Melanoma Research Review™

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Issue 50 - 2022

In this issue:

Abbreviations used in this issue:

AE = adverse event; **ALM** = acral lentiginous melanoma; **CAE** = cutaneous adverse event; **CR** = complete response; **DoR** = duration of response; **ICI** = immune checkpoint inhibition; **NB** = neoantigen burden; **ORR** = objective response rate; **OS** = overall survival; **PD** = progressive disease; **PFS** = progression free survival; **PTPRT** = protein tyrosine phosphatase receptor type T; **RFS** = relapse-free survival; **SD** = stable disease; **SES** = socioeconomic status; **SLN** = sentinel lymph node; **TMB** = tumour mutational burden; **WES** = whole-exome sequencing.

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Welcome to the 50th issue of Melanoma Research Review

Dear Readers,

The melanoma selections this month include several studies on acral melanoma and one on mucosal melanoma. There are also several studies on management aspects which I hope readers will find of interest.

Kind Regards,

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

Authors: Cho KK, et al

Summary: The meta-analysis comprised of 19 nonrandomised studies specifying the treatment outcome of metastatic acral melanoma. The studies included 646 patients with acral melanomas and 1,609 patients with nonacral melanomas treated with systemic therapy including chemotherapy, KIT-targeted drugs, anti-CTLA4 and anti-PD-1 checkpoint inhibitor therapy. The authors concluded patients with acral melanomas had worse prognosis than nonacral cutaneous melanoma (acral overall survival (OS): median 15 months; nonacral cutaneous OS: median 24 months, P <0.001). It was also noted 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: The authors examined results from 19 studies, with a total of 646 patients with acral lentiginous melanoma (ALM) or acral melanoma, and 1,609 non-acral melanoma patients as comparison. No differences were detected in progression free survival (PFS) data, but OS was worse in patients with acral melanomas than nonacral cutaneous melanoma; OS 15 months vs 24 months. Patients treated by anti-PD-1 had better OS at 12 months compared with those treated with ipilimumab (53% versus 34%). Their discussion suggested that the disparity between the objective response rates (ORR) of acral and other forms of cutaneous melanoma may be due to differences in tumour-specific neoantigen peptides that arise from somatic mutations in the cancer genome. Whilst most melanomas are highly mutagenic due to ultraviolet-light driven carcinogenesis, whole genome analysis suggests that acral melanomas have 18-fold less tumour mutation burden compared to other cutaneous melanomas. Their metanalysis included 2 small studies on targeted treatment against mutated KIT, said to occur in 10-20% of acral melanoma. Objective response rate in the small study was 29% and median OS 21.1 months. They conclude the study demonstrated low activity across a breadth of approved drug therapies, including anti-PD-1, the most active therapy in melanoma to date. Further research into treatments for metastatic acral melanoma is needed.

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

Sentinel lymph node biopsy positivity in patients with acral lentiginous and other subtypes of cutaneous melanoma

Authors: Cheraghlou S, et al

Summary: This retrospective cohort study included cases of AJCC-8 clinical stage I to II melanomas from the US National Cancer Database diagnosed from 2012 to 2015. In total 60,148 patients with malignant melanomas, 959 of whom had ALM-subtype disease were identified. The authors reported ALM was independently associated with the highest risk for sentinel lymph node (SLN) positivity among included subtypes (vs superficial spreading melanoma: odds ratio, 1.91). Subgroup analysis by AJCC clinical stage demonstrated that ALM was independently associated with the highest risk for SLN positivity for both stage IB (18.39%) and II (39.53%).

Comment: This important retrospective analysis of 959 patients from a large US database makes a case for ALM to be considered separately to cutaneous malignant melanoma (CMM) in decisions regarding SLN biopsy. They refer to frequent misdiagnosis and late diagnosis as being common and a different biology as being factors in higher rates of SLN positivity. They conclude by recommending that SLN biopsy should be encouraged for patients with clinical stage IB and II ALM and that patients with ALM should be counselled regarding the higher regional metastatic risk of their cancers. Future work using an even larger cohort is required to provide estimates about the rates of SLN positivity for clinical stage IA ALM.

Reference: JAMA Dermatol. 2022 Jan 1;158(1):51-58
Abstract

Survival differences in acral lentiginous melanoma according to socioeconomic status and race

Authors: Yan BY, et al

Summary: The retrospective cohort study compared disease-specific survival in ALM (n=2,245) across socioeconomic status (SES) and race. The investigators reported five-year disease-specific survival was 77.8%. After adjustment, patients in the lowest and second-to-lowest SES quintile had 1.33 and 1.42 times the risk of death, respectively, compared to highest quintile patients. Hispanic White and Black patients had 1.48 and 1.25 times the risk of death, respectively, compared to non-Hispanic Whites. It was noted hazard ratios for ALM-specific death decreased in Hispanic White and Black patients after adjusting for SES and AJCC stage at diagnosis.

Comment: As stated in their introduction ALM is the most common subtype of cutaneous melanoma among people of colour and the least common subtype among non-Hispanic Whites. This study was based on information from the specialised Surveillance, Epidemiology, and End Results (SEER) database. In essence they found survival differences for Hispanic White and Black patients relative to White patients were dependent on stage at presentation and SES. However, late presentation may only partially account for racial disparities in ALM survival, as differences in ALM survival in Hispanic White patients persisted after adjusting for stage and race. The manner in which SES contributes to racial disparities in ALM survival remain to be elucidated but may be attributed to delays in time to treatment and decreased access to immunotherapy and targeted therapies.

Reference: J Am Acad Dermatol. 2022 Feb;86(2):379-386
Abstract

Cutaneous adverse events in 155 patients with metastatic melanoma consecutively treated with anti-CTLA4 and anti-PD1 combination immunotherapy: Incidence, management, and clinical benefit

Authors: Patel AB, et al

Summary: The study cohort included patients from a single institutional database who received at least one dose of ipilimumab in combination with either nivolumab or pembrolizumab for stage IV or unresectable stage III melanoma. The time to next treatment (TTNT) was calculated from the start of checkpoint inhibitor (CPI) therapy to the start of the next treatment or death, and the development of cutaneous adverse events (CAEs) was tested to identify associations with TTNT. Eighty-one patients (52.3%) experienced a total of 92 CAEs, including eczematous dermatitis (25.0%), morbilliform eruption (22.8%), vitiligo (12.0%), and pruritus without rash (8.7%). The median times to the onset and resolution of CAEs were 21 days and 50 days, respectively. Most CAEs resolved after patients entered the CPI maintenance phase and treatment with oral antihistamines with or without topical steroids. CPI discontinuation occurred in 2.6% because of CAEs, in 31.6% because of other immune-related adverse events, and in 12.9% because of melanoma progression or death. For patients definitively treated with CPIs (86.5%), TTNT was significantly longer with CAEs than without CAEs (HR 0.567; P=0.039).

Comment: The authors point out that the increased efficacy of combination anti-CTLA4 and anti-PD-1 therapy is making it the standard of care for many patients. Because of the early onset of CAEs, the authors considered there may be potential for CAEs to be used as predictive markers for more severe, later onset, lower incidence AEs that can be life-threatening or dose-limiting. Their results however, did not show this to be the case. They also examined whether the CAEs would be associated with improved outcomes. They used the TTNT to assess outcomes and found that this was longer in those with CAEs. They conclude that "Early recognition and management of CAEs minimize therapy interruptions or discontinuations and support patients' ability to gain the maximum clinical benefit from CPI therapy".

Reference: Cancer. 2022 Mar 1;128(5):975-983
Abstract

Chemotherapy after immune checkpoint inhibitor failure in metastatic melanoma: A retrospective multicentre analysis

Authors: Goldinger SM, et al

Summary: Patients (n=463) with metastatic melanoma treated with chemotherapy after progression on immune checkpoint inhibitors (ICIs) were identified retrospectively from 24 melanoma centres. The researchers reported 56% had received PD-1-based therapy before chemotherapy. Chemotherapy regimens included carboplatin + paclitaxel (32%), dacarbazine (25%), temozolomide (15%), taxanes (9%, nab-paclitaxel 4%), fotemustine (6%) and others (13%). Median duration of therapy was 7.9 weeks. Responses included 0.4% complete response (CR), 12% partial response (PR), 21% stable disease (SD) and 67% progressive disease (PD). Median PFS was 2.6 months and median PFS in responders was 8.7 months. Twelve-month PFS was 12%. In patients who had received anti-PD-1 before chemotherapy, the ORR was 11%, and median PFS was 2.5 months. The highest activity was achieved with single agent taxanes (n=40), with ORR 25% and median PFS 3.9 months. Median OS from chemotherapy start was 7.1 months. Subsequent treatment with ICIs achieved a response rate of 16% with a median PFS of 19.1 months. They noted no unexpected toxicities were observed.

Comment: Patients failing ICI immunotherapy can very quickly run out of treatment options and chemotherapy is frequently considered in such patients. Addition of chemotherapy to ICI in failed ICI patients has been associated with impressive responses. There is also anecdotal evidence that patients previously treated with ICI may respond better to chemotherapy. However, the present retrospective study on 465 patients failing ICI who received chemotherapy as salvage treatment reported low ORR and median PFS of 5.4 months. The patients reviewed were predominantly (85%) M1c and 66% had elevated LDH and 2 or more therapy lines before chemotherapy so these results need to be viewed in this context. Median PFS in responders was 8.7 months. There may be a stronger case for concurrent ICI and chemotherapy. As pointed out by the authors chemotherapy can induce immunogenic cell death in cancer cells with TLR3 activation and HMGB1 release. Overall, the resulting immunogenic modulation could lead to a release of tumour antigens which subsequently may stimulate an immune response. Given this there still seems scope for prospective studies in this patient population to better understand the use of ICI and chemotherapy combinations.

Reference: Eur J Cancer. 2022 Feb;162:22-33
Abstract

Late-onset adverse events of anti-PD1 therapy in melanoma patients: An observational study from MELBASE, a nationwide prospective cohort

Authors: Carlet C, et al

Summary: This French real-world study evaluated late-onset AEs in unresectable stage III or IV melanoma patients (n=119) treated with anti-PD-1 administered for at least 2 years. 53 patients received nivolumab and 66 patients received pembrolizumab, with median follow up was 41.7 months. The investigators found AEs occurred in 83% of patients (with a median time of 13.3 months) including severe AEs (grade 3 or 4) in 30% of patients. Late-onset AEs, mostly grades 1 or 2, occurred in 43% of patients and led to 4% of patients being hospitalised. Factors associated with late-onset AEs were early-onset AEs (within the first 2 years of treatment) and treatment duration (P=0.02 and P=0.03, respectively).

Comment: This is a useful study that is relevant to how long patients should stay on treatment with anti-PD-1. In this MelBase cohort late-onset AEs (occurring after 2 years of anti-PD-1 treatment) were mostly low-grade toxicities (grades 1 and 2) (97%). Severe late-onset AEs were rare (3%), similar to the 4.8% reported by others. The 4 types of severe late-onset AEs observed were arthralgia, type 1 diabetes mellitus, immune system disorder, and cutaneous rash. The risk of late onset AEs was related to duration of treatment but not the number of infusions. In this cohort, a history of autoimmune disease did not appear to be a risk factor for early or late-onset AEs (10% and 12%, respectively) or their severity (15% of grades 3-4 early-onset AEs and no grade 3-4 late-onset AEs). It was noted that autoimmune cutaneous AEs such as vitiligo were not observed as late-onset AEs. They conclude physicians should consider the benefit-risk balance when choosing to maintain or discontinue anti-PD-1 therapy in patients with advanced melanoma.

Reference: J Am Acad Dermatol. 2022 Feb;86(2):345-352
Abstract

Association of PTPRT mutations with immune checkpoint inhibitors response and outcome in melanoma and non-small cell lung cancer

Authors: Zhang W, et al

Summary: The study objective was to elucidate protein tyrosine phosphatase receptor type T (PTPRT) mutation association with ICI efficacy. The researchers integrated whole-exome sequencing (WES)-based somatic mutation profiles and clinical characteristics of 631 melanoma samples received ICI agents from eight studies and 109 NSCLC samples from two studies. For validation, they analysed 321 melanoma and 350 NSCLC immunotherapy samples with targeted next-generation sequencing and an independent NSCLC cohort contained 240 samples. They showed in the WES melanoma cohort, patients with PTPRT mutations harboured a significantly elevated ICI response rate (40.5% vs. 28.6%, p=0.036) and a prolonged survival outcome (35.3 vs. 24.9 months, p=0.006). In the WES NSCLC cohort, the favourable response and immunotherapy survival were also observed in PTPRT-mutated patients (p=0.036 and 0.019, respectively). For the validation cohorts, the associations of PTRPT mutations with better prognoses were identified in melanoma, NSCLC, and pan-cancer patients with targeted-NGS (all $p < 0.05$). In addition, immunology analyses showed the higher tumour mutational burden (TMB), increased tumour-infiltrating lymphocytes (TILs), decreased- activated-stroma, and immune response pathways were detected in patients with PTPRT mutations.

Comment: Identification of predictors of response to ICI immunotherapy is an ongoing aim. PTPRT is a well-known phosphatase which because of its large size is commonly mutated in melanoma. Its precise role is not clear other than having a role in PD-1 signalling and antigen presentation. The present study analysed existing databanks to show statistically significant response rates and survival in patients with mutations in PTPRT that was associated with increased TILs. The mutation rate was significantly associated with TMB and neoantigen burden (NB). They suggest that "although high TMB is a promising indicator in cancer immunotherapy, some factors, such as uncertain threshold, exome sequencing fees, and bias of distinct platforms largely influence the accurate assessment of the TMB. Instead of performing WES sequencing and determining a certain threshold, PTPRT mutational status could be obtained by using the targeted sequencing methods, which will reduce the sequencing fee and make the TMB evaluation and ICI prognosis prediction more easily. Therefore, PTPRT mutations may be an alternative surrogate for predicting ICI response in melanoma and NSCLC."

Reference: Cancer Med. 2022 Feb;11(3):676-691
Abstract

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Independent commentary by Peter Hersey, FRACP, D Phil

Peter Hersey is an honorary Professor of Immuno Oncology in the University of Sydney and a faculty member of the Melanoma Institute Australia. He has conducted a number of phase I to III trials of immunotherapy in melanoma, including use of modified peptide antigens and dendritic cell vaccines. He has taken a leading role in studies investigating properties of melanoma cells that make them resistant to treatment and new treatment approaches to overcome these properties. He is generally recognized as a pioneer of immunotherapy for melanoma in Australia, and has participated in most of the key clinical trials on immunotherapy with immune checkpoint inhibitors. He continues translational research on melanoma in the Centenary Institute as joint holder of a NHMRC program grant on melanoma.

Toripalimab plus axitinib in patients with metastatic mucosal melanoma: 3-year survival update and biomarker analysis

Authors: Li S, et al

Summary: The phase Ib study of axitinib in combination with toripalimab showed a promising response rate in patients with metastatic mucosal melanoma. This article reports the updated OS, duration of response (DoR), and biomarker analysis results, at median follow-up of 42.5 months. Among 29 chemotherapy-naïve patients with metastatic mucosal melanoma, the median OS was 20.7 months; the median PFS was 7.5 months; and the median DoR was 13.4 months. The OS rates of 1, 2, and 3 years were 62.1%, 44.8%, and 31.0%, respectively. Biomarker analysis found that PD-L1 expression and TMB level were not associated with survival benefits. In contrast, a 12-GEP signature correlated with improved PFS (17.7 vs 5.7 months, p=0.0083) and OS (35.6 vs 17.6 months, p=0.039).

Comment: This is a longer follow up of a phase Ib study on patients treated with a combination of an antiangiogenic and anti-PD-1 reagents. The rationale being that anti-VEGF-targeted drugs could enhance T-cell infiltration into the tumour by normalisation of tumour vasculature and overcome inhibition from the immune microenvironment. Previous studies had showed that the use of anti-VEGF-targeted drugs can increase the infiltration of immune effector cells into tumours and convert the intrinsically immunosuppressive TME to become immunostimulatory. They found that the median OS in 29 patients was 20.7 months which was comparable to the 22.7 months in the mucosal melanoma subgroup in the BMS 067 study. They point out however, that comparisons across studies was difficult as the patients in the BMS 067 study had more advanced disease and were all Caucasians. Expression of PD-L1 and the TMB were not effective biomarkers of response but a gene expression signature incorporating angiogenic and immune signatures did correlate with improved OS. Although a small study the results appear of significance in planning future treatments in mucosal melanoma

Reference: J Immunother Cancer. 2022 Feb;10(2):e004036
Abstract

Detection of clinical progression through plasma ctDNA in metastatic melanoma patients: a comparison to radiological progression

Authors: Marsavela G, et al

Summary: The team retrospectively analysed ctDNA of 108 plasma samples collected at the time of disease progression. They also analysed a validation cohort of 66 metastatic melanoma patients monitored prospectively after response to systemic therapy. ctDNA was detected in 62% of patients at the time of disease progression. For 67 patients that responded to treatment, the mean ctDNA level at PD was significantly higher than at the time of response (P <0.0001). However, only 30 of these 67 (45%) patients had a statistically significant increase in ctDNA by Poisson test. In the validation cohort there was a 56% detection rate of ctDNA at progression, with only two cases showing increased ctDNA prior to radiological progression. It was also noted a correlation between ctDNA levels and metabolic tumour burden was only observed in treatment naïve patients but not at the time of progression in a subgroup of patients failing BRAF inhibition (n=15).

Comment: Much has been made of the value of plasma ctDNA as a monitor of disease in patients with melanoma, but the present study is one of the few that have tested its reliability to detect disease progression in stage IV patients who had responded to prior treatment. In comparison to standard PET radiological detection procedures ctDNA detection rates were particularly low in recurrences in M1a and M1b and M1d disease. They attribute the low detection rate to the comparison with PET scans rather than CT scans as PET scans had higher sensitivity than CT scans. They also query whether ctDNA shedding may be different in recurrent disease and state "The cellular mechanism through which ctDNA is shed is poorly understood and its source has been extended to apoptotic tumour cells tumour-derived extracellular vesicles, disseminated tumour cells and circulating tumour cells." This study is therefore not only of practical value but poses questions for ongoing research.

Reference: Br J Cancer. 2022 Feb;126(3):401-408
Abstract

Molecular characterization of fast-growing melanomas

Authors: Gaudy-Marqueste C, et al

Summary: The observational prospective study investigated the epidemiologic, clinical, and mutational profile of primary cutaneous melanomas with a thickness ≥1mm, stratified by rate of growth. The authors conducted deep-targeted sequencing of 40 melanoma driver genes on primary melanoma samples, comparing fast-growing melanomas (FGMM) (rate of growth > 0.5 mm/month) and non-FGMM (rate of growth ≤ 0.5 mm/month). Of the 200 patients enrolled 70 had FGMM. They found relapse-free survival (RFS) was lower in the FGMM group (P=0.014). Furthermore, FGMM had a higher number of predicted deleterious mutations within the 40 genes than non-FGMM (P=0.033). They noted ulceration (P=0.032), thickness (P=0.006), lower sun exposure (P=0.049), and fibroblast growth factor receptor 2 (FGFR2) mutations (P=0.037) were significantly associated with fast growth.

Comment: Fast growing melanoma are known to be associated with nodular subtype, trunk location, male sex, previous nonmelanoma skin cancer. This study carried out sequencing of 40 oncogenes on formalin fixed samples from 200 patients to identify putative driver oncogenes. Rate of tumour growth was defined as ratio of tumour thickness to patient-reported time of melanoma growth. FGMM were those with rates >0.5mm/month (70 patients). There was no difference in proportions of BRAF, NRAS, NF1 mutations. Univariate analyses found a higher proportion of pathogenic mutations in FGFR2, ALK, ERBB4, IDH1, PDGFRA, PREX2 and RB1 in FGMM. After corrections for multiple comparison, it was confirmed that FGFR2 and IDH1 mutations were associated with fast growth, and noted that 15.7% of FGMM presented FGFR2 mutations, in contrast to 2.3% in the non FGMM group. They point out that selective FGFR2 inhibitors show a decrease in tumour cell proliferation and promising results in early phase trials for multiple cancer types with activating FGFR2 mutations. Hotspot oncogenic IDH1R132C mutations were identified in 4 patients, exclusively in the FGMM group. IDH1 mutations drive a variety of human cancers in addition to melanoma.

Reference: J Am Acad Dermatol. 2022 Feb;86(2):312-321
Abstract