflects the lack of an appropriate standard of care and the unmet therapeutic need for this tumor. ICIs approval largely represents a therapeutic hope for these patients.

Key Message

Advanced cutaneous squamous cell carcinoma represents an unmet clinical need, with a heterogeneous treatment landscape.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent has been collected from participants in order to participate in the study. This study protocol was reviewed and approved by the Ethical Committee of Catholic University of the Sacred Heart, approval number 4470.

Conflict of Interest Statement

Maria Mannino, Alfredo Piccerillo, Sabina Vaccari, Marco Rubatto, Caterina Longo, Stefania Borsari, Chiara Caponio, Giuseppe Argenziano, Giulia Briatico, Luca Bianchi, Alessandro Di Stefani, and Ketty Peris have no conflict of interest to declare. Emi Dika reports grants from Novartis, honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Sun Pharma, Difa Cooper, Novartis, and Bristol Myers, payment for expert testimony from Regeneron, Novartis, and Sun Pharma, support for attending meetings and/or travel from Sun Pharma and Novartis, and participation on a Data Safety Monitoring Board or Advisory Board from Sun Pharma and Novartis. Pietro Quaglino reports advisory board and speaker fee from Sanofi. Giovanni Pellacani reports consulting fee from Sanofi and honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Sanofi. Maria Concetta Fargnoli reports personal honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Sanofi – Regeneron. Cosimo Di Raimondo reports payment or honoraria from HPS Health Publishing and Service SRL, support for attending meetings, and/or travel from Recordati, AbbVie, and Kyowa Kirin. Pier Giacomo Calzavara Pinton reports personal consulting fees from AbbVie, Almirall, and Janssen, and personal honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Cantabria, Leo Pharma, and Sanofi. Iris Zalaudek reports grants from Philogen, honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Sanofi, Sun Pharma, Novartis, MSD, Philogen, Biogena, La Roche Posay, Kyowa Kirin, FotoFinder, and Mallinckrodt, participation on advisory board meetings of Sanofi, Sun Pharma, Novartis, MSD, Philogen, Biogena, La Roche Posay, Kyowa Kirin, FotoFinder, and Mallinckrodt, past president of the International Dermoscopy Society, treasurer of the Melanoma World Society, and board member of the European Association of Dermato-Oncology.

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Author Contributions

Writing and revision of the manuscript and interpretation of data: Maria Mannino and Alfredo Piccerillo. Data collection and study supervision: Maria Mannino, Alfredo Piccerillo, Emi Dika, Sabina Vaccari, Pietro Quaglino, Marco Rubatto, Caterina Longo, Stefania Borsari, Giovanni Pellacani, Maria Concetta Fargnoli, Chiara Caponio, Giuseppe Argenziano, Giulia Briatico, Luca Bianchi, Cosimo Di Raimondo, Pier Giacomo Calzavara Pinton, Iris Zalaudek, Alessandro Di Stefani, and Ketty Peris. Conception and design of the study: Ketty Peris.

Data Availability Statement

All data analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author, Ketty Peris.

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