Skin Cancer Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

AE = adverse event; **MMS** = Mohs micrographic surgery; **OS** = overall survival; **SRT** = superficial radiation therapy; **TIL** = tumour infiltrating lymphocyte.

Welcome to the latest issue of Skin Cancer Research Review.

In this issue, we look at ten interesting studies in skin cancer research. We begin with a study on tumour-infiltrating lymphocyte therapy or ipilimumab therapy in advanced melanoma. This is followed by a study on pembrolizumab versus placebo as an adjuvant therapy in resected stage IIB or IIC melanoma. This study included patients older than 12 years from the KEYNOTE-716 trial. An interesting study included in this issue is the European Prospective Investigation into Cancer and Nutrition study on baseline and lifetime alcohol consumption and the risk of skin cancer. This study found that from 450,112 participants, there was a positive relationship between alcohol intake and skin cancer risk. Finally, we conclude this issue with an interesting study on the malignant potential for ambiguous melanocytic lesions.

We hope that you enjoy this update in skin cancer research, and as always, we welcome your feedback.

Kind Regards,

Dr David Simpson
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Tumor-infiltrating lymphocyte therapy or ipilimumab in advanced melanoma

Authors: Rohaan MW et al.

Summary: This study included 168 patients, 86% of which had disease refractory to anti-programmed death 1 treatment. The median progression-free survival was 7.2 months in the tumour infiltrating lymphocyte (TIL) group and 3.1 months in the ipilimumab group. In terms of objective response, 49% were in the TIL group, and 21% were in the ipilimumab group. Furthermore, the median overall survival (OS) was 25.8 months in the TIL group and 18.9 months in the ipilimumab group. Finally, the treatment-related adverse events (AEs) of grade 3 or higher occurred in all patients who received TILs, and in 57% of those who received ipilimumab; in the TIL group, these events were mainly chemotherapy-related myelosuppression.

Comment: Over the past few years, there have been multiple trials showing the impressive results of immune checkpoint therapies, but the efficacy is lower when patients are re-treated for progressive or recurrent disease. TIL is found within the base of melanomas and can be extracted from metastatic deposits so that they can be infused as an alternative method of immunotherapy – in this case, personalised. Using this technique, TILs were shown to be more effective than ipilimumab and the data suggested that their efficacy may be greater than second-line nivolumab/ipilimumab combination therapy, although this would need a further direct head-to-head study. There were a small number of patients included who were treated with TIL as first-line therapy with good results, and this may be an option in the future with reduced adverse reactions compared to PD-1 blockade.

Reference: N Engl J Med. 2022;387:2113-25
Abstract

Pembrolizumab versus placebo as adjuvant therapy in resected stage IIB or IIC melanoma (KEYNOTE-716)

Authors: Long GV et al.

Summary: This study analysed the distant metastasis-free survival results of a multi-centred, double-blind, randomised phase 3 trial (KEYNOTE-716). Patients included were 12 years or older with newly diagnosed, completely resected, and histologically confirmed stage IIB or IIC cutaneous melanoma. At a median follow-up of 27.4 months, median distant metastasis-free survival was not reached in either group. The study found that pembrolizumab use significantly improved distant metastasis-free survival versus placebo. Median recurrence-free survival was 37.2 months in the pembrolizumab group, and not reached in the placebo group. The risk of recurrence remained lower with pembrolizumab versus placebo. The most common grade 3 or worse AEs were hypertension, diarrhoea, rash, autoimmune hepatitis, and increased lipase. Serious treatment-related AEs occurred in 49 patients in the pembrolizumab group and 11 patients in the placebo. No treatment-related deaths were reported.

Comment: Immunotherapy with PD-1 blockers is now standard therapy for stage III and IV melanoma, but patients presenting with more aggressive primary lesions have a similar risk of disease progressions and distant metastases. This longer-term assessment/update of using pembrolizumab in stage IIB and IIC melanoma showed ongoing benefits of therapy with similar rates of adverse effects as previously reported. As with resected stage III disease, the most likely first presentation of disease progression was distant metastases. Patients whose primary melanoma characteristics have adverse features – thick tumours, ulceration etc. – need to be offered a consultation with an oncologist to ensure they can benefit from adjuvant therapy.

Reference: Lancet Oncol. 2022;23:1378-88
Abstract

Combination dabrafenib and trametinib versus combination nivolumab and ipilimumab for patients with advanced *BRAF*-mutant melanoma

Authors: Atkins MB et al.

Summary: The DREAMseq trial aimed to determine which initial treatment or treatment sequence produced the best efficacy when comparing a combination of nivolumab/ipilimumab or dabrafenib/trametinib in step one and the alternate in step two. A total of 265 patients were enrolled, with 73 proceeding to step two. The 2-year OS and objective response for those starting on nivolumab/ipilimumab was 71.8% and 46%, and in dabrafenib/trametinib, 51.5% and 43%, respectively. Step one progression-free survival favoured nivolumab/ipilimumab. The median duration of response was not reached for nivolumab/ipilimumab, and it was 12.7 for dabrafenib/trametinib. In step two, the objective response for dabrafenib/trametinib was 47.8%, and 29.6% for nivolumab/ipilimumab. Finally, grade ≥ 3 toxicities occurred with similar frequency between groups, and regimen toxicity profiles were as anticipated.

Comment: In patients with BRAF mutant melanoma, there is a choice between treating with targeted therapies or immunotherapy. The benefit of targeted therapy can be a more rapid effect, and in patients with extensive disease, which is evolving fast, these drugs can induce positive results quickly. Unfortunately, recurrence due to treatment resistance is common, and the patients are then switched to immunotherapy. The question remains whether there is any difference in long-term survival between using targeted or immunotherapy as first-line therapy. In this study of patients who had progression of their disease after initial treatment and were then swapped to the other option – targeted therapy of immunotherapy – it was found that initial treatment with combination immunotherapy resulted in a significant overall survival benefit suggesting that all patients should receive immunotherapy first if feasible.

Reference: J Clin Oncol. 2023;41:186-97
Abstract

Safety and efficacy of nivolumab, anti-PD1 immunotherapy, in patients with advanced basal cell carcinoma, after failure or intolerance to sonic Hedgehog inhibitors

Authors: Véron M et al.

Summary: The UNICANCER AcSé NIVOLUMAB trial with basal cell carcinoma evaluated the efficacy and safety of nivolumab in a cohort of 32 patients. All patients in this study received previous Sonic Hedgehog inhibitors, 53% of patients already had chemotherapy, and 75% had radiotherapy. At 12 weeks, they reported 3.1% complete responses, 18.8% of partial responses, and 43.8% of stable diseases. The best response rate to nivolumab reached 12.5% of complete responses, 18.8% of partial responses, and 43.8% of stable diseases. AEs were most commonly grade 2 or 3, and were slightly different to the AEs observed in the treatment of metastatic melanoma.

Comment: Although rare, basal cell carcinoma can become difficult to manage mainly due to locally advanced disease but also in a very small number of cases due to metastases. Hedgehog pathway inhibitors such as vismodegib and sunitinib can be used in these cases but have adverse effects, which may limit the use and limited duration of effectiveness. Using nivolumab in patients who either couldn't tolerate Hedgehog pathways inhibitor therapy or with treatment failure resulted in an overall response rate of 31.2% and a disease control rate of 65.6%. The true response takes several months to be seen, so final response rates were greater than the initial 12-week assessments. This offers a useful option for this group of patients.

Reference: Eur J Cancer. 2022;177:103-11
Abstract

Phase 1b study of cobimetinib plus atezolizumab in patients with advanced $BRAF^{V600}$ wild-type melanoma progressing on prior anti–programmed death-1 therapy

Authors: Sandhu S et al.

Summary: This study was a phase 1b, open-label, international multi-centred study that included 3 cohorts. From the 103 patients enrolled in this study, the median follow-up was 6.9 months, the objective response rate was 14.6%, and the disease control rate was 38.8%. The median duration of response, progression-free survival and OS were 12.7 months, 3.8 months and 14.7 months, respectively. The most common AEs were diarrhoea, dermatitis, acneiform, and nausea. Thirty-four patients in this study died, 33 due to progressive disease and one due to treatment-related oesophagitis.

Comment: When patients develop disease progression after initial treatment with anti-PD1 therapy, it had been shown that second-line immunotherapy can provide significant benefits – the combination of ipilimumab/nivolumab being the most efficacious. In theory, using a MEK inhibitor in BRAF mutant melanoma might be useful, so this study combined cobimetinib with a PDL1 inhibitor. Unfortunately, there was a limited benefit, and at this point, the current combination of immunotherapy remains the best option.

Reference: Eur J Cancer. 2023;178:180-90
Abstract

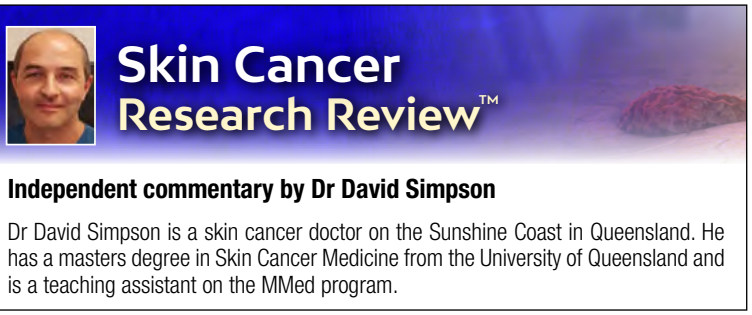
Baseline and lifetime alcohol consumption and risk of skin cancer in the European Prospective Investigation into Cancer and Nutrition cohort (EPIC)

Authors: Mahamat-Saleh Y et al.

Summary: This study included 14,037 skin cancer cases identified among 450,112 participants. The results found that baseline alcohol intake was positively associated with squamous cell carcinoma and melanoma risk in men. However, basal-cell carcinoma, associations were more modest in women. Associations were similar for lifetime alcohol intake, with an attenuated linear trend. Moreover, lifetime liquor/spirit intake was more positively associated with melanoma and basal-cell carcinoma in men. Baseline and lifetime intakes of wine were associated with basal-cell carcinoma risk. There were no statistically significant associations between beverage types and squamous cell carcinoma risk. Finally, intake of beer was not associated with skin cancer risk.

Comment: Experimental studies have shown potential carcinogenic effects of alcohol mainly due to the acetaldehyde produced when ethanol is metabolised. Some of the metabolites of ethanol have also been shown to be photosensitising. In this paper, the authors attempted to get more conclusive evidence that alcohol intake results in increased rates of skin cancer, but although that was their conclusion, the study is full of assumptions and vague conclusions. One of the main weaknesses of this type of study is relying on patients to report their baseline alcohol intake and then assuming that their recollections are accurate and projecting that forward over a number of years with the continued assumption that their intake remains the same. White wine and spirits appeared to be associated with skin cancer but not red wine. Beer consumption wasn't associated with skin cancer. There are multiple competing hypotheses for these findings, including outdoor recreational activities, sports, sunbed use and smoking (which were both increased in those with heavier reported alcohol intake). Higher income is known to be associated with increased melanoma, possibly due to increased outdoor leisure time and holidays, and this may also be a confounding factor here. Overall, I'd say this study failed to convince me that we ought to be focussing our attention on alcohol intake when counselling patients on skin cancer reduction strategies.

Reference: Int J Cancer. 2023;152:348-62
Abstract



Independent commentary by Dr David Simpson

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High resolution dermal ultrasound combined with superficial radiation therapy (SRT) versus non-image guided SRT or external beam radiotherapy in early-stage epithelial cancer: a comparison of studies

Authors: Yu L et al.

Summary: This paper analysed several studies and compared the effectiveness of high-resolution dermal ultrasound-guided superficial radiotherapy (SRT) to non-image-guided radiotherapy, in treating non-melanoma skin cancer. The ultrasound-SRT local control rate was found-to-be statistically superior to each of the four non-image-guided radiation therapy studies, with p-values ranging from $p<0.0001$ to $p = 0.0438$. This study concluded that ultrasound-SRT in local control was statistically significant across all assessments compared to non-image-guided radiation modalities in treating non-melanoma skin cancer.

Comment: Superficial radiotherapy for non-melanoma skin cancers has become a widely used alternative to surgery, especially in cosmetically sensitive areas, recurrent lesions or lesions with positive margins on excision or where patients prefer a non-surgical treatment. Despite this, Mohs micrographic surgery (MMS) surgery is still seen as the gold standard treatment with the lowest recurrence rates and with tissue conservation. This paper examined the efficacy of high-frequency dermal ultrasound-guided superficial radiotherapy; this technique allows visualisation of the lesion's depth, breadth and overall configuration before, during and after treatment. Local control is comparable to MMS, and this may become a cost-effective alternative where MMS is being contemplated.

Reference: BMC Cancer. 2023;23:98
Abstract

Same day biopsy and treatment of non-melanoma skin cancer in patients with field cancerization

Authors: Miles J et al.

Summary: This retrospective chart study reviewed patients with same-day lesion diagnosis and curettage treatment records to determine diagnostic accuracy, treatment failure, and number needed to treat to reduce a follow-up treatment. A total of 237 lesions underwent same-day biopsy and treatment, of which 66% were non-melanoma skin cancers and 23% were actinic keratosis. Patients had at least three months follow-up and a median follow-up of 17 months. A total of 20 lesions either recurred or were deemed to require additional treatment. The study found that majority of the lesions found were basal cell carcinomas or squamous cell carcinomas.

Comment: Patients with severe actinic damage are a high-risk group for developing multiple superficial non-melanoma skin cancers and can be challenging to manage. Often several lesions are found at each visit, and it can be expensive for the patient and time-consuming to deal with all of these. One option which this study examines is to biopsy these clinically superficial lesions with a shave biopsy immediately followed by curettage (± electrocautery). Using this approach, they found that 89% of lesions were proven by histopathology to be skin cancers, with the majority being superficial basal cell carcinomas or squamous cell carcinoma *in-situ*. Not surprisingly, the lesions most likely to recur were the invasive squamous cell carcinomas – 36% recurrence/treatment failure. The lesions where this treatment is most appropriate were superficial basal cell carcinoma and squamous cell carcinoma *in-situ* in non-facial areas, particularly the trunk.

Reference: J Skin Cancer. 2023;2023:9990046. eCollection
Abstract

Disparities in melanoma-specific mortality by race/ethnicity, socioeconomic status, and healthcare systems

Authors: Rosenthal A et al.

Summary: This study used a retrospective analysis to identify insured adults diagnosed with stage I to IV melanoma. This cohort included 14,614 adults diagnosed with melanoma. The multivariable analysis demonstrated that race and ethnicity was not associated with survival disparities. At the same time, socioeconomic status strongly predicted melanoma-specific mortality, particularly for those with other private insurance. Moreover, hazard ratios demonstrate that the poorest patients with other private insurance had a 70% increased risk of dying from melanoma compared to their wealthier counterparts.

Comment: Previous studies have demonstrated disparities in melanoma prognosis related to both socioeconomic status and minority race but did not take into account health insurance status. This study of insured patients in California found that when all patients are insured, there is no difference, indicating that socioeconomic status may be the cause for the disparity. Integrated health insurance systems where care is coordinated with multidisciplinary teams and melanoma registers were found to provide improved melanoma prognosis compared to non-integrated systems. In Australia, patients should have timely access to the full range of medical care, but this is a reminder that higher-risk patients should be enabled to access specialist team care.

Reference: J Am Acad Dermatol. 2023;88:560-7
Abstract

Ambiguous melanocytic lesions

Authors: Vermarien-Wang J et al.

Summary: This retrospective cohort study included patients' incidence and outcome of melanocytic tumours of uncertain malignant potential (MELTUMP) and their superficial atypical melanocytic proliferation of uncertain significance (SAMPUS) in the Netherlands. The results included a total of 1685 MELTUMP patients and 1957 SAMPUS patients. Metastatic behaviour was seen in 0.7% of all initially diagnosed MELTUMP patients. All SAMPUS patients remained free of metastases. The study identified limitations; this included a reassessment of pathology slides and confirmation of clonality between primary and metastatic lesions that remained outside the scope of this study. Finally, the study concluded a low malignant potential for MELTUMP patients, and no malignant potential for SAMPUS patients.

Comment: Melanoma diagnosis can be challenging not only for the clinician but also for the pathologist, and there are some lesions where a definite diagnosis cannot be made. In 2018 the World Health Organisation accepted terminology recognising this uncertainty with SAMPUS (intraepidermal atypical melanocytic proliferation of uncertain significance – differential melanoma in situ), SAMPUS (superficial AMPUS, differential early invasive melanoma) and MELTUMP (differential melanoma in vertical growth phase). Lesions classified as such in Holland were reviewed after three years of follow-up, and only 1.6% showed evidence of local recurrence, progression or metastasis (44 of 2692 patients). There were no metastatic events in the SAMPUS patients but 9 in 1248 MELTUMP cases (0.7%). Dutch guidelines would have recommended the excision of all the MELTUMP cases with 5-10mm margins, but this is not stated for SAMPUS cases. Whilst the malignant potential for these borderline lesions appears low, they still need adequate local excision and follow-up.

Reference: J Am Acad Dermatol. 2023;88:602-8
Abstract

