CONFERENCE REPORT

Immunotherapy in non-melanoma skin cancer: updates and new perspectives

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Introduction

The term 'non-melanoma skin cancer (NMSC)' includes a wide range of cutaneous tumors, including cutaneous squamous cell carcinoma (CSCC) and basal cell carcinoma (BCC), which represent the largest portion of cutaneous lymphomas. CSCC and BCC are numerically the most common human cancers in Caucasians. Their incidence and prevalence have increased constantly since 1960, from 3 to 8% worldwide, despite increased awareness of the harmful effects of sunlight.[1] Distinct from other cancers, the incidence and prevalence of NMSC are not documented in a standardized manner; however, in almost all countries, the evaluation is based on small subsegments or estimates. In the United States, the annual number of cases of NMSC is, approximately, more than one million.[2] In Europe, there are some regional differences, due to registration modalities, genetic background, and/or variability in public awareness and prevention measures, with a trend for an increased incidence in Northern European countries.[3] In Italy, the updated AIRTUM data showed that BCC represents 15% of all neoplasms, with an annual incidence of 31.9/100,000 in males and 22.8/100,000 in females. BCC represents 80% of all NMSCs, while the remaining cases are usually CSCC. CSCC is cured by surgical measures in most cases but, in 3–5% of patients, they can progress into locoregionally advanced or, even, metastatic stages. The low percentages for advanced disease translate into an incidence for males of 4.2 out of 100,000 and for females of 2.4 out of 100,000 – numbers that indicate a 'rare tumor-like' occurrence.[1] Currently, there is no standard therapy for patients who develop locally advanced or metastatic CSCC.[4,5] As per the European Association of Dermatol-Oncology guidelines, curing tumor and preserving function with addition of cosmetics are the main goals of the primary treatment.[3] Surgical resection or biopsy followed by histology should always confirm the diagnosis of precancerous lesions, before using any therapeutic modality different from surgery. Radiotherapy is a fair alternative to surgery for small CSCCs in low-risk areas, for inoperable CSCC or in the adjuvant setting.[3] It may be the first option when complete resection is technically difficult or refused by the patient. Of note, radiotherapy is not curative in the advanced phase of disease.[6] Platinum-based chemotherapy may be used as second-line treatment of CSCC – the response to treatment usually lasts 4–6 months and the toxicity profile precludes its use in many patients because of their pre-existing comorbidities.[5] Epidermal growth factor receptor (EGFR) inhibitors can be used as subsequent line treatment when chemotherapy is unfeasible or there is a progressive disease. Cetuximab is the first chimeric monoclonal antibody anti-EGFR that showed encouraging results in the treatment of CSCC in anecdotal clinical cases[5,7] and achieved a median time to treatment failure of around 4 months.[7] The limitations of current treatments and their failure to achieve therapeutic targets highlight an unmet medical need for advanced CSCC treatment.

In this report, we provide background on NMSC and describe the updates and new perspectives that were discussed during the symposium 'CSCC It Bridge' held in Naples, Italy, 28–29 November 2018.

Overview of NMSC

Skin cancer represents the most frequently diagnosed cancer, as it affects the skin, which is the first barrier against all damaging agents. The most common skin cancers have a

different histological origin: BCC is a slow progressing, non-melanocytic cancer, arising from basal cells, while CSCC arises from malignant proliferation of epidermal keratinocytes.[8] In rare cases, NMSC progresses to locally advanced disease due to negligence, comorbidities, or immunosuppression.[9]

Immunosuppression, UV exposure, and age are risk factors also for Merkel-cell carcinoma (MCC), associated with poor survival.[10,11] MCC is a chemosensitive disease. Chemotherapy responses, however, are seldom durable and thus have little impact on survival.[12–14] Recent reports suggest that checkpoint blockade is the best option to treat patients with advanced MCC.[15]

BCC is most frequently found in males (ratio 2.1:1) and in elderly patients (median age at diagnosis: 67 years); 80% of all BCCs arise in the head and neck region and, rarely, on the hands.[16] BCC can progress to locally advanced BCC with lesions not eligible for surgery or radiotherapy, or to metastatic BCC (mBCC) (0.0028–0.55% of all BCCs), which has a very poor prognosis with a median survival of 8–14 months and a 5-year survival rate of 10%. A mutation of the PTCH1 gene on chromosome 9q, which deregulates the Sonic Hedgehog (SHH) signaling pathway, is present in 30–90% of BCCs.[17,18] In a clinical trial, the inhibition of the deregulated SHH pathway with the small molecule inhibitor, vismodegib, achieved good clinical outcomes. A progression-free survival of 9.3 months in mBCC and 12.9 months in locally advanced BCC was reported together with a duration of response of 12.9 months in mBCC and 26.2 months in locally advanced BCC.[19] An overall survival of 33.4 months in mBCC was also reported.[19] Additionally, long-term exposure to vismodegib was not associated with worsening severity/frequency of treatment emergent adverse events (TEAEs), as stated by the primary analysis of STEVIE (SafeTy Events in VIsmodEgib study).[20]

Clinical trials with immunotherapeutic agents, including cemiplimab, a fully human, anti-PD1, monoclonal antibody, and pembrolizumab, a humanized antibody targeting the PD-1 receptor, are ongoing.

CSCC mostly affects the elderly population and, in the majority of cases, it occurs on the head and neck.[21] It usually originates from precancerous lesions such as actinic keratosis, but it can also develop *de novo*.[8] It is not an aggressive disease and has an excellent prognosis in more than 90% of the cases; however, there are some very aggressive cases with poor outcomes (7% of recurrence at 5 years).[22] The incidence of aggressive biologic behavior is 36-fold higher in organ transplant recipients. In a single institute cohort study, locally advanced CSCC was reported in 4.6% of patients and metastatic CSCC (mCSCC) in about 3.7%.[23] In both cases, these incidences were similar to a rare disease. The thickness of lesion is a predictor for metastatic risk: if the lesion is thicker than 2 mm, the risk of relapse increases. Other risk factors associated with poor outcomes in CSCC are the diameter of lesion (>2 cm), invasion beyond subcutaneous fat (Breslow >6 mm), and poor differentiation.[24]

Current EDF-EADO-EORTC CSCC guidelines[3] stratify patients by prognostic risk factors for recurrence or metastasis and recommend a different treatment according to stage and risk of progression. Currently available treatments for mCSCC include chemotherapy[25] and targeted therapies (EGFR inhibitors).[26]

In patients with CSCC, it was found that there is an increase of PD-L1 expression in high-risk CSCC, and in patients with mCSCC[27] – this may be used to predict the impact that anti-PD-1 can have on these types of tumors. Most recently, Patel and colleagues stated that PD-1 inhibitors may show utility in treating CSCC.[28]

CSCC updates and new perspectives on treatment

The change in the behavior in Western European, Australian, and Northern American areas that led to more vacations in sunny places and more outdoor activities has had an impact on the incidence of NMSC and, particularly, CSCC. In the Netherlands, an increased incidence from 22.2 in 1989 to 35.4 in 2008 in men and from 7.8 in 1989 to 20.5 in 2008 in women was recorded,[29] whereas in Germany there are 180,000 new cases of non-melanoma skin cancer per year, out of which 32,000 are CSCC.[30] If BCC (ratio to CSCC 4:1) is added, the scenario is an epidemic, at least for dermatologic surgeons, who have to deal with diagnosis and first-line treatment.

What has been learnt over recent years is that NMSC is clearly associated with immune status, as proven by the incidence of CSCC in organ transplant patients who are undergoing continuous immunosuppression. On the other hand, melanoma does not increase as much as NMSC, although melanoma is considered very sensitive to the immune system and to its variations. MCC increased 50-fold in transplant patients, Kaposi sarcoma increased 84-fold, and CSCC increased 65-fold, making it a leading cause of death in organ transplant patients.[31]

Looking at predictive factors for recurrence and death, Schmults and colleagues retrospectively considered data from 985 patients with CSCC with a long-term follow-up (close to 50 months).[23] They reported a local relapse rate of 4.6%, lymph node metastases in 3.7% of cases, and death in 2.1%. A German study found that tumor thickness was a strong prognostic impact in CSCC outcome.[32]

These results were confirmed in a meta-analysis of 36 clinical case studies with more than 17,000 patients that correlated tumor thickness to recurrence and metastasis.[33] Invasion beyond the subcutaneous fat layer is a strong predictor, associated with a hazard ratio of 11.21 for developing metastasis. Other factors of critical importance include poor differentiation and localization, in addition to immunosuppression.

Current standard of care for CSCC is surgical resection with histological control of margins. More than 95% of these tumors can be controlled in this way. Problems arise when

the tumor is inoperable, locally advanced, or metastatic and there is no real standard of care. Data on possible therapeutic alternatives, such as platinum-based chemotherapy or cetuximab, are not very promising. On the contrary, checkpoint blockade and immunotherapy offer more hope, based on encouraging data in head and neck cancer from therapies with anti-PD-1 antibodies and the presence of a high UV-mutation burden in CSCC. In animal studies, overexpression of PD-1 ligand in the epidermis accelerated CSCC development, thus suggesting that targeting the immune system could be effective to treat CSCC.

Consistently, a case report described an excellent durable tumor response with pembrolizumab (2 mg/kg every 3 weeks) in a 79-year old man with multifocal, inoperable CSCC with massive infiltration.[34]

A new era in the setting of mCSCC has been paved by the advent of anti-PD-1 immunotherapy, with solid evidence arising not only from single cases but also from the clinical development program that led to FDA approval of cemiplimab, an anti-PD1 antibody developed by Regeneron and Sanofi.

The results from the phase I and phase II studies with cemiplimab were presented at the American Society of Clinical Oncology (ASCO) conference in 2018. The study included patients with locally advanced and metastatic CSCC. In the phase I study, cemiplimab was administered every 2 weeks for up to 48 weeks in 26 patients (10 with metastatic disease and 16 with locally advanced disease).[35] Patients' characteristics included a median age over 70 years, comorbidities, an aging immune system, and an ECOG performance status score of 0 or 1. Most of the patients had undergone previous treatments, including prior radiation therapy and prior systemic treatments (usually chemotherapy). An independent central review committee performed tumor response assessment every 8 weeks to determine the overall response rate. The results showed a partial response rate of 50%, a durable disease control rate of 65.4%, and a quick onset of the clinical response.[35]

In the phase II study,[36,37] cemiplimab was administered for up to 96 weeks to determine the overall response rate, duration of response, stabilization of the disease and the response, progression-free survival, and overall survival. It included 59 patients with metastatic disease (with similar characteristics to the phase I trial) who were treated with cemiplimab, 3 mg/kg or a single dose of 350 mg. The overall response rate was 47.5% and the disease control rate was 61%, with 6.8% of patients achieving a complete response.[36]

Some additional data demonstrated that a high proportion of patients achieved significant tumor shrinkage in the locally advanced and metastatic stage.[37] The overall response rates were clearly associated with the status of prior systemic treatments – patients with no prior systemic treatment had response rates close to 60% and those with prior systemic treatment had response rates close to 40%. The median

duration of response had not been reached at data cutoff and the estimated progression-free survival probability at 1 year was about 50%, whereas the probability of survival at 1 year was more than 80%. These data are very encouraging and may help establish a new standard of care for locally advanced and metastatic CSCC.

The FDA approved cemiplimab for advanced and metastatic melanoma in September 2018, and its approval in Europe is expected by the middle of 2019.

The importance of anti-PD-1 antibodies has been further supported by data on treatment with pembrolizumab, presented at the ASCO meeting 2018.[38,39] A phase II trial with pembrolizumab on 39 patients with unresectable CSCC, with no prior systemic treatment and a median age of 80 years, showed a response rate of 42% and a median progression-free survival of around 7 months.

The CSCC population may be higher than estimated

As happened with BCC and MCC, once a new treatment is approved and marketed, the number of patients to treat may be higher than the estimated population. This has happened with new therapies for CSCC as well – already, when the clinical trials started, there were more patients than those estimated, mainly because registries were not reliable tools for accounting these patients. More than 95% of patients do not metastasize and are mainly managed in the surgical setting. Generally, these patients are elderly patients, with a higher rate of neglect at the end of life. Considering how much CSCC affects quality of life, there is a strong urgency to treat this population appropriately and provide the best care also in this phase of life.

Elderly patients present similar efficacy endpoint results as young patients

Age does not seem to play a role in the immunotherapeutic response. It would even seem that some elderly patients do even better with checkpoint blockade than younger patients. How this may fit with the concept of an aging immune system needs to be further studied. Results of a retrospective analysis showed that immunotherapy in elderly patients had the same efficacy than that in younger patients,[40] and the clinical trials involving anti-PD-1 in the treatment of melanoma and lung cancer have led to similar conclusions.

Conclusion

NMSC represents the most frequently diagnosed human cancer, and its incidence is constantly growing. The most common types of NMSC are BCC and CSCC. More than 95% of

patients are treated and cured thanks to surgery; nevertheless, a small percentage of patients progress to locally advanced or to metastasizing carcinoma, mainly due to negligence, comorbidities, or immunosuppression.

Indicators of poor outcome include lesion thickness, lesion diameter, invasion beyond subcutaneous fat, and poor differentiation. Guidelines present a clear discrimination of patients by prognostic risk factors, leading to a clear differentiation of treatment. Currently available treatments for mCSCC include chemotherapy and targeted therapies. Recent studies suggest that we may be on the verge of a new era of advanced CSCC treatment with the advent of checkpoint control. Clinical studies with anti-PD-1 antibodies, such as cemiplimab and pembrolizumab, have shown promising results in patients with locally advanced and metastatic CSCC. Therefore, there is a strong hope that these new therapies will have an important role in NMSC, by addressing the unmet medical need that affects not only survival but also the quality of life of patients.

References

1. AIRTUM Analisi epidemiologica e caratterizzazione morfologica di pazienti affetti da tumore della cute non melanoma da registro nazionale AIRTUM. https://www.registri-tumori.it/cms/pubblicazioni/report-i-tumori-cutanei
2. Glass AG, Hoover RN. The emerging epidemic of melanoma and squamous cell skin cancer. *JAMA*. 1989;262(15):2097–2100.
3. Stratigos A, Garbe C, Lebbe C, et al. Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. *Eur J Cancer*. 2015;51(14):1989–2007. http://doi.org/10.1016/j.ejca.2015.06.110

4. Harwood CA, Proby CM, Inman GJ, et al. The promise of genomics and the development of targeted therapies for cutaneous squamous cell carcinoma. *Acta Derm Venereol*. 2016;96(1):3–16. http://doi.org/10.2340/00015555-2181

5. Hillen U, Leiter U, Haase S, et al. Advanced cutaneous squamous cell carcinoma: a retrospective analysis of patient profiles and treatment patterns-results of a non-interventional study of the DeCOG. *Eur J Cancer*. 2018;96:34–43. http://doi.org/10.1016/j.ejca.2018.01.075

6. Peris K, Alaibac M, Argenziano G, et al. Cutaneous squamous cell carcinoma. Italian Guidelines by SIDeMaST adapted to and updating EADO/EDF/EORTC guidelines. *G Ital Dermatol Venereol*. 2018;153(6):747–762. http://doi.org/10.23736/S0392-0488.18.06093-5

7. Maubec E, Petrow P, Scheer-Senyarich I, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. *J Clin Oncol*. 2011;29(25):3419–3426. http://doi.org/10.1200/JCO.2010.34.1735

8. Garcovich S, Colloca G, Sollena P, et al. Skin cancer epidemics in the elderly as an emerging issue in geriatric oncology. *Aging Dis*. 2017;8(5):643–661. http://doi.org/10.14336/AD.2017.0503

9. Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. *N Engl J Med*. 2017;377(25):2500–2501. http://doi.org/10.1056/NEJMc1713444

10. Lebbe C, Becker JC, Grob JJ, et al. Diagnosis and treatment of Merkel cell carcinoma. European consensus-based interdisciplinary guideline. *Eur J Cancer*. 2015;51(16):2396–2403. http://doi.org/10.1016/j.ejca.2015.06.131

11. Bichakjian CK, Olencki T, Aasi SZ, et al. Merkel cell carcinoma, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2018;16(6):742–774. http://doi.org/10.6004/jnccn.2018.0055

12. Cowey CL, Mahnke L, Espirito J, et al. Real-world treatment outcomes in patients with metastatic Merkel cell carcinoma treated with chemotherapy in the USA. *Future Oncol*. 2017;13(19):1699–1710. http://doi.org/10.2217/fon-2017-0187

13. Becker JC, Lorenz E, Ugurel S, et al. Evaluation of real-world treatment outcomes in patients with distant metastatic Merkel cell carcinoma following second-line chemotherapy in Europe. *Oncotarget*. 2017;8(45):79731–79741. http://doi.org/10.18632/oncotarget.19218

14. Iyer JG, Blom A, Doumani R, et al. Response rates and durability of chemotherapy among 62 patients with metastatic Merkel cell carcinoma. *Cancer Med*. 2016;5(9):2294–2301. http://doi.org/10.1002/cam4.815

15. Hauschild A, Schadendorf D. Checkpoint inhibitors: a new standard of care for advanced Merkel cell carcinoma? *Lancet Oncol*. 2016;17(10):1337–1339. http://doi.org/10.1016/S1470-2045(16)30441-7

16. Loh TY, Rubin AG, Brian Jiang SI. Basal cell carcinoma of the dorsal hand: an update and comprehensive review of the literature. *Dermatol Surg*. 2016;42(4):464–470. http://doi.org/10.1097/DSS.0000000000000695.

17. Hahn FM, Xuan JW, Chambers AF, et al. Human isopentenyl diphosphate: dimethylallyl diphosphate isomerase: overproduction, purification, and characterization. *Arch Biochem Biophys*. 1996;332(1):30–34. http://doi.org/10.1006/abbi.1996.0312

18. Fecher LA, Sharfman WH. Advanced basal cell carcinoma, the hedgehog pathway, and treatment options – role of smoothened inhibitors. *Biologics*. 2015;9:129–140. http://doi.org/10.2147/BTT.S54179

19. Sekulic A, Migden MR, Basset-Seguin N, et al. Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: final update of the pivotal ERIVANCE BCC study. *BMC Cancer*. 2017;17(1):332. http://doi.org/10.1186/s12885-017-3286-5

20. Basset-Séguin N, Hauschild A, Kunstfeld R, et al. Vismodegib in patients with advanced basal cell carcinoma: primary analysis of STEVIE, an international, open-label trial. *Eur J Cancer*. 2017;86:334–348. http://doi.org/10.1016/j.ejca.2017.08.022

21. Dean NR, Sweeny L, Magnuson JS, et al. Outcomes of recurrent head and neck cutaneous squamous cell carcinoma. *J Skin Cancer*. 2011;2011:972497. http://doi.org/10.1155/2011/972497

22. Khan K, Mykula R, Kerstein R, et al. A 5-year follow-up study of 633 cutaneous SCC excisions: rates of local recurrence and lymph node metastasis. *J Plast Reconstr Aesthet Surg*. 2018;71(8):1153–1158. http://doi.org/10.1016/j.bjps.2018.03.019

23. Schmults CD, Karia PS, Carter JB, et al. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma: a 10-year, single-institution cohort study. *JAMA Dermatol*. 2013;149(5):541–547. http://doi.org/10.1001/jamadermatol.2013.2139

24. Subramaniam P, Olsen CM, Thompson BS, et al. Anatomical distributions of basal cell carcinoma and squamous cell carcinoma in a population-based study in Queensland, Australia. *JAMA Dermatol*. 2017;153(2):175–182. http://doi.org/10.1001/jamadermatol.2016.4070

25. Hiura A, Yoshino K, Maeda T, et al. Chemoradiotherapy could improve overall survival of patients with stage IV cutaneous squamous cell carcinoma: analysis of 34 cases. *Br J Dermatol*. 2019 Feb 21. http://doi.org/10.1111/bjd.17792

26. Trodello C, Higgins S, Ahadiat O, et al. Cetuximab as a component of multimodality treatment of high-risk cutaneous squamous cell carcinoma: a retrospective analysis from a single tertiary academic medical center. *Dermatol Surg*. 2019;45:254–267. http://doi.org/10.1097/DSS.0000000000001755

27. Slater NA, Googe PB. PD-L1 expression in cutaneous squamous cell carcinoma correlates with risk of metastasis. *J Cutan Pathol*. 2016;43(8):663–670. http://doi.org/10.1111/cup.12728

28. Patel R, Chang ALS. Immune checkpoint inhibitors for treating advanced cutaneous squamous cell carcinoma. *Am J Clin Dermatol*. 2019 Feb 8. http://doi.org/10.1007/s40257-019-00426-w

29. Hollestein LM, van den Akker SA, Nijsten T, et al. Trends of cutaneous melanoma in The Netherlands: increasing incidence rates among all Breslow thickness categories and rising mortality rates since 1989. *Ann Oncol*. 2012;23(2):524–530. http://doi.org/10.1093/annonc/mdr128

30. Kraywinkel WU, Katalinic A. Malignant neoplasms of the skin – epidemiology and screening programme. *UMID Umwelt und Mensch Informationsdienst* (Themenheft UV-Strahlung). 2012;2:30–34.

31. Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. *J Am Acad Dermatol*. 2002;47(1):1–17; quiz 18–20.

32. Brantsch KD, Meisner C, Schönfisch B, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. *Lancet Oncol*. 2008;9(8):713–720. http://doi.org/10.1016/S1470-2045(08)70178-5

33. Thompson AK, Kelley BF, Prokop LJ, et al. Risk factors for cutaneous squamous cell carcinoma recurrence, metastasis, and disease-specific death: a systematic review and meta-analysis. *JAMA Dermatol*. 2016;152(4):419–428. http://doi.org/10.1001/jamadermatol.2015.4994

34. Borradori L, Sutton B, Shayesteh P, et al. Rescue therapy with anti-programmed cell death protein 1 inhibitors of advanced cutaneous squamous cell carcinoma and basosquamous carcinoma: preliminary experience in five cases. *Br J Dermatol*. 2016;175(6):1382–1386. http://doi.org/10.1111/bjd.14642

35. Owonikoko TK, Papadopoulos KP, Gil-Martin M, et al. Phase 1 study of cemiplimab, a human monoclonal anti-PD-1, in patients with unresectable locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC): final efficacy and safety data. *Ann Oncol* 2018;29:x24–x38. http://doi.org/10.1093/annonc/mdy487

36. Rischin, D, Midgen MR, Chang A, et al. Primary analysis of phase 2 results for cemiplimab, a human monoclonal anti-PD-1, in patients with metastatic cutaneous squamous cell carcinoma (mCSCC). *J Clin Oncol*. 2018;36(15_suppl):9519.

37. Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *N Engl J Med*. 2018;379(4):341–351. http://doi.org/10.1056/NEJMoa1805131

38. Kudchadkar RR, Yushak ML, Lawson DH, et al. Phase II trial of pembrolizumab (MK-3475) in metastatic cutaneous squamous cell carcinoma (cSCC). *J Clin Oncol*. 2018;36(15_suppl):9543.

39. Maubec E, Boubane M, Petrow P, et al. Pembrolizumab as first line therapy in patients with unresectable squamous cell carcinoma of the skin: interim results of the phase 2 CARSKIN trial. *J Clin Oncol*. 2018;36(15_suppl):9534.

40. Betof AS, Nipp RD, Giobbie-Hurder A, et al. Impact of age on outcomes with immunotherapy for patients with melanoma. *Oncologist*. 2017;22(8):963–971. http://doi.org/10.1634/theoncologist.2016-0450