Dermatology Practical & Conceptual

Advanced Cutaneous Squamous Cell Carcinoma Management in Immunotherapy Era: Achievements and New Challenges

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Key words: Cutaneous Squamous Cell Carcinoma; Immunotherapy; Frail Patients; Neoadjuvant Treatment

Citation: Lorini L, Alberti A, Bossi P. Advanced CSCC Management in Immunotherapy Era: Achievements and New Challenges. *Dermatol Pract Concept*. 2023;13(4):e2023251. DOI: https://doi.org/10.5826/dpc.1304a251

Accepted: August 9, 2023; **Published:** October 2023

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT Introduction of immunotherapy (IT) has radically changed the therapeutic scenario in patients affected by locally advanced and/or metastatic cutaneous squamous cell carcinoma (cSCC) patients. If it is well consolidated the role of immunotherapy in the setting of a disease not amenable to curative surgery and/or radiation, how to integrate immune checkpoint inhibitors in the curative setting is still under evaluation. Surgery combined or not with adjuvant radiotherapy remains the mainstay of curative treatment in localized cSCC; however, promising data with neoadjuvant or perioperative immunotherapy could pave the way towards treatment de-escalation according to the response achieved. On the other side, data on adjuvant treatment with pembrolizumab and cemiplimab after surgery and radiation are still awaited. Several questions related to the activity and the safety of immunotherapy in the real-world setting still remain without answer, and several points need to be better explored. In the current review we will explore the updated literature on the use of immunotherapy in cSCC, and we will show the current challenges in its use.

Immunological Status of cSCC and Differences With BCC

Cutaneous squamous-cell carcinoma (cSCC) is the second most common skin cancer after basal-cell carcinoma (BCC) [1]. BCC-to-SCC prevalence ratio range between 1:1 and 10:1, depending on the population evaluated, as for example solid organ transplant recipients were there is an higher incidence rates of cSCC than BCC [2]. Long-term sun exposure is responsible for the DNA damage from ultraviolet (UVA and UVB) radiation exposure and it is the major risk factor for both histotypes; BCC is caused by intensive UV exposure in childhood/adolescence, while cSCC is related to cumulative UV exposure over decades [1]. Both BCC and cSCC harbor a high tumor mutational burden, which likely results in higher levels of tumor neoantigens that may be targeted by the immune system. The gene signature in cSCC is characterized by NOTCH family genes mutations in 22%-86%, RAS pathway mutations in quite 5-50%, and aberrant activation of the epidermal growth factor receptor (EGFR) and Fyn Src-family tyrosine kinase is common [3]. Tumor suppressor genes like p53 are more frequently altered in cSCC, with 19% mutations at a UV-signature hotspot in KNSTRN gene [3]. Furthermore, the strong link between immunosuppression and the risk of cSCC indicates that natural immuno-surveillance plays an important role in controlling this type of cancer; in cSCC the most relevant is the promotion of an immuno-tolerant microenvironment [4]. This occurs through cytokine manipulation (increased secretion of IL-6, IL-10, and TGF-beta; consumption of IL-2) that promotes the infiltration of T-reg cells, myeloid-derived suppressor cells (MDSCs), and other cell types, such as mature dendritic cells, that inhibit the function of cytotoxic T-cells. These cells can then actively suppress the proliferation of CD4+ and CD8+ T lymphocytes that would otherwise recognize tumor antigens [4,5]. cSCC also upregulates the expression of immune checkpoint molecules such as PD-1 and PD ligand 1 (PD-L1) that promote peripheral T cell depletion [6].The immunogenicity of cSCC and BCC is different, as witnessed by the higher infiltration of CD8+ T cells and CD68+ macrophages in cSCC [7]; also, BCC shows lower expression of immune checkpoints compared to cSCC [8].

Some cSCC cases are associated with high-risk types of HPV, particularly HPV-16, differently from what happens in BCC, where the association with the infection is less relevant. HPV-positive cSCC tends to exhibit a more immunologically active profile compared to HPV-negative cSCC [9]. This is thought to be due to the expression of viral antigens, which can trigger an immune response against the tumor. It is important to note that while cSCC often exhibits an immune-inflamed phenotype, there can be considerable heterogeneity in the immunological status among individual tumors.

Lessons Learned: How to Position Immunotherapy in Advanced cSCC

Immune checkpoint inhibitors (ICIs) have shown efficacy in the treatment of advanced cSCC. Two phase II trials investigated the efficacy of pembrolizumab in cSCC, the KEYNOTE 629 trial and CARSKIN, both open-label, single-arm, multicenter design. In KEYNOTE 629, most patients (87%) had received one or more prior systemic therapies or radiotherapy (RT) (74%). In the entire study population, the objective response rate (ORR) was 34%, with complete (CRR) and partial response (PRR) rates reported in 4% and 31%, respectively. Among the cohort of 36 patients with confirmed disease response, about two-thirds (69%) had a durable response of more than 6 months. At the median follow-up of 10 months, the median progression free survival (PFS) was 7 months and the 1-year overall survival (OS) 60% [10]. In the investigator-initiated CARSKIN trial, where only treatment-naïve patients were enrolled, the ORR, CRR, and PRR in the entire study population was 42%, 7%, and 35% respectively [11]. In the expansion cohort, the ORR was higher among patients with PD-L1 positive disease (55%) than those with negative PD-L1 (17%) (P = 0.02). In the primary cohort, after a median follow-up of 22.4 months, none of the 16 responders had subsequent disease progression; median PFS and OS were 7 and 25 months, respectively [11].

The efficacy of cemiplimab was studied in a phase I multi-cohort study and followed up in the phase II EMPOWER-CSCC 1 study; both studies had an open-label multicenter design [12–16]. The EMPOWER-CSCC study treated patients with cemiplimab 3 mg/kg and included 3 parallel treatment groups; group 1 included patients with metastatic cSCC, while group 2 included patients with locally advanced cSCC; in both groups, cemiplimab was administered at a dose of 3 mg/kg. In group 3 patients with metastatic cSCC were treated with cemiplimab 350 mg [12–14]. ORR was observed in 50.8%, 44.9% and 46.4% of patients in groups 1, 2, and 3, respectively; with a median time to response lower than 2 months. After a median follow-up of 18.5, 15.5, and 17.3 months in the 3 groups, the response observed with cemiplimab in patients with advanced cSCC appeared durable; the median duration of response (DOR) was not reached in the group 1, while was 41.9 and 41.3 months in group 2 and 3, respectively. The median OS was 57.7 and 48.4 months in group 1 and 3, and not reached in group 2.

Cemiplimab and pembrolizumab have been approved (from FDA and EMA the first, from FDA the second one) for locally advanced and metastatic squamous cell carcinoma of the skin, which is not a candidate for curative surgery or curative RT.

Challenges for the Use of Immunotherapy in cSCC

Neoadjuvant Use of Immunotherapy

Despite optimal loco-regional treatment, up to 30% of patients with loco-regional advanced cSCC recur, and in up to 5% disease become no longer amenable to curative treatment, with a consequent worsening in prognosis [17]. Moreover, in case of advanced disease, where the feasibility of a surgery is considered "borderline" (combined or not with RT) there would be a high risk of R1 resection; also, surgical interventions in some advanced cSCC may cause significant disfigurement and functional morbidity, with consequent impact on patient quality of life, social and working activities. Thus, given the activity of anti PD-1 agents in advanced disease [10,13] and the somewhat suboptimal results of surgical strategies in advanced cases, there is a strong rationale for the introduction of anti PD-1 agents in the neoadjuvant setting.

Ferrarotto et alperformed a pilot phase II single arm study of neoadjuvant cemiplimab in loco-regionally advanced resectable head and neck (HN) cSCC [18]. Twenty newly diagnosed or recurrent stage III-IVa (M0) cSCC of the HN region received 2 cycles of cemiplimab, with/without adjuvant RT. Even if the clinical response rate was 30%, one half of the patients reported a pathological complete response (pCR) and 20% a major pathological response (MPR). The 12 months disease specific survival, disease free survival and OS were 95%, 89%, and 95% respectively. Gross et alconducted a phase 2 single arm study on stage II, III, IV (M0) cSCC [19]. The 79 patients enrolled received anti PD-1 cemiplimab 350 mg flat dose for up to 4 cycles before undergoing surgery combined or not with RT. Fifty-one percent of patients reported a pCR and 13% a MPR, while the response according to RECIST 1.1 was 68%. To note, 5 patients with partial response at imaging did not undergo surgical resection, thus being considered as not pathological responders.

At the recent American Society of Clinical Oncology (ASCO) annual meeting, Ascierto et al presented the data of the NEOCESQ study, a phase 2 single arm trial [20]. The 23 enrolled patients, affected by stage III-IV (M0) surgically resectable cSCC, received cemiplimab for two cycles prior to surgery, and for one year after surgery. pCR was obtained in 39% of patients, while MPR, defined as pCR or near pCR with 10% remaining viable tumor cells in the surgical pathology sample, in 48% of the cases. The study is still ongoing, further activity and translational data are awaited (NCT04632433). Zuur et al (NCT04620200) conducted a phase 2, double arm, randomized trial and enrolled 40 patients affected by cSCC with an indication for extensive and/or mutilating surgery [21]. Patients were randomized to receive nivolumab or nivolumab plus ipilimumab followed by surgery, combined or not with RT. A deep or partial pathological response (less of 10% or from 10% to 50% of remaining viable tumor cells in the surgical pathology sample), or a clinically complete response has been assessed in 50% and 61% of cases with nivolumab or nivolumab plus ipilimumab, respectively.

Despite optimal results reported with neoadjuvant strategies, two main questions remain open, thus deserving further trials to be better explored.

Firstly, is it possible to de-escalate treatment in IT responders? In the trial by Ferrarotto et al 55% of the patients did not receive preplanned adjuvant RT, due to pathological response, thus questioning if preoperative treatment may select responsive patients to reduce treatment intensity [18]. Surgery remains the cornerstone of the treatment, as it allows eradicating potential resistant clones and permits to perform a clear evaluation of response to IT, where radiological imaging is not so effective.

However, it is an open issue if surgery needs to be limited to "remnant" disease after neoadjuvant treatment, or if it should encompass the whole area where the tumor was present before treatment. A new concept of de-escalation is being explored by the DESQUAMATE ongoing trial (NCT05025813). This trial is evaluating a de-escalation approach on loco-regionally advanced cSCC candidate to surgical exeresis and post-operative RT. Patients are treated with four cycles of neoadjuvant pembrolizumab and, if restaging imaging and biopsy are negative, they avoid surgery and continue with pembrolizumab for further 17 cycles.

Secondly, the patient selection. Up to 10% of patients experiences a progressive disease as the best response to neoadjuvant treatment, with a consequent risk to overcome the feasibility and the efficacy of the surgery, and patients may lose the opportunity to be curatively treated [18,19]. Gene expression studies revealed an inflamed tumor microenvironment in patients with pathological response, with an enrichment cluster of memory CD8+ T-cell in pCR patients [18]. PDL1 expression and TMB cannot be considered as optimal predictive biomarkers. Responders were identified in both PDL1 positive or negative patients, even if lower PDL1 expression was associated with lower pCR; the tumor mutational burden (TMB) was not associated with tumor response [19].

Adjuvant Immunotherapeutic Treatment

In the case of high-risk cSCC, there is a need to reduce the risk of recurrence after surgery.

The C-POST trial (NCT0396004) is an ongoing randomized, placebo-controlled, double-blind, multicenter phase 3 study to evaluate cemiplimab as adjuvant treatment for patients with high-risk cSCC, based on surgical and

clinicopathologic findings. Patients enrolled must have at least one of the following high-risk features: (1) nodal disease with (a) extracapsular extension (ECE) and at least one node ≥20 mm or (b) at least three lymph nodes positive on surgical pathology report, regardless of ECE; (2) in-transit metastases; (3) T4 lesion; (4) perineural invasion; and (5) recurrent cSCC with at least one other risk factor. Patients receive adjuvant cemiplimab for up to 1 years and the trial has disease-free survival as its primary objective.

The KEYNOTE 630 (NCT03833167) is a similar phase 3 trial in which patients at high risk of recurrence (defined as having one or more high risk features) after surgery and RT are randomized to receive either pembrolizumab or placebo for up to 1 year. The primary efficacy end point is the investigator-assessed and biopsy-confirmed recurrence-free survival.

The optimal duration of adjuvant treatment to elicit treatment efficacy without increasing toxicities is so far not clear. One year duration is based on trials in other diseases, such as melanoma [22]; however, in the context of disease with high response to IT, a shorter period may be enough. Moreover, it is to be clarified if the highest benefit can be IT seems to be more active in surgery naïve patients [10,11]; thus, a neoadjuvant or even a perioperative approach, in case of borderline surgical resectable disease may be the preferred option, also in order also to de-escalate post-operative treatment in case of response.

Treatment of Solid Organ Transplant Patients

The state of immune tolerance induced by broad immunosuppression to prevent allograft rejection leads to an increased risk of the development of cSCC. Both CTLA-4 and PD-1/PD-L1 play a key role in immuno-tolerance required for allograft survival [23,24]. In a preclinical study, the injection of anti-CTLA-4 immunoglobulin in the perioperative period led to acute rejection of liver allograft but did not have any effect on graft survival when it was injected after the establishment of peripheral tolerance [23]. On the contrary, the early infusion of anti PD-1 antibodies prevented the induction of peripheral tolerance, and infusion at a later stage led to complete loss of allograft [23,25,26]. This has not been proved in humans and prospective data from clinical trials go not in this direction. Recently, Hanna et al presented the CONTRACT-1 study results, the first prospective study using the PD-1 inhibitor cemiplimab for kidney transplant recipients, with advanced, incurable cutaneous squamous cell carcinoma [27]. Twelve patients have been enrolled 3-31 years after transplant and a standardized immunosuppression therapy with mTOR inhibitors and prednisone tapering has been established during the treatment. At a median follow-up of 6.3 months (range < 1-24.9), no patients experienced kidney allograft rejection or loss. Of 8 evaluable patients, overall response rate was 50% and at the data cut off no responder had progressed [27]. Several reports in literature warned about the high rates (around 40%) of allograft rejection in patients with cancer who were treated with an immune checkpoint inhibitor, leading to organ failure in 71% of the patients who experienced rejection [24].

Because of the high risk of allograft loss and the poor data of clinical benefit, the use of ICI should be clearly discussed with the patient before the initiation of treatment, and these patients should be monitored closely for signs of rejection.

Real Life Experiences

Next to evidence reported by clinical trials, data about cemiplimab activity in real life are available, especially for subgroups of patients who have not been included in clinical trials because of active autoimmune disease, concomitant malignancies, and those receiving high dose corticosteroids, as well as patients with performance status greater than 1. The results in terms of treatment responses are in line with clinical trial data. On the contrary, frail patients with poor performance status responded less well. Notably, PFS and OS did not differ according to cSCC stage, prior systemic treatment status or immune status. The safety profile of cemiplimab in these series was comparable with what was reported in clinical trials. Most adverse events (AEs) were manageable, except for patients (7% - 10%) who required cemiplimab discontinuation [28–31].

Frail Patients

cSCC patients are usually frail, with critical social conditions, and often with advanced age. In the real life study published by Baggi et al, median age was 79 years old, thus physicians frequently face with the issue to whether treat or not some patients who could be borderline for comorbidities and/or frailty [28]. IT has comparable activity and toxicity in younger and older patients, but the question remains how to identify older and frailer patients at higher risk for toxicities. In oncology, the comprehensive geriatric assessment (CGA) is a multidimensional evaluation of the overall fitness of an older adult to tolerate a proposed cancer treatment plan and follow up. Screening tools to select frail patients that may benefit from CGA exists, such as G-8 and VES 13 [32–34]. Little data exists about the role of CGA and health-related outcomes in older adults receiving IT, either single-agent or in combination [35]. The ELDERS prospective study evaluated the role of the G8 scale screening and of the CGA in predicting immuno-related toxicities [36]: on 140 patients (lung cancer 53% and melanoma 47%), a positive G8 screening correlated with a higher rate of hospital admission, and with a higher risk of death. In a prospective study on 70 years older melanoma patients who underwent IT [37],

frail patients, identified with G8 screening tools, seems to not have an increased risk of immuno-related toxicities if compared with their younger counterparts; however, they have a higher risk of hospital admission due to toxicities and an higher proportion of treatment interruption.

CGA and frailty assessment before starting IT is of outmost importance in such a complex population as cSCC patients. Prospective trials evaluating the role of CGA, specifically on cSCC, are advocated to better understand how to select elderly frail patients that may benefit from IT, or to evaluate how an early supportive intervention on frail patients may be of benefit in reverting some conditions as malnutrition, depression, risk of infections, and possible ameliorating the performance status.

Quality of Life (QoL)

In advanced cSCC treated with cemiplimab, the improvement in Global Health Status (GHS)/QoL is an early event, starting from the 2nd cycle and lasting all treatment. The median time to first clinically meaningful improvement for pain is 2.1 months and this is significantly improved in responders versus non responders ($P < 0.0001$) [38]. Overall, studies on IT in advanced cSCC showed a benefit on QoL and on symptoms both with cemiplimab and pembrolizumab [10,11,13]. However, a well-conducted systematic review [39], showed heterogeneity across cited studies regarding the use of quality of life assessment scales, with low possibility to compare results. Various assessment tools exist to evaluate specifically QoL in cSCC, such as the Skin Cancer Index, Dermatology Life Quality Index, the FACE-Q Skin Cancer Module, the SCQOLIT, and the Basal and Squamous Cell Carcinoma Quality of life questionnaire [40-44]. The EORTC QLQ C-30, has been used for cSCC patients but may lack sensitivity [45]. It should be considered that all these questionnaires have been developed before the introduction of IT in cSCC, thus they might not well address the QoL of such patients. Considering the high activity of IT in cSCC, and the possibility to reach long survival (74% alive at 2 years) [38], it is of importance to reach QoL data from real-life cohorts, in order to better address patients issues during their treatment and in the long-term follow-up.

Conclusions

Treatment of advanced cSCC has dramatically evolved in the last years and the huge benefits of IT in recurrent and/or metastatic setting have allowed designing new approaches in other disease settings. In the next few years, we will obtain the results of ongoing trials with the use of IT in neoadjuvant and adjuvant settings, and new scenarios will open. The revolution of the treatment of advanced cSCC will however be accompanied by several questions about the best integrations, the cutoff for treatment de-escalation, the long-term QoL and the affordability of this treatment in the context of an aging population.

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