Skin Cancer Research Review™

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In this issue:

Abbreviations used in this issue:

BCC = basal cell carcinoma; **CI** = confidence interval; **HR** = hazard ratio; **K17** = stress keratin 17; **MTHFR** = methylenetetrahydrofolate reductase; **OR** = odds ratio; **ORR** = objective response rate; **PD-1** = programmed cell death protein 1; **SCC** = squamous cell carcinoma.

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Welcome to the latest issue of Skin Cancer Research Review.

In light of the positive clinical results achieved with the hedgehog pathway antagonist sonidegib for locally advanced or metastatic basal cell carcinoma (BCC) not amenable to surgery or radiotherapy in Novartis Pharmaceuticals' phase 2 BOLT trial, which led to the approval of sonidegib for this indication by several regulatory authorities including in Australia, the retrospective PaSoS study evaluated effectiveness from patients treated at the Saint-Louis Hospital in Paris. The results, published in *Acta Dermato-Venereologica*, demonstrated a comparable effectiveness in a real-world setting, eliciting rapid and durable responses. Results from a US retrospective, multi-centre study in *Journal for ImmunoTherapy of Cancer* confirmed the effectiveness and tolerability of single-agent programmed cell death protein 1 (PD-1) inhibitor for advanced BCC after prior hedgehog pathway inhibitor therapy and corroborated the trend of improved efficacy for locally advanced versus metastatic disease reported in the REGN 1620 clinical trial. Whether the efficacy of PD-1 inhibitors in the front-line setting for unresectable or metastatic BCC would be improved compared to use as a later-line treatment, as in the case in melanoma and Merkel cell carcinoma, remains to be determined but may offer a less toxic therapeutic alternative to the hedgehog pathway inhibitors, especially in older patients. Multiple trials are underway to examine various therapeutic strategies in both resectable and unresectable BCC including neoadjuvant PD-1 therapy prior to surgery and combination PD-1 plus hedgehog inhibitors or other systemic agents, and results are eagerly awaited. Other research included in this edition of Skin Cancer Research Review includes a preclinical study that investigates the role of stress keratin in immune evasion and resistance to immune checkpoint blockade in head and neck cancer; a comparison of invasive squamous cell carcinoma (SCC) more than 12 months after various treatment modalities for actinic keratosis; and a large Dutch study identified risk factors for incomplete excision of cutaneous SCC.

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

Kind Regards,

Dr David Simpson
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A comparison of invasive squamous cell carcinoma greater than 1 year after treatment with 5-fluorouracil, imiquimod, or photodynamic therapy with aminolevulinic acid

Authors: Cheng B et al.

Summary: In an effort to elucidate the optimal treatment modality for premalignant actinic keratosis lesions in the absence of a standard of care Cheng et al interrogated a large US electronic medical/healthcare and administrative claims database to compare the real-world incidence of skin cancer at least one year after actinic keratosis treatment. Data on patients treated with 5-fluorouracil, imiquimod cream or photodynamic therapy with aminolevulinic acid in an eight-year period encompassing 2012 to 2019 were extracted from the Optum® Clinformatics® Data Mart database and included in the analysis. Results found a comparable efficacy of 5-fluorouracil and imiquimod cream for the prevention of cutaneous SCC with similar longer-term rates of SCC development (hazard ratio [HR] 0.99; 95% confidence interval [CI], 0.90-1.08) and superior efficacy versus photodynamic therapy. The authors commented that previous research demonstrating improved actinic keratosis destruction with 5-fluorouracil compared to imiquimod may not correlate with superior cutaneous SCC prevention efficacy.

Comment: Treatment of actinic keratoses aims to achieve both a short-term skin improvement in texture and appearance as well as long-term anti-neoplastic benefits. Previous studies have demonstrated a superior clearance of actinic keratoses with 5-fluorouracil versus imiquimod and photodynamic therapy. This study showed that when looking at prevention of cutaneous SCC after one year there was no significant difference between imiquimod and 5-fluorouracil and both were superior to photodynamic therapy. The introduction of 5-fluorouracil /calcipotriol combination therapy into routine practice may change these findings and, as always in these studies, they neglected to look at the superior results from fractionated photodynamic therapy or combination therapies using photodynamic therapy.

Reference: J Am Acad Dermatol 2022;87(3):592-96

Abstract

Risk factors for metastatic cutaneous squamous cell carcinoma: Refinement and replication based on 2 nationwide nested case-control studies

Authors: Tokez S et al.

Summary: Tokez et al employed English and Dutch nationwide cancer registries to discern risk factors for metastasis of cutaneous SCC. Retrospective backward conditional logistic regression modelling analysis of 1:1 matched English pathology reports from metastatic and non-metastatic cutaneous SCC cases (n=1,774) identified six factors associated with a significantly increased likelihood of metastatic dissemination – poor differentiation, invasion in/beyond subcutaneous fat, male sex, perineural/ lymphovascular invasion and facial localisation (odds ratios [OR], 4.56, 1.69/4.43, 2.59, 2.12 and 1.57). A positive non-linear relationship was also found between both cutaneous SCC diameter and thickness with metastasis. These six factors were confirmed as independent risk factors for metastasis in a Dutch data set comprised of 434 cases.

Comment: Previous studies have shown that there are several important risk factors for a poor prognosis in cutaneous SCC including a thicker primary tumour >5-6 mm, diameter greater than 2 cm, head and neck location, adverse histological features such as perineural infiltration and poor differentiation and immunosuppression. In this paper they analysed nested control studies using datasets from the UK and the Netherlands and found that whilst the above factors remained significant male sex was also an important adverse risk factor but immunosuppression was not independently linked to a worse prognosis, rather it was associated with developing tumours with the other recognised risk factors. It was hypothesised that men may be less likely to seek medical attention, work or have hobbies in more outdoor settings and have more scalp damage due to hair loss. Interestingly, the tumours in the UK group were thicker and wider than the Dutch group possibly reflecting less access to early diagnosis and treatment.

Reference: J Am Acad Dermatol 2022;87(1):64-71
Abstract

Sonidegib in the treatment of locally advanced basal cell carcinoma: a retrospective study

Authors: Herms F et al.

Summary: The French retrospective, single-centre PaSoS study aimed to assess the real-world effectiveness and tolerability of 200 mg sonidegib for locally advanced BCC not amenable to definitive therapies after its approval for this indication in 2015. A retrospective chart review of all adult patients with locally advanced BCC not suitable for radiotherapy, surgery or other local treatment who received sonidegib according to label as a front- or later-line therapy in routine clinical practice at the Saint-Louis Hospital in Paris between March 2018 and January 2021 (n=21; median age 75 years; 62% male; 62% aggressive histology; 84.6% infiltrative; mean maximum diameter 4.1 cm) was undertaken. Lesions were predominantly located on the head (95%). A single patient had Gorlin and Goltz's eponymous syndrome (nevoid BCC syndrome). Sonidegib was administered in the adjuvant setting after surgical excision in eight patients, 14% had received a previous pharmacological therapy (vismodegib) and 43% proceeded to surgery following sonidegib therapy, indicating sufficient tumour shrinkage to allow surgical resection. At a median follow-up of 18.7 months (median exposure of seven months) a clinical benefit was noted in all patients with at least disease stabilisation (disease control rate 100%). The objective response rate (ORR) was 81% including six patients who attained a complete response. Responses were reported to be rapid (median time to first tumour response, 2.3 months; median time to maximal tumour response, 3.2 months) and durable (median duration of response, 14.1 months). The most common adverse events, predominantly of mild severity, were muscle spasms, dysgeusia and alopecia. Almost 60% of patients had changes to sonidegib posology to manage adverse events and adverse events were the primary cause of treatment discontinuation. It was concluded that the efficacy and safety of sonidegib demonstrated under clinical trial conditions in Novartis' BOLT study were achievable under real-world conditions.

Comment: BCC has been shown to be triggered by aberrant signalling in the hedgehog signalling pathway resulting in cell proliferation and tumour growth. Sonidegib acts as an antagonist to the smoothened receptor in this pathway, thus preventing growth. Whilst it can be very effective in the rare entity of metastatic BCC the most useful application would be for the much more common locally advanced disease. In this retrospective observational study there was a high objective response and all patients achieved disease control with mostly minor adverse effects – muscle cramps, alopecia and dysgeusia (loss of taste) being the most common. If there is disease recurrence previous studies have shown an 85% response rate to further hedgehog inhibitor therapy and after that cemiplimab - a programmed cell death protein 1 (PD-1) blocker – could be used but with a lower efficacy of 30%.

Reference: Acta Derm Venereol 2022;102:1995
Abstract

Risk factors for incomplete excision of cutaneous squamous cell carcinoma: a large cohort study

Authors: Marsidi N et al.

Summary: This Dutch study from the Leiden University Medical Centre examined factors correlating with compromised radical surgical excision of cutaneous SCC. A total of 566 patients (62% male) with over one thousand cutaneous SCCs (n=1,159; median tumour size, 10 mm) surgically removed by wide local excision with 5 mm or ≥ 10 mm margins for low-risk and high-risk cases, respectively, in the 10-year period between January 2004 and December 2013 were included in the analysis. Almost two-thirds of lesions were located on the head and neck, 15% on the upper extremities and a minority on the lower extremities or trunk. An incomplete excision rate of 9% was reported (n=106), roughly half of which had positive side margins only, 34.9% positive deep margins and 18.9% with both side and deep margin positivity post-surgery. Of the four factors identified on univariable generalised estimating equation analysis as increasing the odds of an incomplete SCC excision (immunosuppression, tumour depth beyond the dermis and perineural invasion) only depth beyond the dermis maintained statistical significance on multivariable analysis (OR 5.7; 95% CI, 3.1-10.5). Depth beyond the dermis was also significantly associated with risk of incomplete excision on subgroup analysis by site of incomplete margin (side, deep or both) and the authors stated that to minimise risk of metastasis consideration of deep margins is critical. Immunosuppression was independently associated with an approximate doubling of incomplete deep margin excision (OR 2.2; 95% CI, 1.1-4.3), indicating that a deep plane margin guideline for this patient population may be required.

Comment: Standard excision margins for cutaneous squamous cell carcinoma are 5-10 mm depending on the perceived degree of risk of the primary tumour according to known risk factors such as size, location and immunosuppression. Looking at consecutive patients over a 10-year period this Dutch study found that depth beyond the dermis was the major factor linked to incomplete excision. The other risk factors associated with higher risk tumours were not found to be consistent. Perineural invasion was associated with increased risk of incomplete peripheral margins and immunosuppression was linked to incomplete deep margins. This supports ensuring that when excising cutaneous SCC, it is vital to include the underlying subcutaneous tissue.

Reference: J Eur Acad Dermatol Venereol 2022;36(8):1229-34
Abstract

Stress keratin 17 expression in head and neck cancer contributes to immune evasion and resistance to immune-checkpoint blockade

Authors: Wang W et al.

Summary: This preclinical research from a research group at the McArdle Laboratory for Cancer Research in the US utilised mouse tumour-bearing models of oral cavity SCC to characterise the role of stress keratin 17 (K17) in head and neck cancer pathogenesis and immunotherapy resistance. They showed, using single cell RNA sequencing methods, that K17 was highly expressed in immunologically cold syngeneic murine models (MOC2) resistant to immune checkpoint blockade but that knockout of K17 converted the tumours from cold to hot, impaired tumour growth and reinstated immune checkpoint blockage sensitivity. Further evaluation of K17 expression in head and neck tumours is warranted to explicate its value as a biomarker to predict response to immunotherapy and as a therapeutic target.

Comment: Stress keratin is expressed in epithelial cells during wound healing, inflammation and in autoimmune disease. Previous studies have shown that K17 overexpression is associated with downregulating T cell infiltration in human papillomavirus (HPV) infected cells. K17 overexpression is seen in a number of malignancies including breast cancer and pancreatic cancer and is a poor prognostic marker. It was found that head and neck cancers with a high level of K17 expression had a shorter survival and in immunocompetent mice led to tumour growth – in immunocompromised mice tumour growth did not need K17 and so other mechanisms are involved. High levels of K17 were found to result in a poor response to immune checkpoint blockade with pembrolizumab and it appears that K17 offers a degree of immune therapy evasion which needs further evaluation.

Reference: Clin Cancer Res 2022;28(13):2953-68
Abstract

Porocarcinoma: an epidemiological, clinical, and dermoscopic 20-year study

Authors: De Giorgi V et al.

Summary: De Giorgi and colleagues retrospectively analysed clinical outcomes in patients with porocarcinomas treated at one of two Italian medical centres over a 20-year period from 2020 onwards. The study population included 52 patients (59.6% male; median age 82 years, age range 49-96) with a histopathologically diagnosed porocarcinoma (total of 53 tumours), most commonly located on the head and neck or lower limb. Most tumours (91%) were excised and at five-year follow-up low rates of local recurrence (2% plus one case of second primary tumour) or lymph node metastasis (6%) were found. There was one cancer-related mortality in a patient with lymph node plus visceral metastasis. Other cases of metastasis were treated with adjuvant radiotherapy and had maintained disease-free status at two-year follow-up.

Comment: Porocarcinoma is a rare skin malignancy representing 7% of skin adnexal tumours and presents as an ulcerated nodule or verrucous plaque which may be rapidly or slowly enlarging and is mainly seen on the lower legs followed by the head/scalp and upper limbs. It may be red, purple or brown and is often mistaken for another diagnosis initially. In this paper looking at 20 years of cases the most common appearance was an erythematous nodule with ulceration present in 58% of cases. Dermatoscopy showed three distinct patterns: A round/oval homogenous pink pattern, an SCC-like pattern and a BCC-like pattern. The disease was less aggressive in this series than has previously been reported which may reflect earlier diagnosis and management and whilst dermatoscopy is difficult with non-specific features it should prompt biopsy and subsequent definitive management.

Reference: Int J Dermatol 2022;61(9):1098-105
Abstract

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Clinical activity of PD-1 inhibition in the treatment of locally advanced or metastatic basal cell carcinoma

Authors: In G et al.

Summary: PD-1 inhibitor monotherapy is an efficacious treatment option for patients with advanced BCC according to results from this US retrospective, multi-centre study published in *Journal for ImmunoTherapy of Cancer*. The study included 29 patients (median age 70 years) with unresectable locally advanced (69%) or metastatic disease treated with pembrolizumab, cemiplimab or nivolumab between August 2016 and June 2021. The study cohort was predominantly male (75.9%) with tumours located on the head and neck. Almost two-thirds of patients had an aggressive histology such as basosquamous, morpheaform or micronodular. At a median follow-up of 11 months (median of six anti-PD-1 agent cycles) a complete or partial response was achieved in 31% of the cohort and the disease control rate was 62.1%. Responses were durable (median duration of response not reached in responding patients). A trend of reduced efficacy in metastatic versus locally advanced disease was noted although statistical significance was not reached (ORR, 22.2% vs 35%; disease control rate, 55.5% vs 65%). Kaplan-Meier estimates of progression-free survival and overall survival were 12 months and 32.4 months, respectively. Mild to moderate (≤ grade 3) adverse events included fatigue, dermatological symptoms and endocrinopathies. Severe adverse events of grade 3-4 severity were reported in two patients but there were no fatalities. Overall, the treatment discontinuation rate due to adverse events was 13.8% (n=4).

Comment: PD-1 immune checkpoint blocker therapy is now approved using cemiplimab in patients with locally advanced or metastatic BCC who have previously received hedgehog pathway inhibitors such as vismodegib and sonidegib. In keeping with previous reports there was a 31% response rate to PD-1 inhibitor therapy with an acceptable level of adverse reactions. It will be interesting to see whether the response rate and durability is superior when PD-1 therapy is used as first-line therapy in BCCs.

Reference: J Immunother Cancer 2022;10(5):e004839
Abstract

Independent commentary by Dr David Simpson

Dr David Simpson is a skin cancer doctor on the Sunshine Coast in Queensland. He has a masters degree in Skin Cancer Medicine from the University of Queensland and is a teaching assistant on the MMed program.

What causes the death of patients with cutaneous squamous cell carcinoma? A prospective analysis in 1400 patients

Authors: Eigentler T et al.

Summary: Deaths attributable to cutaneous SCC are rare but risk factors influence death due to local infiltration, locoregional metastases or distant metastases to differing extents, according to this German study. In an adjusted multivariable subdistribution hazard analysis of mortality from cutaneous SCC overall in 1,400 patients bone invasion was found to adversely impact mortality to the greatest extent with a HR of 10.06. Two other negative factors for survival – desmoplasia and immunosuppression – were also identified (HR 4.52 and HR 3.19; both $p<0.005$). Desmoplasia and bone invasion had the greatest impact on death by local infiltration, increasing the risk of death by more than 15-fold and almost 17-fold, respectively (HR 15.39 and HR 16.9; both $p<0.01$). In contrast, immunosuppression was the sole independent prognostic factor for death by metastatic disease (locoregional metastasis, HR 3.27; distant metastasis, HR 4.54).

Comment: Unlike melanoma, most patients die from the effects of local infiltration but fortunately, the mortality is low at around 2.8%. Deaths were evenly spread between local extension, locoregional spread and distant metastases. Patients dying from distant metastases and local extension tended to be younger than those dying from locoregional disease and thicker tumours were linked to death by local infiltration whilst deaths due to distant metastases were linked to broader tumours. Certain features suggest an increased risk of death and this study found that tumour desmoplasia – defined as the presence of dense connective tissue/stroma, low cellularity and disorganised blood vessel infiltration – and bone invasion were both linked to death by local infiltration. Immunosuppression was liked to death by distant metastases and locoregional spread.

Reference: Eur J Cancer 2022;172:182-90
Abstract

Dark green leafy vegetable intake, *MTHFR* genotype, and risk of cutaneous squamous cell carcinoma

Authors: Hughes M et al.

Summary: The protective effect of green leafy vegetable consumption against cutaneous SCC may be mediated by polymorphisms in folate metabolism genes such as methylenetetrahydrofolate reductase (*MTHFR*) according to an Australian study in *Dermatology* by Hughes et al. The study assessed associations between dietary intake of green leafy vegetables such as spinach, kale, arugula, bok choy and rapini over a five-year period (evaluated using the Food Frequency Questionnaire between 1992 and 1996) and cutaneous SCC incidence over 16 years (1992-2007) in over one thousand individuals (n=1,128) stratified by genotypes of two *MTHFR* gene variants – C677T and A1298C. Generalised linear models with negative binomial distribution and offset with person-years of follow-up revealed that a high level of dietary green leafy vegetable intake conferred a significantly reduced risk of cutaneous SCC only in carriers of the C677T variant (CT or TT genotypes; relative risk 0.42) or individuals homozygous for wild-type A1298C (AA genotype; relative risk 0.43).

Comment: A high intake of dark green leafy vegetables has previously been shown to be associated with a lower risk for cutaneous SCC. The abundant folate within dark green leafy vegetables is suspected to be the most important active ingredient and there are various polymorphisms of the *MTHFR* gene responsible for the conversion of folate into active forms. This can result in increased susceptibility to disorders including hypertension, pregnancy loss, clotting and cancers. The results of the study showed that certain *MTHFR* mutations conferred a decreased risk of cutaneous SCC compared to the wild-type.

Reference: Dermatology 2022;238(4):657-61
Abstract

Atypical Spitz tumours: an epidemiological, clinical and dermoscopic multicentre study with 16 years of follow-up

Authors: De Giorgi V et al.

Summary: De Giorgi and colleagues provide a characterisation of atypical Spitz tumours to aid in diagnosis. They describe the dermoscopic and histopathology characteristics, therapeutic approach and outcomes for a cohort of 99 patients from the databases of four Italian Dermatology Units with long-term follow-up. The cohort was predominantly female (63%). Tumours impacted a wide range of ages with the youngest patient two years old and the oldest 70 years but a bimodal distribution of ages was noted with almost 60% of patients aged 18-50 years and 30% of cases in paediatric patients. All tumours were surgically excised and 29 patients also underwent sentinel lymph node biopsy plus complete lymph node dissection in cases of micrometastasis (n=3; 10.3%). An excellent clinical outcome in all patients with no mortality, recurrence or distant metastasis with a median follow-up of over six years (range, 6 to 216 months) was reported. The authors noted that diagnosis of amelanotic atypical Spitz tumours was easier than pigmented or hypopigmented tumours with differentiation from achromic melanoma possible by examination of morphology and vascular distribution pattern.

Comment: Melanoma diagnosis can be tricky and even when subjected to rigorous histological and immunohistochemical analyses there can be borderline lesions sometimes called MELTUMP or melanocytic lesions of unknown malignant potential. Atypical Spitz naevi come under this label. All lesions in this series had wide excision with 10 mm margins and three patients had positive sentinel lymph nodes resulting in lymphadenectomy. Seventy-three percent presented as papules, over 46% were amelanotic or hypopigmented. The most common dermatoscopic pattern was multicomponent followed by homogenous and non-specific and the most common vessels were coiled/glomerular evenly spread across the lesion. The study followed patients for a mean of 81 months and there were no cases of recurrence or metastases, which provides some reassurance.

Reference: Clin Exp Dermatol 2022;47(8):1464-71
Abstract

