Skin Cancer RESEARCH REVIEW™

Making Education Easy

Issue 6 – 2021

In this issue:

Abbreviations used in this issue
BCC/SCC = basal/squamous cell carcinoma
LDH = lactate dehydrogenase
OS = overall survival
PD-1/PD-L1 = programmed cell death (ligand)-1
PFS = progression-free survival
RFS = recurrence-free survival

Welcome to the sixth issue of Skin Cancer Research Review.

This issue includes research reporting that patients who relapse after adjuvant targeted therapy for *BRAF*-mutated stage III melanoma respond well to subsequent anti-PD-1-based therapy with outcomes similar to those seen with first-line anti-PD-1 therapy for stage IV melanoma. We have also included a long-term safety report from three of the KEYNOTE trials of pembrolizumab monotherapy for melanoma. Research conducted in participants from a dermoscopy masterclass found that the accuracy of diagnosing lentigo maligna improved after they were trained in the inverse approach, added to the classic pattern analysis. This issue concludes with an Australian study investigating discrepancies between biopsy results and final excised specimens in keratinocyte carcinomas.

We hope you enjoy the research selected, and we look forward to your comments and feedback.

Kind regards,

Dr Annie Wong
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Association of histologic regression with a favorable outcome in patients with stage 1 and stage 2 cutaneous melanoma

Authors: El Sharouni M-A et al.

Summary: The association between histologically confirmed regression and survival from cutaneous invasive melanoma was explored in two cohorts of adults with histologically proven, stage 1 or 2 primary disease. The two cohorts included 17271 Dutch patients and 4980 Australian patients followed for medians of 4.5 and 11.1 years, respectively. Disease regression was associated with: i) improved RFS and OS in the Dutch cohort (respective hazard ratios 0.55 [95% CI 0.48, 0.63] and 0.87 [0.79, 0.96]) and in the Australian cohort (0.61 [0.52, 0.72] and 0.73 [0.64, 0.84]); ii) improved RFS and OS for superficial spreading melanomas (respective hazard ratios 0.54 [0.46, 0.63] and 0.86 [0.76, 0.96] in the Dutch cohort, and 0.67 [0.52, 0.85] and 0.72 [0.59, 0.88] in the Australian cohort); and iii) improved RFS for thin and intermediate Breslow thickness melanomas (both cohorts).

Comment (SS): Histological regression in a melanoma is common, occurring in up to half of cutaneous melanomas. Some suggest this could be associated with a worse prognosis, as it can reduce the Breslow thickness of the melanoma and underestimate its depth, whereas others suggest activation of the host immune system against the tumour could be helpful and improve prognosis. This large Dutch and Australian study found survival outcomes were better for patients with histological regression, particularly for those with thin and intermediate thickness melanomas and superficial spreading melanomas.

Reference: JAMA Dermatol 2021;157:166–73

Abstract

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Independent commentary by Dr Susan Simpkin

Dr Susan Simpkin is a specialist Dermatologist based at the Skin Centre in Tauranga where she has a special interest in skin cancer surveillance and medical dermatology. She is a New Zealand trained Dermatologist, with experience in New Zealand Hospitals and the NHS England.

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Melanoma recurrence patterns and management after adjuvant targeted therapy

Authors: Bhave P et al.

Summary: These authors reported on 85 patients with *BRAF*-mutated stage III melanoma from 21 centres who experienced recurrence after adjuvant targeted therapy; relapse occurred in 19 patients during adjuvant targeted therapy. The median time to first melanoma recurrence was 18 months and the median follow-up period after first recurrence was 31 months. Around two-thirds of the patients (68%) received first-line systemic therapy with immunotherapy or targeted therapy at either first or subsequent recurrence and were assessable for response. The respective proportions of patients who responded to anti-PD-1 therapy (with or without trial agent), ipilimumab plus nivolumab, targeted therapy rechallenge and ipilimumab monotherapy were 63%, 62% 25% and 10%, and the respective 2-year OS rates were 84%, 92%, 49% and 45%. All 28 deaths were due to melanoma.

Comment (AW): Approximately 40% of metastatic melanomas carry a constitutively active *BRAF* mutation, which can be treated with targeted therapy in the metastatic setting to improve survival. There is interest in bringing these treatments forward in the disease course, in effort to improve cure rates. Both targeted therapy and immunotherapy are options that have been shown to reduce the risk of relapse; however, the optimal adjuvant treatment is not known as neither treatment has demonstrated an OS benefit. This current study by Bhave and colleagues reported on an international, multisite retrospective study that investigated the patterns of relapse in patients whose disease recurred after adjuvant targeted therapy for resected stage III or IV melanoma (AJCC 8th edition). Eighty-five patients with a median age of 47 years, mostly stage IIIB or IIIC (25% and 61% of patients, respectively), had a median time of relapse of 18 months. Interestingly, 95% of patients had received therapeutic lymph-node dissection, which may have altered the pattern of relapse. The majority of patients (62%) relapsed with systemic disease, which was mostly (57%) detected by imaging. Eighty-five percent (22/26) of patients who underwent surgery for first recurrence without systemic treatment had a further relapse, suggesting systemic treatment is necessary in this population who have already had a therapeutic dissection. Fifty-eight patients received immunotherapy or targeted therapy as first-line systemic treatment after disease recurrence, and the response rate to immunotherapy was approximately 60%, whereas the response rate to targeted therapy was unsurprisingly lower at 25%. Only five patients in this cohort had innate resistance to targeted therapy (i.e. developed recurrence during adjuvant targeted therapy), and none of these patients responded to subsequent immunotherapy either. Overall this study provides some reassurance that adjuvant treatment with targeted therapy does not diminish response rates to subsequent immunotherapy in the majority of patients. However, the optimal adjuvant treatment choice for *BRAF*-mutated early-stage melanoma still remains an open question.

Reference: Br J Cancer 2021;124:574–80
Abstract

The presence of eccentric hyperpigmentation should raise the suspicion of melanoma

Authors: Borsari S et al.

Summary: Two evaluators with different expertise examined the dermatoscopic images of 107 melanomas and 133 naevi typified by eccentric hyperpigmentation to determine if eccentric hyperpigmentation is an accurate determinant of melanoma on analysis *in toto* versus a partial analysis with only the eccentric hyperpigmentation or the non-hyperpigmented portion visible. Melanomas typically exhibited three or four colours (44.8% and 41.1% of cases, respectively) and an atypical network (88.1% in lesions with eccentric hyperpigmentation). The diagnostic accuracy of the two evaluators did not differ significantly. Compared with evaluation of eccentric hyperpigmentation or the non-hyperpigmented portion alone, evaluation of whole lesions was associated with greater mean sensitivity (89.7% vs. 62.6–72.7%), and specificity was increased (51.4%) when eccentric hyperpigmentation was evaluated. The positive predictive value for eccentric hyperpigmentation evaluation was 52.3% and the likelihood ratio was 1.4 (i.e. around one out of two cases with eccentric hyperpigmentation was a melanoma).

Comment (SS): Some benign naevi, such as combined naevi or atypical naevi, may also have eccentric hyperpigmentation that can mimic melanoma. This retrospective study with two blinded evaluators suggested dermoscopic features such as colour variegation (three or more colours) or atypical network in the hyperpigmented area can improve specificity for melanoma, but that eccentric hyperpigmentation alone was still a useful dermoscopic feature for raising the suspicion of melanoma.

Reference: J Eur Acad Dermatol Venereol 2020;34:2802–8
Abstract

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Long-term safety of pembrolizumab monotherapy and relationship with clinical outcome

Authors: Robert C et al.

Summary: Adverse events over median follow-up of 42.4 months were reported for 1567 KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006 trial participants who had received pembrolizumab for advanced melanoma. While most adverse events were mild or moderate, 17.7% of the participants experienced grade 3–4 treatment-related adverse events. There were two deaths that were attributed to pembrolizumab. Any-grade immune-mediated adverse events were recorded for 23.0% of the participants and typically emerged within 16 weeks of starting treatment; the most common were hypothyroidism (9.1%), pneumonitis (3.3%) and hyperthyroidism (3.0%); 6.9% of participants experienced grade 3–4 immune-mediated adverse events. A landmark analysis revealed that compared with participants who did not develop immune-mediated adverse events (n=384), those who did (n=79) had similar objective response rates, times to and durations of response, PFS and OS. Compared with systemic corticosteroid nonrecipients (evaluable n=62), systemic corticosteroid recipients (evaluable n=17) had a similar objective response rate and time to response, but numerically shorter duration of response, PFS duration and OS.

Comment (AW): This study reports on the pooled long-term safety outcomes of patients with metastatic melanoma treated with pembrolizumab in the KEYNOTE-001 (phase 1b), KEYNOTE-002 (ipilimumab-refractory) and KEYNOTE-006 (treatment-naïve) clinical trials. With a median follow-up of 42.4 months, 1567 patients were included in the analysis. There were no new safety signals from this analysis. 98.7% of patients had an adverse event due to any cause, and 10.5% of patients experienced ≥1 adverse event. The most common adverse events were fatigue (32.5%), pruritus (24.4%), rash (18.6%) and diarrhoea (17.8%). Eighteen percent of patients experienced severe or life-threatening treatment-related adverse events: colitis (1.5%), diarrhoea (1.4%) and fatigue (1.3%). There were two deaths (one sepsis, and one colitis/pneumonia). Most toxicities occurred within the first 16 weeks of treatment. There have been anecdotal reports of improved tumour response to immunotherapy in patients who experienced toxicity (possibly due to increased immune response); however, this analysis did not find any significant difference between patients who experienced toxicity and those who did not.

Reference: Eur J Cancer 2021;144:182–91
Abstract

Risk factors and timing of subsequent cutaneous squamous cell carcinoma in patients with cutaneous squamous cell carcinoma

Authors: Rodriguez M et al.

Summary: The risk for and timing of subsequent cutaneous SCC after an initial diagnosis of cutaneous SCC were evaluated in a retrospective cohort of registrants with ≥2 primary invasive cutaneous SCCs diagnosed 2 months apart; 299 primary cutaneous SCCs were included in the analysis. The respective proportions of patients who had developed a second cutaneous SCC at 6 months, 1 year, 3 years and 5 years after their initial cutaneous SCC diagnosis were 18%, 32%, 68% and 89%. Factors that were significantly associated with an increased risk of subsequent cutaneous SCC included age at initial diagnosis, T2 stage and poor tumour grade.

Comment (SS): There is limited data to determine the most appropriate follow-up interval for skin cancer surveillance in those with a previous history of SCC. The American Academy of Dermatology recommends at least annual total body skin examination, with adjustment of follow-up frequency depending on individual risk factors. This study supports increasing the frequency of total body skin examination for older patients and those presenting with more advanced or poorly differentiated SCC who are at higher risk of developing a subsequent SCC elsewhere.

Reference: J Am Acad Dermatol 2021;84:719–24
Abstract

Nivolumab plus ipilimumab for treatment-naïve metastatic uveal melanoma

Authors: Piulats JM et al.

Summary: Fifty-two treatment-naïve adults with progressive metastatic uveal melanoma received nivolumab 1 mg/kg once every 3 weeks and ipilimumab 3 mg/kg once every 3 weeks for four inductions, followed by nivolumab 3 mg/kg once every 2 weeks until progressive disease, toxicity or withdrawal in this phase 2 trial; the respective proportions of patients with liver M1, extra-liver M1 and elevated LDH levels were 78.8%, 56% and 32%. The most common outcome was stable disease at 51.9%, which was also the 12-month OS rate (primary endpoint). The respective median OS and PFS durations were 12.7 months and 3.0 months, with PFS influenced by higher LDH levels.

Comment (AW): Uveal melanoma has a poor prognosis of approximately 9 months survival. Its response to anti-PD-(L)1 therapy is poor (with a response rate of 3%) hence the funding for anti-PD1 was delisted for this indication in NZ by PHARMAC last year. Piulats and colleagues have reported on GEM-1402, a phase 2 clinical trial led by the Spanish Multidisciplinary Melanoma Group, which evaluated combination ipilimumab and nivolumab (combination immunotherapy) in patients with treatment-naïve uveal melanoma. Unlike the high response rate observed in cutaneous melanoma, this combination immunotherapy was associated with a low response rate of 11.5% in 52 evaluable patients. The 12-month OS rate (the primary endpoint of the study) was 51.9%. The median OS and PFS durations were 12.7 months and 3.0 months, respectively. The treatment was associated with severe-to-life-threatening toxicity in 58% of patients, with two treatment-related deaths. While this combination immunotherapy is an option in first-line treatment for advanced uveal melanoma, there is clearly a need for more efficacious and less toxic treatments.

Reference: J Clin Oncol 2021;39:586–98
Abstract

Independent commentary by Dr Annie Wong

Dr Annie Wong is a NZ-trained consultant medical oncologist at Wellington Blood & Cancer Centre. Her oncological sub-specialities include melanoma, head and neck cancer, as well as genitourinary cancers. She is passionate about patient care, research and teaching. She completed her medical oncology training in Wellington and subsequently completed a medical oncology fellowship at Peter MacCallum Cancer Centre in Melbourne, Australia. During her fellowship she was inspired by the transformative outcomes with immunotherapy, and investigated novel biomarkers for melanoma immunotherapy as part of her PhD studies. She actively participates in the MelNet as well as the Australasian Melanoma and Skin Cancers Trials group. She also holds honorary positions as a clinical senior lecturer at Otago University and researcher at Peter MacCallum Cancer Centre.

The dermoscopic inverse approach significantly improves the accuracy of human readers for lentigo maligna diagnosis

Authors: Lallas A et al.

Summary: In this research, clinical and dermoscopic images of histopathologically diagnosed lentigo maligna, pigmented actinic keratoses and solar lentigo/flat seborrhoeic keratoses were used to investigate if training on the inverse approach rather than classical pattern analysis would increase the diagnostic accuracy of readers from a dermoscopy masterclass. For the respective timepoints associated with pretraining, pattern analysis training and subsequent inverse approach training, the mean sensitivity values for diagnosing lentigo maligna were 51.5%, 56.7% and 83.6%, the respective mean proportions of readers providing correct answers were 62.1%, 65.5% and 78.5%, and the respective percentages of readers who outperformed a convolutional neural network were 6.4%, 15.4% and 53.9%.

Comment (SS): Where the distinction between early lentigo maligna, pigmented actinic keratosis and solar lentigo is more subtle, taking an inverse approach by first looking for benign features can improve the sensitivity for early lentigo maligna detection. This small experimental study improved diagnostic accuracy amongst participants of a dermoscopy masterclass by teaching the inverse method. If the lesion has a benign feature of pigmented actinic keratosis, seborrhoeic keratosis or solar lentigo that occupies more than half of the lesion's surface then this would favour a benign diagnosis, whereas if these features are absent or present in small areas then this is enough to consider the lesion as suspicious for lentigo maligna, even if no other features of lentigo maligna are seen. This method enables earlier detection of lentigo maligna and ultimately better patient outcomes.

Reference: J Am Acad Dermatol 2021;84:381–9
Abstract

Cutaneous toxicities in patients with melanoma receiving checkpoint inhibitor therapy

Authors: Edwards CL et al.

Summary: These authors reviewed the retrospective records of adults with melanoma from a single large specialist tertiary referral centre who had been treated with checkpoint inhibitor therapy over a 12-year period. Cutaneous toxicity occurred in 24% of the patients but was generally manageable, with <5% of patients needing to discontinue their treatment.

Comment (AW): This single-centre retrospective study is the largest real-world report on the cutaneous toxicities from immune checkpoint inhibitors in patients with advanced melanoma treated at Royal Marsden NHS Foundation Trust from 2006 to 2018. In total, 692 patients received immune checkpoint inhibitors over this time, and 258 cutaneous toxicity cases were reported, with the majority being pruritus and maculopapular rash (27% and 40% of toxicities, respectively). Most skin toxicities occur within the first month, but some can start as late as 2 years after the onset of treatment. Approximately a third of rashes were mild and required either observation or antihistamines. The other half of patients required mostly topical steroids (45%) and some systemic steroids (8%), and 5% of patients had to discontinue treatment as a result of skin toxicity. Importantly, a rare toxicity is the development of bullous eruption, and this severe condition requires urgent consultation with the oncology and dermatology multidisciplinary team.

Reference: Clin Exp Dermatol 2021;46:338–41
Abstract

Histopathological discrepancy between biopsy and Mohs micrographic surgery in keratinocyte carcinoma

Authors: Stewart N et al.

Summary: These authors reviewed 406 BCCs and 58 SCCs entered in an Australian Mohs micrographic surgery database to explore the relationship between the preoperative lesion diagnosis according to the formal pathology report and the histopathological results reported at the time of Mohs micrographic surgery. They found an overall discrepancy rate in the histopathological classification of keratinocyte carcinoma of 42.2%, and the proportion of cases in which the biopsy underestimated the aggressiveness of the tumour was 12.9%; both these values were found to be consistent with similar studies identified in a systematic review. The proportion of biopsies that failed to identify an aggressive BCC subtype was 31.6%, and the proportion of biopsy-proven superficial BCCs for which an invasive component was identified on Mohs micrographic surgery was 79.3%; both these values were higher than reported in comparable studies, possibly due to high prevalence of mixed histopathological subtypes, especially among BCCs with discordant histopathological results.

Comment (SS): This retrospective review comparing Mohs histopathology results from the Australian MMS database and preoperative biopsy results highlighted a discordance similar to that seen in previous studies. Histopathological discordance was noted in up to 42.4% of BCCs and 39.7% of SCCs, with subtype reported as over- or underestimated in terms of its aggressiveness, particularly for superficial BCCs. This serves as a reminder as always to interpret histology results carefully together with clinical findings before making any management decisions.

Reference: Australas J Dermatol 2021;62:41–6
Abstract

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