Skin Cancer Research Review™

Making Education Easy

Issue 15 - 2023

In this issue:

Abbreviations used in this issue:

ATP = adenosine triphosphate;
BRAF = v-RAF murine sarcoma viral oncogene homolog B1;
KC = keratinocyte cancer; **MAPK** = mitogen-activated protein kinase;
MBM = melanoma brain metastases; **MCC** = Merkel cell carcinoma;
MEK = mitogen-activated protein kinase; **MIA** = Melanoma Institute of Australia;
MSKCC = Memorial Sloan Kettering Cancer Center;
NAD+ = nicotinamide adenine dinucleotide;
NRAS = neuroblastoma RAS viral oncogene homolog;
PD-1 = programmed death cell receptor 1.

Welcome to the latest issue of Skin Cancer Research Review.

We begin this issue with an N Engl J Med study on nicotinamide for skin cancer chemoprevention in transplant recipients. This is followed by a phase two randomised trial on neoadjuvant plus adjuvant or adjuvant-only therapy in advanced melanoma. Also included in this issue is a multi-institutional study on cutaneous immune-related adverse events in advanced cancer patients. Finally, we conclude this issue with a retrospective study by the J Am Acad Dermatol on tumour distributions and survival characteristics of patients between primary melanomas and single primary melanomas.

We hope you enjoy this skin cancer research update and welcome your feedback.

Kind Regards,

Dr David Simpson
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Nicotinamide for skin-cancer chemoprevention in transplant recipients

Authors: Allen NC et al.

Summary: This phase 3 trial randomly assigned 158 participants to either 500mg of nicotinamide or placebo twice daily for 12 months. The trial was stopped early owing to poor recruitment. At 12 months, there were 207 new keratinocyte cancers (KC) in the nicotinamide group and 210 in the placebo group. The study found no significant difference between the two groups for squamous-cell and basal-cell carcinoma counts, quality-of-life scores or actinic keratosis counts. There were also no differences in adverse events or changes to laboratory variables between the two groups.

Comment: Ultraviolet light causes DNA damage and immunosuppression in the skin resulting in KC. Nicotinamide (Vit B3) is a precursor of nicotinamide adenine dinucleotide (NAD+), which is an essential co-enzyme for ATP production, and a deficiency of nicotinamide can lead to an impaired DNA damage response and increased genomic instability. The ONTRAC study found that at a dose of 500mg twice daily, oral nicotinamide reduced the number of new KCs by 23%. Solid organ transplant patients are 50 times more likely to develop KCs than the general population due to their immunosuppression, and this study aimed to investigate the benefits of the ONTRAC study regime on this high-risk group. Unfortunately, there was no significant benefit seen at 12 months. The authors hypothesised that this could be due to a combination of factors, including the fact that many of the high-risk patients were already taking nicotinamide and so were ineligible to be recruited into the study and also that the effect of immunosuppressant medications may be too great to be overcome by B3 supplementation.

Reference: N Engl J Med. 2023;388:804-12
Abstract

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Neoadjuvant–adjuvant or adjuvant-only pembrolizumab in advanced melanoma

Authors: Patel SP et al.

Summary: This phase two trial randomly assigned patients with clinically detectable stage IIIB to IVC melanoma. After a median follow-up of 14.7 months, the neoadjuvant-only group had a longer event-free survival than the adjuvant-only group. This study undertook a landmark analysis and found that event-free survival at two years was 72% in the neoadjuvant-adjuvant combined group compared to 49% in the adjuvant-only group. In addition, the percentage of patients with treatment-related adverse events of grade 3 or higher during therapy was 12% in the neoadjuvant-adjuvant combined group and 14% in the adjuvant-only group. This study concluded that among patients with resectable melanoma, event-free survival was significantly longer in those who received pembrolizumab both before and after surgery than in those who received adjuvant pembrolizumab alone.

Comment: Immunotherapy using PD-1 receptor blockers prevents cancerous cells from inhibiting T cell proliferation and anti-tumour activity and has resulted in durable survival benefits in patients with stage III and IV melanoma. The survival benefits suggest a systemic effect whereby activated T cells can eliminate micro-metastases throughout the body. Recent small studies using nivolumab in combination with ipilimumab (a CTLA-4 inhibitor) or relatlimab (a LAG-3 blocker) have demonstrated improved efficacy when the first doses are given prior to surgery (neoadjuvant therapy), and studies on mice breast cancer models have shown similar benefits. By taking a non-excisional biopsy of metastatic deposits in lymph nodes or distant organs, the tumour infiltrating T cells are able to proliferate due to the action of PD-1 blockade inhibiting tumour-mediated immune checkpoint activation. The use of neoadjuvant pembrolizumab showed a 23% increase in event-free survival after two years, and it is likely that this will become the preferred immunotherapy protocol.

Reference: N Engl J Med. 2023;388:813-23
Abstract

Brain metastasis and survival outcomes after first-line therapy in metastatic melanoma

Authors: Franklin C et al.

Summary: This prospective, multi-centre real-world study included 1704 patients, 916 were BRAF wild type, and 788 were BRAFV600 mutant. The primary outcome of this study included the incidence of brain metastasis, which was achieved after 24 months, where therapy with BRAF+MEK resulted in a higher incidence of brain metastasis compared with PD-1±CTLA-4. For brain metastasis-free survival, tumour stage and age were longer. CTLA-4+PD-1 did not result in better brain metastasis-free, progression-free, and overall survival. The study concluded that in BRAF mutant patients, therapy with PD-1±CTLA-4 immune checkpoint inhibitor therapy resulted in a delayed and less frequent development of brain metastasis compared to BRAF+MEK target therapy.

Comment: Over the past few years, multiple regimes have been studied as first-line treatment for patients with advanced melanoma, including treatments targeting the MAPK signalling pathway in those with an activating BRAF V600 mutation or immune checkpoint inhibitors such as nivolumab, ipilimumab or a combination of both. Since melanoma brain metastases (MBM) account for around 50% of melanoma-related deaths, it is vital to choose the regime with the lowest incidence of MBM. Combination immune checkpoint inhibitor therapy resulted in a lower risk of MBMs and the greatest overall survival. Whilst first-line use of targeted therapies in BRAF mutant melanoma resulted in a greater progression-free survival, combination immune checkpoint therapy showed the lowest risk of MBSs and greater overall survival. When disease recurred, second-line targeted therapy was valuable for BRAF mutant patients leading to improved overall survival compared to BRAF wild-type patients.

Reference: J Immunother Cancer. 2023;11:e005828
Abstract

Efficacy and toxicity of adjuvant radiotherapy in recurrent melanoma after adjuvant immunotherapy

Authors: Bhave P et al.

Summary: This retrospective study identified 71 patients, 30 were BRAFV600E mutants, and 43 were stage IIIC at diagnosis. The results of this study included a median time to first recurrence of 7 months, with 24 patients who received adjuvant radiotherapy and 47 patients who did not. The study identified three patients who developed a second recurrence at a median of 5 months. At first-recurrence adjuvant radiotherapy was associated with an improved recurrence-free survival rate, and there was no effect on the risk of distant recurrence or overall survival. The rate of locoregional relapse at second recurrence was lower in those who received adjuvant radiotherapy when compared to those who did not.

Comment: Studies in the pre-immunotherapy era showed an improved locoregional recurrence-free survival in patients treated with adjuvant radiotherapy at first recurrence, but whether this would still be of additional benefit now that immunotherapy and targeted therapies are being used widely was unknown. Adding adjuvant radiotherapy for the treatment of sites of recurrent melanoma during or after immunotherapy showed a reduction in locoregional recurrent disease and an increase in time to second recurrence. In both the pre-immunotherapy studies and the current study, there was no reduction in distant metastases or improved overall survival. Adding a second adjuvant medication, either targeted BRAF/MEK inhibitor therapy or combination immunotherapy at recurrence, also increased the period of recurrence-free survival to a second locoregional recurrence.

Reference: J Immunother Cancer. 2023;11:e006629
Abstract

Advancing survivors knowledge (ASK Study) of skin cancer surveillance after childhood cancer

Authors: Geller AC et al.

Summary: This randomised control trial in the childhood cancer survivor study included three intervention groups: patient and provider activation and patient and provider activation with teledermoscopy, compared with patient activation alone. For the primary outcome, which was receiving a physician skin examination at 12 months after the intervention, the rates of physician skin examinations increased significantly from baseline to 12 months in all three groups, patient and provider outcome, 24% to 39%, patient and provider activation, 24% to 39% and patient and provider activation with teledermoscopy, 29% to 58%. The second primary outcome was the rates of skin-self-examination after 18 months; these rates increased over the 18 months, with the most being in the patient and provider activation with the teledermoscopy group from 29% to 58%.

Comment: In survivors of childhood cancer who have received radiotherapy as part of their treatment, skin cancers are the most common subsequent malignancy. After about 20 years since their radiation exposure, they are 30 times more likely than the general population to develop basal cell carcinoma in the radiation field and 2.5-5 times more likely to develop melanoma in this area. The ASK Study used a combination of patient-directed information materials and physician-directed information to improve awareness of these skin cancer risks in this group of patients. After 18 months of follow-up, there was an increase in both skin examinations by the patient's physician and patient self-examination but no significant differences between the group which only provided patients with information and the two groups which involved the patient's physician (one group involved teledermatoscopy, but less than 20% of patients provided images). The message seems to be that directing educational advice and encouraging skin examinations is worthwhile but best directed directly to the patients.

Reference: J Clin Oncol. 2023;41:2269-80
Abstract

Durability of response to immune checkpoint inhibitors in metastatic Merkel cell carcinoma after treatment cessation

Authors: Weppler AM et al.

Summary: Forty patients were included in this study, which assessed patients who discontinued immune checkpoint inhibitor therapy for a reason other than progression. The study found that the median time on treatment was 13.5 months. The reasons other than progression for stopping immune checkpoint inhibitor therapy were treatment-related toxicity, disease progression, patient preference to stop therapy, complete and partial response and those with stable disease. The study found a longer progression-free survival rate in those who discontinued immune checkpoint inhibitor therapy electively (29 months) compared to those who stopped due to toxicity (11 months).

Comment: Immune checkpoint inhibitor therapy has been shown to be very useful for treating metastatic and unresectable Merkel Cell Carcinoma (MCC), but the optimal duration of treatment and the durability of response is uncertain. Whilst for melanoma, it has been found that ceasing immunotherapy due to immune-related adverse effects can lead to improved durability of response, the opposite was seen in these MCC patients. Patients who ceased immunotherapy electively due to a complete or partial response had a median progression-free survival of 29 months, whilst those who ceased due to adverse reactions had a median progression-free survival of 11 months, despite the fact that most of these patients were in complete or partial response at the time of treatment cessation. Re-treatment with the same immunotherapy, in most cases avelumab, showed a high response rate.

Reference: Eur J Cancer. 2023;183:109-18
Abstract

Age-related next-generation sequencing mutational analysis in 1196 melanomas

Authors: Santamaria-Barria JA et al.

Summary: This study analysed 1194 patients with a common set of 30 genes. The most commonly mutated genes in patients <40 years old were BRAF (59%), TP53 (31%), NRAS (17%), and PTEN (14%); in those between 40 and 59 years old, the genes were BRAF (51%), NRAS (30%), TP53 (26%), and APC (13%); and in those ≥60 years old, the genes were BRAF (38%), NRAS (33%), TP63 (26%), and KDR (19%). The study identified a mutational burden that increased with age, with a mean of 2.92, 2.92, and 3.67, in patients <40, 40-59, and ≥60 years old, respectively.

Comment: Melanoma is one of the cancers with the highest mutational burden, and this is likely related to chronic ultraviolet radiation damage. By examining a large database of fully sequenced melanomas, both primary and metastatic, it was found that mutation load increased as expected with age. In younger patients, BRAF mutations predominated, whilst NRAS mutations became more common in older age groups. The presence of BRAF or NRAS mutations appeared to be mutually exclusive. A variety of other less common mutations were found and were seen more in older patients. Medications targeting various mutations are now becoming available, and this should lead to personalised treatment regimens for those patients with less common mutations in future.

Reference: J Surg Oncol. 2023;127:1187-95
Abstract

Skin Cancer Research Review™

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.

Are the MIA and MSKCC nomograms useful in selecting patients with melanoma for sentinel lymph node biopsy?

Authors: Hoesin S et al.

Summary: This net benefit analysis study used the Melanoma Institute of Australia (MIA) and Memorial Sloan Kettering Cancer Center (MSKCC) nomograms which are used to guide sentinel lymph node biopsy decisions, to quantify their clinical utility compared to the alternate strategy of biopsying all patients. The study found that the MIA nomogram provided added net benefit at-risk threshold of 9% but net harm at 5% to 8% and 10%. For the MSKCC nomogram, the study found added net benefit at thresholds of 5% and 9% to 10% but net harm at 6% to 9%. The study concluded that compared to sentinel lymph node biopsy, neither model consistently provided added net benefit.

Comment: Sentinel lymph node biopsy in melanoma care has become the most important staging procedure, and positivity aids treatment decision-making and qualifies patients to receive further targeted or immunotherapy. Based on the MSLT trials, the risk of a positive sentinel lymph node is less than 5% for thin lesions (less than 1mm Breslow thickness) but is greater than 5% for lesions 0.75-1mm thick with another adverse feature such as ulceration, a high mitotic count, Clark level IV/V or Lymphovascular invasion. The Melanoma Institute Australia in Sydney and The Memorial Sloane Kettering Cancer Centre in New York have developed nomograms based on their databases to calculate the likelihood of a resected node being positive for melanoma. Using these calculators in two historic databases where pathology was known, it was found that there was no benefit in avoiding unnecessary SLNB or in detecting positive biopsies compared to simply following the previously established 5% and 10% risk thresholds.

Reference: J Surg Oncol. 2023;127:1167-73
Abstract

Cutaneous immune-related adverse events are associated with longer overall survival in advanced cancer patients on immune checkpoint inhibitors

Authors: Zhang S et al.

Summary: This multi-institutional cohort study included 3,731 immune checkpoint inhibitor therapy recipients, 18.1% of whom developed a cutaneous immune-related adverse event. The study found that patients who developed cutaneous immune-related adverse events were associated with decreased mortality, particularly in those with melanoma. The cutaneous immune-related adverse events identified in this study were lichenoid eruption, psoriasiform eruption, vitiligo, isolated pruritus without visible manifestation of a rash, acneiform eruption and non-specific rash; these were significantly associated with better survival after multiple comparisons adjustment.

Comment: Previous small studies have shown improved prognosis in cancer patients treated with immune checkpoint inhibitors who developed cutaneous immune-related adverse reactions. In this retrospective assessment of a large group of patients, the investigators manually examined patient records to verify cutaneous adverse reactions and mortality. A positive mortality benefit was seen across all cancer patients, but the benefit was most strongly seen in melanoma cases. The incidence of cutaneous immune-related adverse reactions was 18% which was lower than reported in previous clinical trials (up to 40%) and may be because the mild reactions are less likely to be reported to treating physicians outside of clinical trials. Vitiligo was a particularly positive skin reaction, and the authors speculate that a broadening of the anti-melanocyte effect may be beneficial. They also speculated that immune checkpoint inhibitor therapy may re-activate T cells that have previously reacted against the malignant melanocytes at an early stage in the disease.

Reference: medRxiv. 2023.01.16.23284635.
Abstract

Survival and tumor characteristics of patients presenting with single primary versus second primary melanoma lesions

Authors: Sarver MM et al.

Summary: This retrospective cohort study compared tumour distributions and survival characteristics between patients with second and single primary melanomas. The synchronous and asynchronous cohorts demonstrated significantly improved survival outcomes compared to the single primary cohort. When compared with first-identified synchronous and asynchronous lesions, the single primary lesions were significantly thicker.

Comment: Patients with a history of melanoma are a high-risk group for developing further melanomas. The survival curves after a single melanoma compared to the survival following a second melanoma showed an advantage for the latter group. After correcting for Breslow thickness etc., this advantage was only seen in melanomas developing more than three months after the initial melanoma. Several factors may influence this finding, but it is likely that improved patient self-examination, enhanced patient education regarding the signs of melanoma and more frequent physician full-body skin examinations play a role. It is also possible that the immune response to a second melanoma may be enhanced.

Reference: J Am Acad Dermatol. 2023;88:1033-9
Abstract

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