Melanoma Research Review™

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Issue 39 - 2021

In this issue:

Abbreviations used in this issue:

ICI = immune checkpoint inhibitor; **LDH** = lactate dehydrogenase **MSS** = melanoma-specific survival; **ORR** = overall response rate; **OS** = overall survival; **PFS** = progression-free survival; **RFS** = recurrence-free survival; **SN** = sentinel node; **SSM** = superficial spreading melanoma.

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Welcome to the 39th issue of Melanoma Research Review.

The lead article is a retrospective study exploring the effects of antibiotics on outcomes among patients receiving ICI therapy. The authors report patients with stage III and IV melanoma exposed to antibiotics prior to ICI had statistically significantly worse OS than unexposed patients. Two studies in this issue report on the use of combined ipilimumab and nivolumab for patients with metastatic uveal melanoma. A Spanish open-label phase II trial showed the combination in the first-line setting had a modest improvement in OS over historical benchmarks of chemotherapy. Results from a single-arm phase II study found the combination demonstrated activity with sustained confirmed responses. The phase III IMspire170 study found cobimetinib plus atezolizumab did not improve PFS compared with pembrolizumab monotherapy in patients with BRAFV600 wild-type advanced melanoma. Another article reported patients who relapse after adjuvant targeted therapy respond well to subsequent anti-PD-1 based therapy and have outcomes similar to those seen when first line anti-PD-1 therapy is used in stage IV melanoma.

A number of articles focus on prognostic factors for melanoma. Researchers analysing large Dutch and Australian cohorts concluded sentinel node biopsy in patients with melanoma improves the accuracy of staging when added to clinicopathological features of the primary tumour. An important study addressed the significance of regression in primary cutaneous melanoma. The authors reported regression was a favourable prognostic factor for patients with stage 1 and 2 melanomas, especially in those with thin and intermediate thickness tumours and those with superficial spreading melanoma subtype. Results from the concluding article demonstrate the extent of ulceration has an independent prognostic impact in primary cutaneous melanoma. The investigators recommend ulceration should be recorded as a required element in pathology reports.

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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Association of antibiotic exposure with survival and toxicity in patients with melanoma receiving immunotherapy

Authors: Mohiuddin JJ, et al

Summary: Patients with stage III and IV melanoma exposed to antibiotics within 3 months prior to the first infusion of immune checkpoint inhibitors (ICIs) were selected from an institutional database. Of the study cohort of 114 patients, 35.9% had stage III disease. The authors reported with stage IV disease, the antibiotic-exposed group had statistically significantly worse overall survival (OS, HR = 1.81; P <.001). This was also the case among antibiotic-exposed patients with stage III disease (HR = 2.78; P =.007). Furthermore, when limited to only patients who received adjuvant ICIs (n = 89), antibiotic-exposed patients had statistically significantly worse OS (HR = 4.84, P =.04).

Comment: This is a retrospective report exploring the effects of antibiotics on outcomes among patients receiving ICI therapy. The study included patients with Stage 3 and 4 disease and subdivided patients by those who had received no antibiotics or those who had received them 1.5 or 3 months prior to ICI therapy. Patients who received perioperative antibiotics were excluded from this study. As with other previous studies, outcomes were poorer (relapse free and overall survival) for patients receiving antibiotics. Patients with an anticipated better prognosis who received antibiotics appeared to suffer disproportionately worse. Penicillins, cephalosporins and fluroquinolones appeared to be the most harmful agents. Of note the patients who received antibiotics were more likely to develop colitis (9.8 % versus 4.6%) and were more likely to require steroids. The authors make the point that it would be unethical to carry out a randomised trial of antibiotics and fortuitous retrospective analyses such as this report combined with similar results reported by others argue for care in prescribing antibiotics for patients likely to receive ICI therapy.

Reference: J Natl Cancer Inst. 2021 Feb 1;113(2):162-170

Abstract

Nivolumab plus ipilimumab for treatment-naïve metastatic uveal melanoma: An open-label, multicenter, phase II trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402)

Authors: Piulats JM, et al

Summary: The study objective was to assess the efficacy of nivolumab plus ipilimumab as first-line therapy in 52 patients with metastatic uveal melanoma who were not eligible for liver resection. Overall, 78.8%, 56%, and 32% of patients had liver M1, extra-liver M1, and elevated lactate dehydrogenase (LDH). The investigators reported stable disease in 51.9% of patients and 12-month OS was 51.9%. The median OS and progression free survival (PFS) were 12.7 months and 3.0 months, respectively. PFS was influenced by higher LDH values. It was noted the toxicity profile was manageable.

Comment: See comment below.

Reference: J Clin Oncol. 2021 Feb 20;39(6):586-598
Abstract

Nivolumab and ipilimumab in metastatic uveal melanoma: Results from a single-arm phase II study

Authors: Pelster MS, et al

Summary: The combination regimen nivolumab with ipilimumab was assessed in 33 patients with metastatic uveal melanoma. Any number of prior treatments was permitted. The overall response rate (ORR) was 18%, including one confirmed complete response and five confirmed partial responses. The median PFS was 5.5 months and the median OS was 19.1 months. Forty percent of patients experienced a grade 3-4 treatment-related adverse event.

Reference: J Clin Oncol. 2021 Feb 20;39(6):599-607
Abstract

Comment: Two studies report use of combined ipilimumab and nivolumab for patients with metastatic uveal melanoma. Previous studies of single agent anti-CTLA4 or PD-1 therapy reported minimal benefits for this notoriously difficult disease. These studies were small with 33 and 52 patients and reported similar results with an OS of approximately 12 months. Objective response rates were similar (18 and 11%). Progression free survivals were 6 and 3 months, respectively. There was a suggestion in both studies that patients with extrahepatic disease only had improved outcomes although the numbers were very small. These results, while still poor, indicate a small improvement in outcome for patients treated with combination ICI.

Sentinel node biopsy in patients with melanoma improves the accuracy of staging when added to clinicopathological features of the primary tumor

Authors: El Sharouni MA, et al.

Summary: The team investigated whether sentinel node (SN) status provides more accurate prognostic information than basic clinicopathological features of a primary cutaneous melanoma. They analysed data from a Dutch population-based cohort of melanoma patients (n = 9,272) and a validation cohort from a large Australian melanoma treatment centre (n = 5,644). Patients had histologically-proven, primary invasive cutaneous melanoma and underwent SN biopsy. The team showed the Dutch cohort had an improved C-statistic from 0.74 to 0.78 for OS and from 0.74 to 0.76 for recurrence-free survival (RFS), when SN status was included in the model with Breslow thickness, sex, age, site, mitoses, ulceration, regression and melanoma subtype. In the Australian cohort, the C-statistic increased from 0.70 to 0.73 for OS, 0.70 to 0.74 for RFS and 0.72 to 0.76 for melanoma-specific survival (MSS). In addition, 3-year and 5-year risk of death or recurrence were more accurately classified with a model that included SN status. At 3 years, sensitivity increased by 12% for both OS and RFS in the development cohort, and by 10% and 6% for OS and RFS, respectively, in the validation cohort.

Comment: This paper is significant for two reasons. Firstly, it refutes the unfortunately too commonly held view that SN biopsy adds little or no prognostic information over standard clinicopathological variables and secondly the data may help to refine the group of potential patients who may or may not benefit from the procedure. In summary there are unequivocal but modest benefits of SN biopsy. The evolving nature of adjuvant therapy for patients with stage IIC and stage III melanoma and ongoing attempts to further refine indications for the procedure such as the nomogram recently published by the MIA team highlight the fact that the indications for SN biopsy are likely to change in time. For the time being SN biopsy is recommended for all patients with melanomas thicker than 1 mm.

Reference: Ann Oncol. 2021 Mar;32(3):375-383
Abstract

Cobimetinib plus atezolizumab in BRAF V600 wild-type melanoma: Primary results from the randomized phase III IMspire170 study

Authors: Gogas H, et al

Summary: Patients with previously untreated BRAFV600 wild-type advanced melanoma were randomised to receive cobimetinib plus atezolizumab (n = 222) or pembrolizumab (n = 224). Median follow-up was 7.1 months for cobimetinib plus atezolizumab and 7.2 months for pembrolizumab. The authors reported median PFS was 5.5 months with cobimetinib plus atezolizumab versus 5.7 months with pembrolizumab (stratified HR 1.15; P = 0.30). They noted higher tumour mutational burden was associated with improved clinical outcomes in both treatment arms. The most common grade 3-5 adverse events were increased blood creatine phosphokinase (10.0% with cobimetinib plus atezolizumab versus 0.9% with pembrolizumab), diarrhoea (7.7% versus 1.9%), rash (6.8% versus 0.9%), hypertension (6.4% versus 3.7%), and dermatitis acneiform (5.0% versus 0). Serious adverse events occurred in 44.1% of patients with cobimetinib plus atezolizumab and 20.8% with pembrolizumab.

Comment: Based on preclinical data which indicated an immunomodulatory effect of MEK inhibition regardless of BRAF status, it was anticipated that the combination of MEK inhibition and PD-1 inhibition would lead to improved outcome in patients with BRAF wild-type metastatic melanoma. Surprisingly this study found no advantage for the combination of MEK inhibition and anti-PD-1 checkpoint inhibition over single agent anti-PD-1 therapy. Subgroup analyses also failed to demonstrate a difference between the two groups. PD-L1 expression was associated with improved but similar outcomes in both arms.

Reference: Ann Oncol. 2021 Mar;32(3):384-394
Abstract

Melanoma Research Review™

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).

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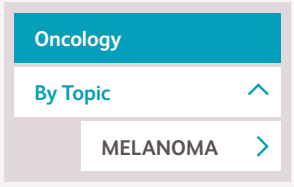

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Association of histologic regression with a favorable outcome in patients with stage 1 and stage 2 cutaneous melanoma

Authors: El Sharouni MA, et al

Summary: This study included 2 large cohorts of patients with histologically proven, stage 1 and 2 primary, invasive cutaneous melanoma with known regression status. The Dutch cohort (n = 17,271) had median follow-up times of 4.5 years and the Australian cohort (n = 4,980) had median follow up of 11.1 years. The researchers found survival outcomes were better for patients with disease regression, in both cohorts. For Dutch patients, the HR for those with disease regression was 0.55 (P < .001) for RFS and 0.87 (P = .004) for OS. For Australian patients, the HR was 0.61 (P < .001) for RFS and 0.73 (P < .001) for OS. They noted the presence of regression improved RFS within thin and intermediate Breslow thickness melanomas in both cohorts. For patients with superficial spreading melanoma (SSM) subtype, regression improved RFS and OS in both cohorts. For Dutch patients with SSM, the HR for those with disease regression was 0.54 (P < .001) for RFS and 0.86 (P = .009) for OS. For the Australian patients with SSM, the HR was 0.67 (P = .001) for RFS and 0.72 (P = .001) for OS.

Comment: This is an important study which aimed to resolve the issue of the significance of regression in primary cutaneous melanoma. Generally previous studies have indicated either improved survival or no difference for regression but most of these studies were characterised by small numbers or limited follow-up. The current study involves large numbers (approximately 50,000 patients) and prolonged follow-up. Defining characteristics included dermal fibrosis but not necessarily lymphocytic infiltration. This study identified regression as a favourable characteristic on both univariate and multivariate analysis but appears to be limited to patients with SSM or lymph node negative T1-T3 lesions (<4 mm). This is a definitive study and confirms that regression as defined in this study is a favourable prognostic factor and compares favourably with other primary tumour features including ulceration, Breslow thickness et cetera.

Reference: JAMA Dermatol. 2021 Feb 1;157(2):166-173
Abstract

Long-term outcomes of Mohs micrographic surgery for invasive melanoma of the trunk and proximal portion of the extremities

Authors: Burnett ME, et al

Summary: This prospective study evaluated long-term outcomes of Mohs micrographic surgery in 1,416 cases of invasive melanoma of the trunk and proximal portion of the extremities. The authors reported true local scar recurrences occurred at a rate of 0.14% (2/1416), after a mean follow-up period of 75 months and were not associated with tumour depth. They concluded Mohs micrographic surgery of primary cutaneous invasive melanoma resulted in local control of 99.86% of tumours and an overall disease-specific death rate superior to that of wide local excision.

Comment: This is another essentially retrospective small series (1,416 patients) collected over 35 years attempting to argue that Moh's micrographic surgery is a suitable substitute for standard surgical excision of melanomas of the trunk and proximal limb. Three quarters of the patients had T1 lesions (0-1 mm) and the vast majority (97%) required a 1 cm margin to achieve complete control. The local recurrence rate was small (< 0.5%) but consistent with contemporary results. Currently all the major international guidelines recommend a standard 1 cm margin for T1 melanomas. The authors do not make a case for the adoption of Moh's micrographic surgery for thin cutaneous melanoma and it cannot be recommended in standard clinical practice.

Reference: J Am Acad Dermatol. 2021 Mar;84(3):661-668
Abstract

Melanoma recurrence patterns and management after adjuvant targeted therapy: A multicentre analysis

Authors: Bhave P, et al

Summary: The study cohort comprised of 85 patients with recurrent melanoma after adjuvant targeted therapy. Median time to first recurrence was 18 months and median follow-up from first recurrence was 31 months. 68% of patients received immunotherapy or targeted therapy as first line systemic therapy at either first or subsequent recurrence and had disease that was assessable for response. Response to anti-PD-1, combination ipilimumab-nivolumab, targeted therapy rechallenge and ipilimumab monotherapy was 63%, 62% 25% and 10% respectively. Two-year OS was 84% for anti-PD-1 therapy, 92% for combination ipilimumab and nivolumab, 49% for targeted therapy and 45% for ipilimumab monotherapy (p = 0.028).

Comment: This is an important report which describes outcomes of patients receiving adjuvant therapy who relapse on or after either targeted therapy or immunotherapy. The data was collected retrospectively from 22 melanoma centres, but the number of cases was relatively small (85). The takeaway messages include firstly that patients who receive immunotherapy after failing adjuvant targeted therapy fare similarly to patients who received targeted therapy after adjuvant immunotherapy. The response rates to subsequent treatment with either single agent or combination immunotherapy having failed adjuvant targeted therapy were similar (63% and 68%). The risk of recurrence after surgery alone for recurrent disease after adjuvant therapy were disappointingly high indicating that further systemic therapy should be considered in these patients. The patterns of recurrence differ between targeted therapy and immunotherapy, in patients receiving adjuvant immunotherapy most recurrences occur early during therapy rather than later while the reverse is true for patients receiving adjuvant targeted therapy.

Reference: Br J Cancer. 2021 Feb;124(3):574-580
Abstract

The prognostic impact of the extent of ulceration in patients with clinical stage I–II melanoma: A multicentre study of the Italian Melanoma Intergroup (IMI)

Authors: Portelli F, et al

Summary: The investigators analysed data for 477 patients with primary cutaneous melanoma to investigate whether the extent of ulceration predicts RFS and OS. They concluded there was a significant interaction emerged between Breslow thickness and extent of ulceration, considering both RFS (P < 0.0001) and OS (P = 0.0006). In addition, there was a significant negative impact of extent of ulceration on RFS [HR (1-mm increase) 1.26, P = 0.0047] and OS [HR (1-mm increase) 1.25, P = 0.0120] in patients with Breslow thickness ≤ 2 mm, after adjusting for Breslow thickness, age, tumour-infiltrating lymphocytes, sentinel lymph node status and mitotic rate. They found no impact of extent of ulceration in patients with 2·01-4 mm and > 4 mm Breslow thickness.

Comment: Ulceration as defined histologically is a significant prognostic factor for early-stage melanoma and is currently incorporated into the eighth edition AJCC staging system. This is a relatively small retrospective study which investigated the prognostic significance of the extent of ulceration. Based on their results, the authors have chosen a cut off of 2 mm. Regardless of tumour thickness, patients with ulceration less then 2 mm in size had similar survival to patients without ulceration. Overall survival and relapse free survival were poorer for patients with ulceration exceeding 2 mm in diameter, but this effect was confined to patients with thinner melanomas (T1, T2). Clearly for thicker melanomas other prognostic variables assume greater importance. Given that ulceration is incorporated in the current staging system, greater understanding of the biology behind ulceration and its relationship to survival is of interest. If extent of ulceration is to be utilised as a prognostic marker standardisation of pathology reporting will be critical.

Reference: Br J Dermatol. 2021 Feb;184(2):281-288
Abstract

