Melanoma Research Review™

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Issue 46 - 2021

In this issue:

Abbreviations used in this issue:

AE = adverse event; **CR** = complete response; **HR** = hazard ratio; **ICI** = immune checkpoint inhibitor; **MSS** = melanoma specific survival; **ORR** = objective response rate; **OR** = odds ratio; **OS** = overall survival; **PFS** = progression-free survival; **PR** = partial response; **TIL** = tumour-infiltrating lymphocyte; **TT** = targeted therapy.

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Welcome to the 46th issue of Melanoma Research Review.

The lead article assessed the prognostic significance of tumour-infiltrating lymphocytes in a large cohort of patients with melanoma. The study provides evidence that brisk tumour-infiltrating lymphocytes represent an independent prognostic factor for overall survival among patients with primary cutaneous melanoma. Findings from a meta-analysis support the diagnostic importance of dermoscopic structures associated with melanoma detection. Other interesting research reviewed in this issue includes tebentafusp treatment in metastatic uveal melanoma and trametinib treatment in non-V600 BRAF mutant melanoma.

An important article included in this issue explores rechallenge and retreatment with immune checkpoint blockade in melanoma patients. The authors conclude retreatment, rechallenge and escalation are available options for patients with melanoma who relapse in the adjuvant or advanced setting. Another article reports on real-life data for first-line combination immune-checkpoint inhibition and targeted therapy in patients with melanoma brain metastases. The concluding article is a Dutch registry study evaluating the outcomes for systemic therapy in older patients with metastatic melanoma. The authors report patients with metastatic melanoma ≥ 75 years are less frequently treated. However, when treated there is no statistical significant increase in toxicity and only a borderline statistical significant difference in melanoma specific survival compared to younger patients.

I hope you find the research in this issue useful to you in your practice and I look forward to your comments and feedback.

Kind Regards,

Professor Michael Henderson

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Assessing the prognostic significance of tumor-infiltrating lymphocytes in patients with melanoma using pathologic features identified by natural language processing

Authors: Yang J, et al

Summary: This retrospective cohort study analysed the medical records of 14,436 patients with cutaneous melanoma to assess the prognostic significance of tumour-infiltrating lymphocytes (TILs). The researchers used natural language processing to establish a study cohort of 2,624 patients who had vertical growth phase melanoma with TIL status scored. They identified absent TILs in 434 patients (16.5%), nonbrisk TILs in 1,916 patients (73.0%), and brisk TILs in 274 patients (10.4%). The 5-year survival rate was 71.0% among patients with an absence of TILs, 73.8% among patients with nonbrisk TILs and 85.2% among patients with brisk TILs. Brisk TILs were significantly associated with improved overall survival (OS) (adjusted HR, 0.63; P = 0.03; 14.2% OS advantage at 5 years), and nonbrisk TILs were not associated with improved OS (adjusted HR, 0.87; P = 0.25), compared with the absence of TILs. It was noted brisk TILs were significantly associated with improved OS (adjusted HR, 0.63; P = 0.03; 14.2% OS advantage at 5 years), and nonbrisk TILs were not associated with improved OS (adjusted HR, 0.87; P = 0.25), compared with the absence of TILs.

Comment: This is an interesting study firstly for the way the data was gathered and secondly for the results which confirm the prognostic significance of TILs. The authors used an artificial intelligence natural language processing algorithm, which they developed to trawl through the pathology report database of 15,000 reports of patients treated at their institution to identify 2,624 patients who had complete pathology information including assessment of TILs. They performed a number of verification procedures to confirm the accuracy of this strategy and assess that they identified 98% of patients with 100% precision of the data. Clearly this approach allowed them to efficiently collect a very large database with the result this study is the largest to date investigating the significance of TILs. Apart from confirming improved survival with TILs on both univariate and multivariate analysis, this study also found they were more frequently found in younger patients and thinner melanomas (< 2 mm thick).

Reference: JAMA Netw Open 2021 Sep 1;4(9):e2126337
Abstract

Metastatic acral melanoma treatment outcomes: A systematic review and meta-analysis

Authors: Cho KK, et al

Summary: This meta-analysis included 19 non-randomised studies with 646 patients with acral melanomas and 1,609 patients with nonacral melanomas treated with systemic therapy including chemotherapy, KIT-targeted drugs, as well as anti-CTLA-4 and anti-PD-1 checkpoint inhibitor therapy. The authors reported patients with acral melanomas had worse prognosis than nonacral cutaneous melanoma (acral OS median 15 months versus nonacral cutaneous median 24 months; P < 0.001). In addition, acral melanoma patients treated with anti-PD-1 monotherapy had higher OS at 12 months (53%) compared with anti-CTLA-4 monotherapy (34%; P < 0.001).

Comment: Acral melanoma (occurring on soles and palms or involving the nail apparatus) or acral lentiginous melanoma account for < 5% of cutaneous melanoma but are distinguished by lower mutational burden, different somatic mutation signatures, pathology variables and response to treatment. This study was a meta-analysis of 646 patients from 19 studies including 7 from Japan and 6 from China. All the studies were retrospective. Compared to patients with cutaneous melanoma, median survival was poorer (15 months versus 24 months). There were only sufficient patients to compare anti-PD-1 monotherapy with anti-CTLA-4 monotherapy indicating a significant benefit for anti-PD-1 therapy but significantly less than previously reported for cutaneous melanoma. The objective response rate, ORR (CR and PR) was 20% for patients receiving anti-PD-1 monotherapy in this study compared with 58% for the combination and 45% for single agent therapy in CheckMate 067. Metastatic acral melanoma remains a difficult disease to control.

Reference: Melanoma Res 2021 Oct 1;31(5):482-486
Abstract

Assessment of diagnostic accuracy of dermoscopic structures and patterns used in melanoma detection: A systematic review and meta-analysis

Authors: Williams NM, et al

Summary: The meta-analysis evaluated a total of 40 studies including 22,796 skin lesions and 5,736 melanomas. The authors found structures and patterns with the highest odds ratios (ORs) were shiny white structures (OR, 6.7), pseudopods (OR, 6.7), irregular pigmentation (OR, 6.4), blue-white veil (OR, 6.3), and peppering (OR, 6.3). The structures with the highest specificity were pseudopods (97.3%), shiny white structures (93.6%), peppering (93.4%), and streaks (92.1%). Features with the highest sensitivity were irregular pigmentation (62.3%), blue-white veil (60.6%), atypical network (56.8%), and a multicomponent pattern (53.7%).

Comment: Dermatoscopy is an important aid in the evaluation of pigmented lesions and has been shown to improve diagnostic accuracy, reduce the benign to malignant ratio and reduce the number of negative biopsies. Given that dermatoscopy is a subjective assessment, much attention has been given to evaluating dermatoscopic features supporting the diagnosis of melanoma. The commonest features seen in melanomas included atypical network, streaks, dots/globules et cetera but the features most predictive of melanoma (highest odds ratio) were not necessarily those with the highest sensitivity and specificity. The authors concluded that their analysis indicates that an overall disorganised dermatoscopic pattern rather than the more organised features of benign nevi was critical. The most important significant features were shiny white structures and blue-and-white veil. The importance of these features and others and the strength of their association with melanoma are critical information for frontline clinicians using dermatoscopy.

Reference: JAMA Dermatol 2021 Sep 1;157(9):1078-1088
Abstract

Overall survival benefit with tebentafusp in metastatic uveal melanoma

Authors: Nathan P, et al

Summary: This open-label, phase 3 trial randomly assigned untreated HLA-A*02:01-positive patients with metastatic uveal melanoma to receive tebentafusp (n = 252) or the investigator's choice of therapy with single-agent pembrolizumab, ipilimumab, or dacarbazine (n = 126). The investigators reported OS at 1 year was 73% in the tebentafusp group and 59% in the control group (HR for death, 0.51; 95% CI, 0.37 to 0.71; P<0.001) in the intention-to-treat population. They also found progression-free survival (PFS) was significantly higher in the tebentafusp group than in the control group (31% versus 19% at 6 months; HR for disease progression or death, 0.73; 95% CI, 0.58 to 0.94; P = 0.01). The most common treatment-related adverse events (AEs) in the tebentafusp group were cytokine-mediated events and skin-related events, including rash (83%), pyrexia (76%), and pruritus (69%).

Comment: This report presents a significant advance in the management of metastatic uveal melanoma. Tebentafusp is a bi-specific protein consisting of a T-cell receptor recognising a peptide fragment derived from degradation of intracellular GP 100 (found in tumour cells and melanocytes) presented by HLA molecules fused to anti-CD3, which recruits T cells to target cells expressing the degraded GP 100 peptide. Tebentafusp was compared with investigator preferred treatment (anti-PD-1, anti-CTLA-4 or dacarbazine). HLA restriction meant this therapy was suitable for approximately 50% of patients with metastatic uveal melanoma. Overall survival at 12 months was significantly improved by tebentafusp (73% v 59%). Outcomes were superior even in patients who failed to respond to tebentafusp. Adverse effects were cytokine related (T cell activation) or cutaneous (melanocytes also express the GP 100 peptide). Side effects were generally low grade and only 2% of patients discontinued treatment due to AEs.

Reference: N Engl J Med 2021 Sep 23;385(13):1196-1206
Abstract

The concepts of rechallenge and retreatment with immune checkpoint blockade in melanoma patients

Authors: Zaremba A, et al

Summary: This review evaluated data from clinical trials and retrospective studies to explore outcomes of rechallenge and retreatment with immune checkpoint inhibitors (ICIs) in melanoma patients. The authors conclude retreatment, rechallenge and escalation are available options for patients with melanoma who relapse in the adjuvant or advanced setting.

Comment: This is an important article reviewing the management of patients with advanced melanoma who progress after treatment with ICI and is authored by many of the major opinion leaders. Retreatment is defined as further treatment (for recurrence) with a similar class of agent after completion of adjuvant treatment. Patients who received adjuvant anti-PD-1 monotherapy appear to derive no benefit from further anti-PD-1 monotherapy and switch or escalation of therapy is indicated. Conversely, further treatment with targeted therapies appears to offer significant clinical benefit.

Rechallenge is defined as further treatment with the same therapeutic class after disease progression in patients with metastatic disease who have previously responded. Escalation of anti-PD-1 therapy by the addition of ipilimumab is more effective (and toxic) than anti-PD-1 monotherapy. The role of newer agents is also highlighted. This is an in-depth and incisive review and is strongly recommended.

Reference: Eur J Cancer 2021 Sep;155:268-280
Abstract

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Independent commentary by Professor Michael Henderson.

Michael A Henderson is Professor of surgery in the University of Melbourne and surgeon in the multidisciplinary Melanoma and Skin Service at the Peter MacCallum Cancer Centre in Melbourne. He is a graduate of the University of Melbourne and after obtaining a Fellowship of the Royal Australasian College of Surgeons spent 2 1/2 years undertaking a fellowship in surgical oncology at the University of Texas MD Anderson Cancer Centre. His clinical practice is confined to surgical oncology. His major clinical interests are in the management of patients with melanoma and maintains an active clinical and translational research interest in melanoma. He led a major international multicentre study of adjuvant radiotherapy after link for melanoma and is currently the principal investigator of a multicentre international trial of margins of excision of intermediate and thick melanoma (MELMART).

Real-life data for first-line combination immune-checkpoint inhibition and targeted therapy in patients with melanoma brain metastases

Authors: Hilbers M, et al

Summary: The researchers assessed efficacy and outcomes of combined ICI ipilimumab/nivolumab or targeted therapy (TT) as first-line treatment in melanoma brain metastases within 3 months after diagnosis. 53 patients received combination ICI, 32% had symptomatic melanoma brain metastases and 33.9% elevated LDH. 71.7% required local treatment. The disease control rate was 60.3%. Intracranial response rate was 43.8% at 3-months with durable responses at 6- (46.5%) and 12-months (53.1%). Extracranial response rate was 44.7% at 3-months and 50% at 12-months. Median PFS was 9.6 months and median OS 44.8 months. 63 patients received combination TT, 55.6% of patients had symptomatic melanoma brain metastases, 57.2% of patients had elevated LDH and 68.3% of patients required local treatment. The disease control rate was 60.4%. Intracranial response rate was 50% at 3-months, but dropped at 6-months (20.9%). Extracranial response rate was 69.2% at 3-months and 17.6% at 12-months. Median PFS was 5.8 months and mOS 14.2 months. In BRAFV600 patients, 26.7% of patients received combination ICI and 73.3% combination TT with OS (P = 0.0053) and mPFS (P = 0.03) in favour to ICI.

Comment: This study reviews the real world experience with ICI therapy or TT and includes patients usually excluded from clinical trials including multiple brain metastases, recent steroid use, elevated LDH, et cetera. The majority of patients also received radiotherapy (71%). Durable intracranial responses occurred in 53% at 12 months. Among the patients with BRAF mutated melanoma most received TT probably reflecting initial higher disease burden (symptomatic, on steroids, elevated LDH, more extracranial sites and intracranial lesions). This study confirms the effectiveness of ICI or TT even in patients with poor prognostic features. For patients with BRAF mutated melanoma, responses at three months favoured TT but by 12 months ICI therapy gave superior outcomes.

Reference: Eur J Cancer 2021 Oct;156:149-163
Abstract

Multiparametric MRI of early tumor response to immune checkpoint blockade in metastatic melanoma

Authors: Lau D, et al

Summary: This prospective study investigated early microstructural and functional changes within melanoma metastases following ICI therapy using multiparametric MRI. The study cohort included 15 treatment-naïve metastatic melanoma patients (total 27 measurable target lesions). Imaging was performed at baseline and following 3 and 12 weeks of treatment on ICI using T2-weighted imaging, diffusion kurtosis imaging, and dynamic contrast-enhanced MRI. Differential tumour growth kinetics in response to ICI were measured in individual metastases within the same patient. Early detection of tumour cell death or cell loss was observed in both responding and pseudo-progressive lesions after 3 weeks of treatment. It was noted tumour heterogeneity was consistently higher in the pseudo-progressive and true progressive lesions, compared with the responding lesions throughout the first 12 weeks of treatment. These preceded tumour regression and significant tumour vascularity changes detected after 12 weeks of immunotherapy.

Comment: In the absence of effective biomarkers to predict which patients are likely to respond to ICI therapy, assessment of response particularly early in treatment is important. Pseudo-progression although uncommon limits the efficacy of standard imaging with CT and PET scan certainly in the early weeks of treatment. This is a small study, which has comprehensively examined MRI changes before and throughout ICI therapy. Early results suggest changes in the T2 weighted signal intensity identifies pseudo-progression. Other features suggesting pseudo-progression include changes in cell density and tumour vasculature. The complexity of assessing response is highlighted by marked intra-lesional, inter-metastatic and inter-patient heterogeneity in MRI appearances over the first three months of treatment. Further investigation is necessary before response evaluation by MRI for patients receiving ICI is standard of care.

Reference: J Immunother Cancer 2021 Sep;9(9):e003125
Abstract

Efficacy and safety of trametinib in non-V600 BRAF mutant melanoma: A phase II study

Authors: Nebhan CA, et al

Summary: In this open-label, multicentre, phase II study, nine patients with advanced melanoma harbouring mutations in BRAF outside V600 (non-V600) or BRAF fusions received trametinib 2.0 mg daily. Patients were divided into cohorts based on the intrinsic catalytic activity of BRAF mutation (high; low/unknown). Among all patients, the ORR was 33%. The ORR was 67% in the high BRAF mutation cohort and 17% in the low/unknown BRAF mutation cohort. Two patients had stable disease as best response, and six patients had some degree of tumour shrinkage. The median PFS was 7.3 months. Treatment-related adverse events occurred in all patients; 89% were grade 1-2.

Comment: In up to 5% of patients with BRAF mutated melanomas, the mutation occurs at a site other than at the V600 codon. Some of these mutations lead to downstream MAP kinase activation while others facilitate upstream MEK/ERK signaling. In a further small proportion, fusions between BRAF and over 30 partner proteins in some cases facilitating downstream activity occurs potentially leading to downstream activation.

The number of patients in this study was small (nine) and overall responses were seen in one third including two thirds of patients with downstream MAP kinase activation responded. Clearly these numbers are too small to alter treatment recommendations at present but the authors make the point that next-generation sequencing may be of value in a small but substantial subset

Reference: Oncologist 2021 Sep;26(9):731-e1498
Abstract

Outcomes for systemic therapy in older patients with metastatic melanoma: Results from the Dutch melanoma treatment registry

Authors: Jochems A, et al

Summary: The investigators analysed a real-world cohort of 3,054 patients with metastatic melanoma stratified for age (≤ 65 years, 66-74 years and ≥ 75 years), and BRAF status. Overall, 52.2% of patients were ≤ 65 years and 18.4% of patients ≥ 75 years. BRAF mutated tumours were found less often in patients ≥ 75 years: 34.5% versus 65% in patients ≤ 65 years. Patients ≥ 75 years received systemic therapy less frequently compared to their younger counterparts independent of the BRAF status. There was no statistical significant difference in grade 3 or 4 toxicity. Three year OS rate was 13.7% in patients ≥ 75 years versus 26.7% in patients ≤ 65 years, with a HR of 1.71, P < 0.001. Three year melanoma specific survival (MSS) was 30.4% versus 34.0%, HR 1.26, P = 0.005 with an adjusted HR of 1.21, P = 0.049.

Comment: This is the largest study to date reporting management of advanced melanoma in an elderly (> 75 years) population. Strengths include the number of patients from an extensive national database but lacks information on patient comorbidities and performance status. Over the time period surveyed, the use of TTs and ICIs in the elderly increased. Elderly patients were less likely to have BRAF mutated melanomas but had thicker tumours. There was little difference in significant morbidity (grade 3+). OS was poorer in the elderly compared to patients < 65 years but there was no difference in MSS suggesting a greater impact of competing mortality in the elderly. The data presented here is consistent with other smaller reports and supports the author's conclusion that age should not be used as a single criteria to deny treatment for advanced melanoma in the elderly population.

Reference: J Geriatr Oncol 2021 Sep;12(7):1031-1038
Abstract

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