Pattern of response of unresectable and metastatic cutaneous squamous cell carcinoma to programmed death-1 inhibitors: A review of the literature

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Abstract

Cutaneous squamous cell carcinoma (cSCC) is the second most frequent non-melanoma skin cancer (NMSC). The majority of in situ cSCC [cSCC (Tis)] can be cured surgically, while local advanced and metastatic ones require other treatments, but there are no therapies approved by U.S. Food and Drug Administration (FDA). Available treatments for these stages included radiotherapy, chemotherapy as cisplatin, but responses to these treatments are usually of short duration. Programmed death-1 (PD-1) inhibitors (pembrolizumab, nivolumab, and cemiplimab) are an innovative immunologic treatment that now has been shown to be useful for the treatment of advanced cSCC. Nowadays, data about the response rate with the use of PD-1 inhibitors in cSCC are still few and, especially, the duration of the response after the start of treatment is short. Moreover, the number of cases is too small to express the beneficial effects of these treatments, although most data reported in the literature show quite good response rates. This review focused on some of the studies and associated results through an interesting research on search engines of all the cases about these systemic drugs, analyzing effects and side effects, and the research has been conducted considering published cases since March 2016 to October 2019.

1 | INTRODUCTION

Nonmelanoma skin cancer (NMSC) represents one-third of all malignancies, and the most common are basal cell carcinoma (BCC) (80%) and cutaneous squamous cell carcinoma (cSCC) (20%) (Rogers, Weinstock, Feldman, & Coldiron, 2012). The exact incidence is unknown, but a recent study demonstrated an overall 263% increase in the incidence of cSCC in the periods between 1976 and 1984, and 2000 and 2010, probably due to growing elderly population and the awareness of skin cancers. Risk factors for this tumor include (a) sun exposure, (b) advanced age, (c) immunosuppression, and (d) fair skin. The majority of cSCC (Tis) can be cured surgically or with other destructive approaches (about 95%), whereas local advanced or metastatic ones (Stage III/IV) require other treatments, but their responses

are usually of short duration. Generally, cSCC has a low risk of metastasis, approximately of 1.9–2.6%, but prognosis of these patients remains poor. Relevant factors that increase the risk of death for this tumor include (a) diameter exceeding 20 mm, (b) poor differentiation, (c) location on special areas (i.e., lip, ear or temple), (d) perineural invasion, and (e) immunosuppression (Stratigos et al., 2015). Nowadays, there are no therapies approved by U.S. Food and Drug Administration (FDA) for advanced stages, and the combination of chemotherapy and radiotherapy did not improve conspicuously the prognosis (Behshad, Garcia-Zuazaga, & Bordeaux, 2017). Historically, the most frequent treatments included 5-fluorouracil, cisplatin, carboplatin, or paclitaxel, alone or in combination (Martinez, Otley, Okuno, Foote, & Kasperbauer, 2014). As second-line treatment, frequently target therapies with epidermal growth factor receptors (EGFR) inhibitors

(i.e., cetuximab) are used (Trodello, Pepper, Wong, & Wysong, 2017). Immunologic therapies are new therapeutic strategies, but they are usually prescribed off-label (Conforti, Corneli, Harwood, & Zalaudek, 2019).

cSCC is an example of tumor responding to systemic immune therapy, and this is because its mutation burden is high and the risk of cSCC is greater among immunosuppressed patients (Chalmers et al., 2017; Euvrard, Kanitakis, & Claudy, 2003; Pickering et al., 2014). Those who have been under immunosuppressive treatment after undergoing solid-organ transplantation have been demonstrated to have the risk of cSCC 65–250 times higher than in the general population (Euvrard et al., 2003). Programmed death-1 (PD-1) inhibitors are innovative immunologic treatments, and they have been shown to be useful for different types of cancers (i.e., melanoma, non-small cell lung cancer, renal cell carcinoma, and others) (Brahmer et al., 2012; Lipson et al., 2015). Some trials demonstrated the usefulness of PD-1 antibodies in recurrent and metastatic SCC of the head and neck, suggesting the potential efficacy in cSCC (Ferris et al., 2016; Seiwert et al., 2016). Pembrolizumab, nivolumab, and cemiplimab are the most commonly studied drugs among PD-1 inhibitors, and they are currently used for treatment of advanced and metastatic stages. This review reports some of the studies and results with patients undergoing PD-1 inhibitor therapy. The search was performed through search engines such as PubMed: the period covered was from March 2016 to October 2019; all subsequent cases were not included.

1.1 | A brief summary of the PD-1 inhibitors

PD-1 inhibitors are an innovative category of immunotherapeutic drugs, now approved for some skin tumors, including melanoma (Brahmer et al., 2012). The PD-1 pathway plays an important role as a mediator of immune regulation and comprehends the inhibitory coreceptor PD-1 expressed in T cells, B cells, and NK cells and its ligands PD-L1/L2 localized on antigen-presenting cells and dendritic cells, respectively. In case of neoplasm, PD-1 is expressed on tumor-infiltrating lymphocytes, whereas PD-L1/L2 on tumor cells and so the cancer can avoid the immunological surveillance by suppressing T-cell function (Pardoll, 2012). PD-1 inhibitors work by blocking PD-1 or PD-L1, leaving the immune system to act against the tumor cells and prevent deactivation of T lymphocytes, promoting self-tolerance. The number of cancers responsive to PD-1 antibodies is wide and the effectiveness of other tumors is currently in clinical testing. cSCC is an example of a tumor capable of responding to drug activity, due to the high expression of PD-1 and its ligands, as demonstrated by immunohistochemistry analysis (Blum et al., 2018; Stevenson et al., 2017). Stevenson et al. (2017) showed that PD-L1 has an increased expression on infiltrative cSCC and in cases of perineural invasion (Stevenson et al., 2017). Ribas and Hu-Lieskovan (2016) demonstrated that in some tumors (melanoma, head and neck cancer, and lung cancer), PD-L1 positivity of >1% predict the response (Ribas & Hu-Lieskovan, 2016), although lack of it does not preclude the result (Daud et al., 2016; Pickering et al., 2014). Other studies showed that cSCC is characterized by numerous genomic alterations and the latter are presented more often in immunosuppressed patients (Al-Rohil et al., 2016; Clark et al., 2008). The analysis of the whole exome sequencing of aggressive cSCC revealed the presence of 11 drivers of tumors (Pickering et al., 2014, so the study of patient mutation burden could help to identify what kind of patient may benefit from PD-1 treatments (Pickering et al., 2014). Mutational heterogeneity induces the expression of neoantigens attracting T lymphocytes, so that cancer with high mutational load could be responsive to immune checkpoint inhibitors (Palmieri et al., 2017). Table 1 summarizes the characteristics of reported cases in the literature about PD-1 inhibitors, particularly pembrolizumab, nivolumab, and cemiplimab.

1.1.1 | Pembrolizumab

Pembrolizumab (Keytruda; Merck Inc, Kenilworth, New Jersey), the first-in-class PD-1 inhibitors, was introduced since 2011 from FDA for the treatment of advanced melanoma alone or in association with ipilimumab. Recently introduced for the treatment of head and neck squamous cell carcinoma (HNSCC), similar histological appearance justified its use in cSCC. It is a human antibody able to block PD-1, avoiding the interaction with its ligand PD-L1/L2. Recommended doses are 3 mg for kilograms of weight every 3 weeks as intravenous (iv) infusion for a period of 30 minutes. Among the different PD-1 inhibitors, the number of patients treated is the widest, about 28 reported in the literature (Assam et al., 2016; Borradori et al., 2016; Chang et al., 2016; Degache et al., 2018; Deinlein et al., 2017; Ferrarotto, 2017; Lipson et al., 2016; Ravulapati et al., 2017; Stevenson et al., 2017; Tran et al., 2017; Winkler et al., 2017; Zalaudek et al., 2019), excluding the ongoing trials in Phase I and II (Licitra et al., 2017; Kudchadkar et al., 2018; Maubec et al., 2019). Although the larger number of reported cases, responses data are not enough and in addition with short period of follow-up. Chang et al. (2016) published the first case report of patient with Stage IV treated with pembrolizumab (2 mg/kg instead of 3 mg/kg usually reported). In their case, the patient showed complete response after only two cycles and after six cycles the patient was still progression free. Subsequently, Assam et al. (2016) (level of evidence [LE] 4 following Oxford CEBM Levels of Evidence) showed a case of complete response after two cycles of treatment and the maintenance of free of disease recurrence for 12 months. The latter underlined for the first time the importance of the mutational burden, evidencing the mutation in MLH1 and in the DNA miss match repair. While Stevenson et al. (2017) (LE 4 following Oxford CEBM Levels of Evidence) showed the abundant expression of PD-1 in cSCC, mainly in cases with perineural invasion. Deinlein et al. (2017) (LE 4 following Oxford CEBM Levels of Evidence) proposed for the first time pembrolizumab in Stage IV cSCC in patient affected by Xeroderma Pigmentosum (XP), a genomic syndrome due to loss of function of nucleotide excision repair pathway, causing high sensitivity to ultraviolet (UV) radiation. In this case, a rapid complete response after only three cycles was evidenced. Other reported cases of pembrolizumab in XP include, first of all Hauschild

TABLE 1 PD-1 inhibitors (such as pembrolizumab, nivolumab, and cemiplimab) are humanized antibodies used in cancer immunotherapy and it targets the programed cell death 1 (PD-1) receptor of lymphocytes. In this table, the main treatments available for unresectable or metastatic cutaneous squamous cell carcinoma are summarized

References	N	Stage	Treatment	Best overall response	Side effects	Follow-up
Deinlein et al. (2017)	1	Stage IV	Pembrolizumab	Complete response (3 cycles)	NP	8 months (11 cycles)
Chang, Kim, Luciano, Sullivan-Chang, and Colevas (2016)	1	Stage IV	Pembrolizumab	Complete response (2 cycles)	Weight loss, fatigue	4.5 months (8 cycles)
Falchook et al. (2016)	1	Stage IV	Cemiplimab/REGN2810	Complete response	NP	13 months
Tran, Colevas, and Chang (2017)	6	Stage IV	Pembrolizumab (5) Nivolumab (1)	Partial or complete response (5) Progression (1)	Fatigue, endocrine hypofunction, hip fracture	8 months
Stevenson et al. (2017)	1	Stage III	Pembrolizumab	Complete response (4 cycles)	NP	11 months
Degache et al. (2018)	2	Stage III	Pembrolizumab	Complete response (pt1 6 cycles pt2 1 cycle)	NP	NP
Ferrarotto (2017)	11	Stage IV	Pembrolizumab	Partial response (4) Stable disease (1) Progression (5)	NP	NP
Assam, Powell, and Spanos (2016)	1	Stage IV MLH1mutation	Pembrolizumab	Complete response (3 cycles)	Fatigue only after infusion	12 months
Blum et al. (2018)	3	Stage IV	Nivolumab	Partial response (2) Stable disease (1)	NP	12 months
Chen, Ali, Boasberg, and Ho (2018)	1	Stage III	Nivolumab + Cetuximab	Complete response (6 months)	NP	12 months
Miller, Faulkner-Jones, Stone, and Drews (2017)	1	Stage IV	Nivolumab + Ipilimumab	Complete response (4 cycles)	Fever, nausea vomiting, abdominal pain, oliguria, allograft rejection (patient with renal transplant)	Cardiac death 5 months later probably due to long diabetic story
Borradori, Sutton, Shayesteh, and Daniels (2016)	4	Stage IV (1) Stage III (3)	Nivolumab (2) Pembrolizumab (2)	Partial response (3) (5 cycles) 1 death due to arrhythmias (Nivolumab)	Fatigue	7 months
Migden et al. (2018)	85	Stage III (26) (Phase I) Stage IV (59) (Phase II)	Cemiplimab	Partial response 5 deaths (Stage III) 11 deaths (Stage IV)	Diarrhea, fatigue, nausea, rash constipation	7.9 months
Licitra et al. (2017)	120	Stage III/IV	Pembrolizumab KEYNOTE-629	NP	NP	2 years
Kudchadkar et al. (2018)	Phase I (12) Phase II (13)	Stage IV	Pembrolizumab MK-3475	I stage cl. trial Complete response (1) Partial response (3) Stable disease (1) Progressive disease (2) Not evaluable (3)	Hepatitis and pneumonitis	2 years

(Continues)

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TABLE 1 (Continued)

References	N	Stage	Treatment	Best overall response	Side effects	Follow-up
Maubec et al. (2019)	Stage I (19) Stage II (39)	Stage III/ IV	Pembrolizumab CARSKIN	I stage cl. Complete response (1) Progression disease (7)	Grade 3 colitis (1), rash, pruritus fatigue dysthyroidism, diarrhea	2 years
Sellah et al. (2019)	3	Stage III	Nivolumab	Complete response (8–4 cycles)	Anemia, autoimmune thyroiditis, headache	8 months
Lipson et al. (2016)	1	Stage IV	Pembrolizumab	Complete response but stopped after 2 months	Acute cell-mediated allograft rejection in patient with transplanted kidney	2 months
Ravulapati, Leung, Poddar, and Tu (2017)	1	Stage IV	Pembrolizumab	Partial response (7 cycles)	NP	NP
Winkler et al. (2017)	1	Stage IV	Pembrolizumab	Complete response (after 2 months) and progression disease (after 5 months to the beginning)	NP	4 months and stop for progressive disease
Schwab, Heine, Weimann, Kristiansen, and Brossart (2016)	1	Stage IV	Nivolumab	Partial response (8 cycles)	Generalized muscle weakness, fatigue, acute autoimmune hemolysis	5 months and stop for acute hemolysis

et al. (2017) (LE 4 following Oxford CEBM Levels of Evidence) subsequently Salomon et al. (2018) (LE 4 following Oxford CEBM Levels of Evidence) and they demonstrated a parallel therapeutic response of metastatic melanoma and primary cutaneous carcinomas. About adverse events, the most frequent are fatigue, rash, diarrhea, nausea or abdominal pain, and dysthyroidism. Only one case (Lipson et al., 2015) (LE 4 following Oxford CEBM Levels of Evidence) of acute allograft rejection is reported in a patient with Stage IV disease who has undergone renal transplantation. Nowadays, the widest open trial is KEYNOTE-629, a Phase II study enrolling 120 patients with Stage III and IV disease (Licitra et al., 2017) (LE 1b following Oxford CEBM Levels of Evidence). Maubec et al. (2019) reported partial results of the Stage I trial (CASKIN), including 19 patients (LE 1b following Oxford CEBM Levels of Evidence). Response rate (RR) of 42% at 15 weeks, corresponding to seven partial response (PR) and one complete response (CR) and only one responder progressed. The second stage of CASKIN is ongoing, enrolling an additional 39 patients, but pembrolizumab monotherapy provided encouraging clinical activity (LE 1b following Oxford CEBM Levels of Evidence). MK-3475 (Kudchadkar et al., 2018) is a Phase II open-label study, enrolling 12 patients in Phase I and additional of 13 patients subsequently (LE 1b following Oxford CEBM Levels of Evidence). Partial results of Phase I reported 10% (1) CR, 30% (3) PR, 10% (1) stable disease (SD) and 20% (2) progressive disease (PD). No deaths have been occurred, but in second grade 3 adverse events are reported including hepatitis and pneumonitis. Another ongoing clinical trial is NCT02964559 that is examining pembrolizumab as a primary treatment for advanced cSCC (Merck Sharp & Dohme Corp., 2017) (LE 1b following Oxford CEBM Levels of Evidence).

1.1.2 | Nivolumab

Nivolumab (Opdivo) is a human monoclonal antibody, approved for the first time by FDA in December 2014 for metastatic melanoma, alone (Weber et al., 2017) or in combination with ipilimumab (Wolchok et al., 2017). Subsequently, it has been approved for the treatment of other tumors including advanced non-small cell lung cancer (Horn et al., 2017) or advanced HNSCC (Ferris et al., 2016). The action of the antibodies is to block the PD-1 so that there is no interaction with PD-L1/L2 expressed on solid cancer. Recently, nivolumab has been assessed for the treatment of advanced and metastatic cSCC considering similar histological pattern with HNSCC. Recommended dose depends on the treated neoplasm and its dose for cSCC is 3 mg/kg of weight every 2 weeks administered as iv infusion over 30 minutes. About the efficacy of this drug, the number of reported cases is only 12 (Blum et al., 2018; Borradori et al., 2016; Miller et al., 2017; Pickering et al., 2014; Schwab et al., 2016; Sellah et al., 2019; Tran et al., 2017), with a short duration follow-up, the longest about 12 months (Blum et al., 2018). Blum et al. (2018) proposed three cases of Stage IV patients treated for over 12 months demonstrating partial response without particular adverse events (LE 4 following Oxford CEBM Levels of Evidence). Reports with complete response were

proposed by Sellah et al. (2019), which showed three cases of Stage III, one of them with eight cycles and 10 months of follow-up free of disease recurrence with only anemia reported among adverse events (LE 4 following Oxford CEBM Levels of Evidence). Good response was demonstrated by Chen et al. (2018) and Pickering et al. (2014) with one patient in Stage IV who has undergone a combine therapy with Nivolumab and Cetuximab, an antibody against EGFR, and after 12 months of treatment the patient remained free of disease (LE 4 following Oxford CEBM Levels of Evidence). Another example of combination therapy was reported by Miller et al. (2017) and Sellah et al. (2019) with the association of Nivolumab with Ipilimumab, an anti-CTLA-4 antibody (LE 4 following Oxford CEBM Levels of Evidence). The patient affected by diabetes and undergone renal transplantation, highlighted acute allograft rejection and subsequently death for cardiac injury not associated to the treatment but for his long history of diabetes (Sellah et al., 2019). Regarding the adverse events, it seems to be the same of the others PD-1 inhibitors, fatigue, anemia, autoimmune thyroiditis and no associated therapy deaths are revealed. As aforementioned for pembrolizumab, nivolumab was proposed in patients with XP (Chambon et al., 2018) affected by botryomycomas on the scalp (sarcomatoid cancer) and several BCCs and cSCCs (LE 4 following Oxford CEBM Levels of Evidence). Nivolumab was effective for the sarcomatoid cancer but did not prevent the development of others skin cancers.

1.1.3 | Cemiplimab

Recently approved, cemiplimab (Libtayo, REGN2810, SAR439684, and cemiplimab-rwlc) is a potent human monoclonal antibody G4 and its action is directed against PD-1 expressed on activated T cells and B cells, blocking the interaction with PD-L1/L2. It is a big protein with molecular weight of about 146,000, developed by Regeneron Pharmaceuticals and Sanofi (Markham & Duggan, 2018). This drug was granted a first approval on September 2018 in the United States and subsequently in European Union for the treatment of advanced and metastatic cSCC (Kaplon & Reichert, 2019). Other tumors are under testing to evaluate the response to cemiplimab, including non-small cell lung cancer, HNSCC, and advanced BCC (Falchook et al., 2016). Recommended doses for the treatment of cSCC include 3 mg per kilogram of body weight every 2 weeks administered as iv infusion over 30 minutes. About partial results of this drug, an ongoing study in Phase II demonstrated a response rate of 47% after 1.9 (median) months in 59 patients enrolled with metastatic cSCC (NCT02760498) (Migden et al., 2018) (LE 1b following Oxford CEBM Levels of Evidence). Median follow-up was 7.9 months and among the enrolled patients, four (7%) had complete response, 24 (41%) had partial response and 9 had SD. The duration of response was ≥6 months in 16 of 28 (57%) responders (Migden et al., 2018). Adverse events are similar to others PD-1 inhibitors, including diarrhea, fatigue, nausea, constipation and rash. Cases of death are reported by Migden et al. with 11 patients, in which 8 for progression disease and three for adverse events (Migden et al., 2018). Another trial (NCT02383212) evaluated the effects of cemiplimab in advanced cSCC enrolling 26 patients (Migden et al., 2018) (LE 1b following Oxford CEBM Levels of Evidence). The response rate was of 50%, and of these patients, no one achieved a complete response, 13 partial response and 6 SD with a follow-up of 11 months. Nowadays, other open trials are underway evaluating cemiplimab in advanced and metastatic cSCC including: NCT03198130 (Phase I) (LE 1b following Oxford CEBM Levels of Evidence), NCT03565783 (Phase II) (LE 1b following Oxford CEBM Levels of Evidence) and NCT02760498 (Phase II) (LE 1b following Oxford CEBM Levels of Evidence).

2 | CONCLUSIONS

Immune system plays an important role in tumors, because it is able to identify and destroy new developing cells. The importance of the immunosurveillance is confirmed by cases of skin cancers in immunosuppressed patients. The risk of metastatic NMSC grows in long-term immunosuppression as demonstrated in organ-transplanted patients. In addition, patients affected by lymphoproliferative disorders such as chronic lymphocytic leukemia tend to express numerous cSCCs. The introduction of PD-1 inhibitors represents a valid therapeutic strategy, but little is known about them. They include pembrolizumab, nivolumab, and the newest cemiplimab. They work by blocking the activity of PD-1 or PD-L1, in this way, preventing the deactivation of T-lymphocytes.

cSCC is an example of cancer characterized by high expression of PD-1 and its ligands, as demonstrated by immunohistochemistry analysis. In some tumors, such as melanoma, head and neck cancer, or lung cancer, PD-L1 positivity of >1% predict the response, although lack of it does not preclude the result. In addition, cSCC includes numerous genomic alterations as demonstrated by genomic analysis, so study of patient mutation burden could help to identify what kind of patient may benefit from PD-1 treatments. This is because high mutational heterogeneity induces the expression of neoantigens attracting T-lymphocytes, so that cancer with high mutational load could be more responsive to immune checkpoint inhibitors.

Pembrolizumab is the first-in-class approved for advanced stage of melanoma since 2014 from FDA. Its introduction in cSCCs has been shown to encourage clinical responses, but the results are only partial and other studies are necessary to approve this drug for cSCC.

Nivolumab, the second-in-class approved by FDA for metastatic melanoma 3-year after pembrolizumab, is another PD-1 inhibitor introduced in cSCC. The number of reported cases is smaller than the ones for pembrolizumab and each of them of short duration of follow-up. The aforementioned reports have been demonstrated good responses in association therapy too.

The newest drug cemiplimab, approved since 2018 for the treatment of metastatic and advanced stages of cSCC, has been proving encouraging results. The ongoing trials are only a few, but all of them are highlighting the effectiveness of this systemic drug.

Disposition data revealed good response with PD-1 inhibitors not only alone, but in combination with other target or immunological

therapies. Some authors proposed the combination of nivolumab with the EGFR-inhibitor cetuxibam, revealing the synergistic effect in the prevention of immune suppression. Others have attempted with the combination of nivolumab and ipilimumab, but the acute kidney injury led to the interruption of the treatments.

Regarding the adverse events, the most frequent are rash, fatigue, diarrhea, abdominal pain, and autoimmune diseases, mainly thyroiditis. The worst adverse events included hepatitis, pneumonitis, acute auto-immune haemolysis, and acute allograft rejection. The latter was reported in two cases of patients undergone to renal transplantation. Barnett, Barta and Jhaveri (2017) showed the allograft prevention in a patient treated with nivolumab with an immunosuppressive regimen consisting of sirolimus and prednisone. Most of the reported cases (Table 1) showed good tolerance to the drug without serious adverse events. Established deaths related to the treatment are not reported, but deaths during the therapy were described.

All the data about the response rate with the use of PD-1 inhibitors in advanced cSCCs are only a few and, above all the duration of the response after the initiation of the treatment is short. In addition, the number of cases is too few to express the beneficial effects of PD-1inhibitors (Table 1). The study of PD-1 expression in advanced stage could be a helpful way to predict the response to treatment, but as demonstrated by some authors, lack of expression does not preclude the failure. The study of the mutational burden could be another valid method, but it is not as necessary to understand the response to treatment. Although most studies report promising response rates of immunotherapy for advanced cSCC, it must be admitted that long-term data are currently not available. More data about long-term effect of immunotherapy with PD-1 antibodies are needed to assess the true impact of immunotherapy for advanced cSCC.

CONFLICTS OF INTEREST

The authors declare no potential conflict of interest.

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