Skin Cancer Research Review™

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Independent commentary by Associate Professor Andrew Haydon

Associate Professor Andrew Haydon is a full-time Medical Oncologist at the Alfred Hospital and a member of the Victorian Melanoma Service, having joined the service in 2001. He is also an Adjunct Senior Lecturer at the Department of Epidemiology and Preventive Medicine, Monash University and an Honorary Associate and Member of the NHMRC Clinical Trials Centre, School of Public Health, University of Sydney. Andrew completed his PhD at Monash University/Cancer council Victoria in 2004. Over the last 18 years, he has been the principle investigator for over 30 international clinical trials that he has run at the Alfred Hospital for patients with advanced melanoma, with many of these studies leading to major changes in the treatment of this disease. Dr Haydon has authored or co-authored over 60 peer reviewed journal publications and has given numerous local and international presentations on the management of metastatic melanoma.

Welcome to the latest issue of Skin Cancer Research Review.

This issue we focus on new therapeutic options in advanced cutaneous squamous cell carcinoma (cSCC). Whilst surgical excision of the primary tumour successfully treats the majority of patients with cSSC, for those patients who are ineligible for surgery or have metastatic or locally recurrent cancer, systemic therapeutics are limited and a poor long-term prognosis is common. New therapies including epidermal growth factor (EGFR) receptor tyrosine kinase inhibitors and immune checkpoint inhibition targeting programmed cell death protein 1 or its ligand (PD-1/ PD-L1) such as the monoclonal antibodies pembrolizumab and cemiplimab offer new hope in this arena showing high efficacy with minimal adverse effects. Two phase 2 trials of pembrolizumab – the global KEYNOTE-629 trial and the French CARSKIN trial – demonstrate its efficacy in patients with unresectable cSCC, both in the front-line setting in treatment-naïve patients and in the recurrent/metastatic setting, where it has demonstrated a clinically meaningful, durable antitumour activity and conferred delays in disease progression and survival benefits. A subgroup analysis of the CARSKIN trial showed improved responses in patients with PD-L1-positive tumours indicating that treatment optimisation may be allowed by treatment pre-screening. The US Food and Drug Administration recently approved pembrolizumab for use in cSCC based on the efficacy and safety results from the KEYNOTE-629 trial. The efficacy of PD-1 inhibition is supported by a real-world retrospective analysis of pembrolizumab, nivolumab or cemiplimab in Germany which reports even higher response rates than that achieved in clinical trials with a very safe profile that was tolerated even in very elderly patients. We also look at preliminary evidence for the efficacy and safety of immune checkpoint inhibition in solid transplant recipients with advanced cSCC and an indirect comparison of systemic therapies.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,

Associate Professor Andrew Haydon

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Clinical outcomes among unresectable, locally advanced, and metastatic cutaneous squamous cell carcinoma patients treated with systemic therapy

Authors: Cowey C et al.

Summary: This retrospective analysis of data from patients with advanced (locally advanced or metastatic) cSCC in the US Oncology Network provides real-world information regarding outcomes of front-line systemic therapy in an era before the availability of cemiplimab. A total of 82 patients (median age 75 years; 17 with locally advanced disease and 65 with metastatic disease; disease most commonly located on the head and neck) who were not eligible for curative-intent radiotherapy or surgery and underwent systemic therapy in the eight-year period encompassing 2008 to 2015 were included in the study. In the overall population, platinum and taxane combinations and platinum-based regimens were the most frequently prescribed front-line therapy, given to half of all patients (carboplatin plus paclitaxel, cisplatin plus 5-fluorouracil, carboplatin plus cetuximab and paclitaxel, cisplatin monotherapy or 5-fluorouracil plus cisplatin and cetuximab) but monotherapy with the EGFR-targeting agent cetuximab was used in almost one-quarter of patients (24.4%). In patients with metastatic disease, cetuximab monotherapy was the most commonly used front-line therapy, used by over half of patients (52.9%), followed by platinum and taxane combination regimens. Efficacy was limited with an overall response rate of 18.3% (17.6% vs 18.5% for locally advanced vs metastatic disease, respectively) with a median duration of 2.4 months of therapy. Kaplan-Meier overall survival (OS) estimates were 16.2 months in the population with locally advanced disease and 15.3 months in metastatic disease. Less than 30% of patients progressed to second-line therapy.

Comment: This was a retrospective study of patients who were treated with any form of systemic therapy between 2008 and 2017 within The US Oncology Network for locally advanced or metastatic cSCC. The US Oncology Network is made up of a large group of community based oncologists. As such, these patients received therapy prior to the availability of cemiplimab (and very likely other anti-PD-1 treatments). Most patients received platinum-based regimens (usually with paclitaxel or 5-fluorouracil /capecitabine), however, a significant proportion (24%) received cetuximab alone. Median OS was 15.3 months, with physician-reported response rates of 18.3% for the entire cohort of 82 patients. Given that recent data for anti PD-1 therapy is not randomised against chemotherapy, these data at least give us some benchmark for comparison, when we try to assess outcomes from studies using immunotherapy in these patients.

Reference: Cancer Med 2020;9(20):7381-87

Abstract

Abbreviations used in this issue:

CI = confidence interval; **cSCC** = cutaneous squamous cell carcinoma; **EGFR** = epidermal growth factor receptor; **OR** = odds ratio; **ORR** = objective response rate; **OS** = overall survival; **PD-1/PD-L1** = programmed cell death protein 1/ligand 1; **PFS** = progression-free survival; **PNI** = perineural infiltration.

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Phase II study of pembrolizumab as first-line, single-drug therapy for patients with unresectable cutaneous squamous cell carcinomas

Authors: Maubec E et al., for the Groupe de Cancérologie Cutanée, de la Société Française de Dermatologie, Paris, France

Summary: The French phase 2, open-label, non-randomised CARSKIN trial (ClinicalTrials.gov Identifier: NCT02883556) assessed front-line pembrolizumab monotherapy for patients with unresectable cSCC. A total of 39 chemotherapy and EGFR inhibitor naïve patients with baseline biopsy characterisation received pembrolizumab (200 mg every three weeks) until disease progression or unacceptable toxicity. At week 15 the objective response rate (ORR) was 41% in the primary cohort, consisting of three complete responses and 13 partial responses. Efficacy outcomes at a median follow-up of 22.4 months showed anti-tumour activity with a median progression-free survival (PFS) of 6.7 months and OS of 25.3 months. The median duration of response was not reached. Analysis of an expansion cohort (n=18) revealed a significantly improved ORR in patients with PD-L1 positive tumours (55% vs 17%; p=0.02).

Comment: This is a multicentre, open label, phase 2 study that was conducted in 25 hospitals across France and enrolled 39 systemic therapy naïve patients with unresectable (75%) or metastatic (25%) cSCC. All patients were treated with pembrolizumab 200 mg three-weekly. The response rate at 15 weeks was 41%. Five patients who were in partial response at 15 weeks went on to achieve a complete response between weeks 15 and 72. With a median follow-up of 22 months, none of the responders had progressed, suggesting a very impressive duration of response in this population. Median OS was 25.3 months, which compares favourably with historical controls treated with chemotherapy. Patients with PD-L1 positive tumours were more likely to respond to pembrolizumab (55% vs 17%).

Reference: J Clin Oncol 2020;38(26):3051-61
Abstract

Pembrolizumab monotherapy for recurrent or metastatic cutaneous squamous cell carcinoma: a single-arm phase II trial (KEYNOTE-629)

Authors: Grob J-J et al.

Summary: Interim results from the phase 2 KEYNOTE-629 trial (ClinicalTrials.gov Identifier: NCT03284424) of pembrolizumab monotherapy published in the *Journal of Clinical Oncology* by Jean-Jacques Grob et al. indicate that pembrolizumab monotherapy is an effective therapeutic for recurrent and/or metastatic cSCC. The global single-arm Merck Sharp & Dohme Corp.-sponsored trial enrolled a total of 105 adult patients with cSCC into two cohorts – the recurrent/metastatic cohort with disseminated disease distant to the primary and the locally advanced cohort. All patients had unresectable disease not amenable to curative-intent surgery, radiotherapy or systemic therapy and received pembrolizumab 200 mg every three weeks for up to 35 infusions. This report provides interim results from the recurrent/metastatic cohort with a median of 11.4 months follow-up (data cut-off April 8, 2019). A disease control rate of 52.4% was revealed. The median PFS was 6.9 months with 32.4% of patients free of disease progression at 12-months. The median OS and the median duration of response were not reached.

Comment: Keynote-629 is an open-label, multi-national phase 2 study of pembrolizumab for locally advanced or recurrent/metastatic cSCC. Treatment was given for up to two years, and the primary end-point was response rate. 105 patients were enrolled, making this a reasonably large study in this population, however, the median follow-up was only 11 months, so conclusions regarding survival and duration of response are hard to be confident about. The ORR was 34%, with only 4% achieving a complete response. The number of complete responses may have been higher with longer follow-up as late conversions from partial to complete response can occur in this setting. Median OS had not been reached, but 60% of patients were alive at 12-months. This study confirms the activity of PD-1 based therapy in cSCC. Given this is the first interim analysis of KEYNOTE-629, longer follow-up will be needed to see how durable responses are and what the survival benefits may be.

Reference: J Clin Oncol 2020;38(25):2916-25
Abstract

Programmed cell death protein 1 inhibitors in advanced cutaneous squamous cell carcinoma: real-world data of a retrospective, multicenter study

Authors: Salzmann M et al.

Summary: Martin Salzmann and colleagues report a retrospective analysis of the real-world efficacy of PD-1 inhibition in German patients with advanced cSCC. A total of 46 patients (median age 76 years) treated at one of six German skin cancer centres with pembrolizumab, nivolumab or cemiplimab were included. An ORR of 58.7% was reported in patients with either locally advanced or metastatic disease with 15.2% of patients achieving a complete response that was durable. Median PFS and OS was not reached. Primary disease that was located on the leg and high baseline lactate dehydrogenase serum levels were negative prognostic factors. The treatment was reported as safe and tolerated even by very elderly patients.

Comment: Another retrospective study, this time from Germany, looking at the outcomes of patients treated with anti-PD-1 immunotherapy for cSCC. Patients received either nivolumab, pembrolizumab or cemiplimab. Response rates were high at 59% and seen across the three agents used, and although the study was clearly not designed to compare between the three agents, no difference was seen. This study did suggest a poorer outcome in patients with an elevated lactate dehydrogenase serum level, a well-recognized prognostic marker in melanoma, which is worthy of further investigation.

Reference: Eur J Cancer 2020;138:125-32
Abstract

Recurrent and metastatic cutaneous squamous cell carcinomas in a cohort of 774 patients in Finland

Authors: Korhonen N et al.

Summary: In this medical record and pathology database study Niina Korhonen and colleagues report the rates of local recurrences and metastases from cSSC in a Finnish cohort. The cohort of 774 patients with a total of 1,131 tumours had a local recurrence rate of 2.2% and a metastasis rate of 4.2%. More than half of metastases (58%) were identified within three months of original diagnosis and were noted even in cases of thin carcinoma (3/8; invasion depth ≤ 2 mm). The authors suggest risk ascertainment for patients with cSCC and monitoring in high-risk cases.

Comment: In this retrospective study, patients with cSCC were identified from a search of the pathology database in Finland and then data collected from reviewing the patient's medical records. 25 of 774 patients developed a local recurrence with risk factors for local recurrence being depth of invasion, poorly differentiated tumours and tumour location on scalp/face, however none of these factors statistically significantly predicted local recurrence risk. On the other hand, location (face/scalp), degree of differentiation and depth of invasion were all highly significant predictors of development of metastatic disease (p< 0.001 for all three factors). Interestingly, the researchers failed to show any association between the use of immunosuppressive agents and risk of recurrence which is contrary to established beliefs. The other finding of note was that most recurrences occurred early and all occurred within two years, suggesting close follow up for the first few year's post resection of a high-risk tumour.

Reference: Acta Derm Venereol 2020;100(8):adv00121
Abstract

Prognostic impact of perineural invasion in cutaneous squamous cell carcinoma

Authors: Haug K et al.

Summary: This retrospective study of 1,399 cSCC tumours (from 1,434 patients) from a group at the University of Tübingen, Germany, finds that the presence of perineural infiltration (PNI) is a negative prognostic indicator, associated with a high-risk of both local cancer recurrence and metastasis. PNI was identified though histological examination. PNI manifestation was only found in desmoplastic type tumours, present in 14.5% of cases. Patients with desmoplastic type tumours and PNI had significantly more lymph node metastases (29% vs 3% vs 17%, respectively), local recurrences (64% vs 3% vs 26%) and higher tumour-specific mortality (54% vs 4% vs 25%) compared to patients with non-desmoplastic tumours or desmoplastic tumours without PNI. Multivariate analysis found tumour thickness ≥ 6 mm, tumour horizontal size ≥20 mm, immunosuppression, desmoplasia and PNI all significant independent factors for disease recurrence.

Comment: This study also demonstrates nicely the prognostic value of PNI in predicting recurrence risk in CSCC. It also demonstrated the relationship between PNI and desmoplasia and in particular the danger of tumours with both PNI and desmoplasia pose.

Reference: J Invest Dermatol 2020;140(10):1968-75
Abstract

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Time to response
Median time to response was at the first assessment for Groups 1-3 (time of first assessment was 8 or 9 weeks, depending on dosing group)[1]

Duration of response[*]
Median duration of response was not reached for Groups 1-3[1]

*Data cut-off was Sep 20, 2018 for Groups 1 and 3 patients, and Oct 10, 2018 for Group 2 patients.[1]

†Median duration of follow up for Group 1: 16.8 months (mCSCC), Group 2: 9.3 months (laCSCC), Group 3: 8.1 months (mCSCC)[1]

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▼This medicinal product is subject to additional monitoring in Australia due to provisional approval. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

Abbreviations: CSCC, Cutaneous Squamous Cell Carcinoma; **ORR,** overall response rate.

References: 1. LIBTAYO® (cemiplimab) Approved Product Information. July 2020.

Sanofi and Regeneron are collaborating in the global development and commercialisation for LIBTAYO (cemiplimab).

SANOFI GENZYME

Comparative efficacy of cemiplimab versus other systemic treatments for advanced cutaneous squamous cell carcinoma

Authors: Keeping S et al.

Summary: This systematic review provides an indirect comparison of systemic therapies for advanced cSCC (locally advanced or metastatic) with the aim of elucidating the efficacy of the PD-1 inhibitor cemiplimab compared to pembrolizumab, EGFR inhibitors and chemotherapy. An online search of Excerpta Medica Database (Embase), Medical Literature Analysis and Retrieval System Online (MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL) and the WHO International Clinical Trials Registry Platform identified 27 studies (14 non-randomised, non-blinded clinical trials and 13 observational studies) that provided treatment-related outcomes in cSCC. A total of 11 studies that included Kaplan-Meier curves for PFS and OS were included in the analysis – seven studies of EGFR inhibitors (n=262, erlotinib, cetuximab, gefitinib, dacomitinib and panitumumab), two studies of pembrolizumab (n=144) and one trial of platinum-based chemotherapy (n=18). Reported outcomes were compared to the Regeneron Pharmaceuticals-sponsored phase 2 trial of cemiplimab (ClinicalTrials.gov Identifier: NCT02760498; n=193) in an unadjusted comparison, a regression-based simulated treatment comparison and a matching-adjusted indirect comparison using propensity score weighting. The longest reported median PFS was achieved with the PD-1 inhibitors cemiplimab and pembrolizumab with 18.4 and up to 14.2 months, respectively. The extension of PFS with cemiplimab treatment ranged from over six months compared to that achieved with chemotherapy (median PFS 9.8 months) to between 8.7 and 14.6 months compared to EGRF inhibitors (median PFS, 3.8 -9.7 months). Similarly, the best survival outcomes were achieved with the PD-1 inhibitors with median OS not reached with either cemiplimab or pembrolizumab compared to a median OS of 8.1-17.5 months with chemotherapy and 11-17.5 months with EGFR inhibitors. The authors concluded that cemiplimab may confer a protective effect against disease progression and death with a reduced risk of death between 48% and 93% (HR range: 0.07–0.52) and a reduced risk of disease progression of between 33% and 70% (HR range: 0.30-0.67) compared to other systemic therapies.

Comment: The authors performed a systematic review of the literature and identified 27 reports (14 clinical trials and 13 observational studies) that reported on outcomes for patients with cSCC that were treated with systemic therapy. None of the studies were randomized controlled studies. They attempted to adjust for stage of disease (locally advanced versus metastatic) and compared survival outcomes of various treatments to cemiplimab based on the report of the registrational phase 2 study. In both unadjusted and adjusted comparisons, cemiplimab had better PFS and OS than cetuximab, platinum-based chemotherapy and single-agent pembrolizumab. The authors state, "since trials directly comparing systemic treatment options do not exist for cSCC, treatment comparisons adjusted for differences in study populations had to be undertaken." Given these are essentially all across trial comparisons one cannot conclude with certainty that cemiplimab is a superior treatment, but without randomized data this is the best we have when having to make treatment decisions.

Reference: Future Oncol 2020; Oct 14 [Epub ahead of print]
Abstract

Identifying risk factors for the prognosis of head and neck cutaneous squamous cell carcinoma

Authors: Zeng S et al.

Summary: This systematic review and meta-analysis from a Chinese group investigated the prognostic potential of baseline disease characteristics in cSCC. Meta-analysis was based on a total of 43 studies encompassing 21,530 patients and 28,627 cases of cSCC that were identified from a search of PubMed, EmBase, and Cochrane Library databases with a cut-off date of February 2020. Random-effects model analysis revealed that poor differentiation, PNI and Breslow > 2 mm were all associated with poor prognosis with increased risks of recurrence, metastasis and disease-specific death. The baseline factor most impacting on survival was PNI with a greater than six-fold increased risk of death (odds ratio [OR] 6.64, 95% CI, 3.63–12.12; $p<0.001$), followed by poor differentiation (OR, 5.97; 95% CI, 1.82–19.62; $p=0.003$) and Breslow > 2mm (OR, 3.42; 95% CI, 1.76–6.66; $p<0.001$). The risk of metastasis and cancer recurrence was highest in patients with PNI with a more than seven-fold increased risk of metastasis (OR, 7.15; 95% CI, 4.73–10.83; $p<0.001$) and more than three-fold increased risk of recurrence (OR, 3.27; 95% CI, 1.60–6.67; $p=0.001$). Poor differentiation (ORs 6.82 and 3.54, respectively), Breslow > 2 mm (ORs 6.11 and 5.47), diameter > 20 mm (ORs 5.01 and 4.62) and location on temple (ORs 2.77 and 3.20) also increased the risk of both metastasis and recurrence.

Comment: This meta-analysis with over 20,000 patients aims to identify tumour characteristics that predict for recurrence, development of distant metastases and disease-specific deaths from cSCC. The results are consistent with a previous, smaller meta-analysis. Poor differentiation, perineural invasion, tumour site, thickness and diameter are all found to be predictive of a poorer outcome. cSCC's that occur on the head and neck region generally have a worse outcome. Although the study fails to demonstrate a relationship between immunosuppression and poor outcome, they do suggest a very strong trend with the HR of 1.94 (1.00-3.76) for recurrence, HR 1.57 (1.00-2.58) for metastasis and HR 1.90 (0.77- 4.66) for disease-specific survival. These results allow clinicians to identify patients at higher risk for recurrence and the need for closer follow up.

Reference: PLoS One 2020;15(9):e0239586
Abstract

A pilot study of checkpoint inhibitors in solid organ transplant recipients with metastatic cutaneous squamous cell carcinoma

Authors: Tsung I et al.

Summary: Tsung et al provide a retrospective chart review to analyse the short-term efficacy of checkpoint inhibition in seven solid organ transplant recipients (four kidney, two liver, one lung) with advanced head and neck cSCC. Patients who received a solid organ transplant at the University of Michigan and subsequent immune checkpoint inhibition with a minimum of 30 days follow-up (predominantly with cemiplimab, one patient with pembrolizumab) for metastatic head and neck cSSC that had not responded to surgery and adjuvant radiotherapy were identified through the institution's records and the Data Office for Clinical and Translational Research (stage 4 disease; median age 75 years). Four patients had also undergone prior systemic therapies including chemotherapy, EGFR inhibition or tyrosine kinase inhibition and all patients had attempted immunosuppression minimisation (minimizing calcineurin inhibitors or conversion of calcineurin inhibitors to mammalian target of rapamycin inhibitors) prior to checkpoint inhibition. The five patients with available tumour genetic profiling demonstrated high tumour mutation burdens. The overall tumour response rate with a median follow-up of 7.1 months was 57.1% and was comprised of one complete response and three partial responses. There were four deaths, two of which were attributed to tumour progression. The authors concluded that this preliminary study provides evidence for the efficacy of immune checkpoint inhibition, in combination with prophylactic steroids, in patients with advanced cSCC who have undergone a solid organ transplant.

Comment: This is an important publication looking at the use of immunotherapy (specifically anti-PD-1 checkpoint inhibitors) in patients who had solid organ transplants and had developed metastatic cSCC. There were seven patients identified (four renal transplants, two liver and one lung transplant) and all received cemiplimab (n=6) or pembrolizumab (n=1). The response rate was 57% despite patients still being on immunosuppression. Of particular interest was that only one patient, a renal transplant recipient, developed acute rejection – this was biopsy proven. Immunosuppression was minimized prior to starting anti-PD-1, but all patients were on prednisolone. Three patients had a prophylactic regime of prednisolone 40 mg the day before immune checkpoint inhibition and then 20 mg/day on days 1-10 and 10 mg/day on days 11-20. This study suggests that anti-PD-1 can be given safely following solid organ transplant and that the efficacy seems to be maintained in this group of patients. Importantly, these patients all had metastatic disease and were many years post-transplantation, with only one of the seven having had any prior rejection. This does raise the question of the role of prednisolone in potentially preventing transplant rejection.

Reference: Oncologist 2020; Sep 23 [Epub ahead of print]
Abstract

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