Melanoma Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

MAL = Melanoma-associated leukoderma;
MDSLA = multispectral digital skin lesion analysis;
OCT = optical coherence tomography;
OS = overall survival; **RCM** = reflectance confocal microscopy

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Welcome to the 13th issue of Melanoma Research Review.

We lead this issue with a phase 3 trial evaluating ipilimumab in patients who had undergone complete resection of stage III melanoma. The authors concluded ipilimumab resulted in significantly higher rates of recurrence-free survival and overall survival than placebo. Preliminary results of CheckMate 069 trial are also reviewed in this issue. Analysis suggests that the combination of first-line nivolumab plus ipilimumab might lead to improved outcomes compared with first-line ipilimumab alone in patients with advanced melanoma. Another study found pazopanib efficacy was limited in patients with BRAF wild-type melanoma and response is associated with low M2-like macrophage density and increased expression of several chemokines.

A cross-sectional study of patients with atypical-appearing pigmented lesions concluded reflectance confocal microscopy exhibited superior sensitivity and specificity compared with multispectral digital skin lesion analysis. Another study reports perianal melanocytic nevi were common and were associated with prominent and atypical nevi elsewhere. An online survey conducted in the USA aimed to evaluate to practice patterns of US dermatologists for management of patients with primary cutaneous melanoma and found management varied from published guidelines. There were also significant management differences noted for dermatologists by practice setting and by years in practice.

We hope you enjoy these and the other papers selected for this issue and welcome your comments and feedback.

If you have colleagues or friends within Australia who would like to receive our publication, send us their contact email and we will include them for the next issue.

Kind Regards,

Dr Helena Collgros and **Assoc Prof Pascale Guitera**

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Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy

Authors: Eggermont AM, et al

Summary The phase 3 trial evaluated ipilimumab in patients who had undergone complete resection of stage III melanoma. Patients were randomly assigned to 10mg/kg ipilimumab (n=475) or placebo (n=476) every 3 weeks for four doses, then every 3 months for up to 3 years or until disease recurrence or an unacceptable toxicity. The authors concluded ipilimumab resulted in significantly higher rates of recurrence-free survival, overall survival, and distant metastasis-free survival than placebo. They also noted there were more immune-related adverse events with ipilimumab than with placebo.

Comment: Following the encouraging results of the phase 2 trial, which showed an improved recurrence-free survival for stage III melanoma on adjuvant ipilimumab treatment, the present study also assesses overall survival and distant metastasis–free survival. These outcomes are important, given that interferon alfa, the only other drug approved for adjuvant treatment, has a minimal effect on overall survival. The inclusion period lasted for 3 years finishing in August 2011. At 5 years, the study shows an improvement of approximately 10% in all the end points with ipimumab compared to placebo (recurrence-free survival 40.8% vs 30.3%, overall survival 65.4 vs 54.4%, and distant metastasis–free survival 48.3% vs 38.9%). However nearly half of the patients receiving ipilimumab had grade 3 or 4 immune-related adverse events and 1.1% died because of this. In view of the high incidence of adverse effects we need to weigh the pros and cons of the treatment. Although survival benefit was consistent across subgroups, we may consider treating only stage IIIb and IIIc, as patients with stage IIIa have higher survival rates or find a better way to assess which patients in each group are more at risk to develop recurrence. For instance, the study shows that patients with microscopic involvement (sentinel node positive) benefit more from ipilimumab than those with macroscopic involvement. However, in contrast to interferon alfa, with ipilimumab improved survival in both of them, and similarly occurs with non-ulcerated/ulcerated melanoma.

Approval from the FDA was granted in 2015 on the basis of the preliminary results of this trial. Currently there is an ongoing trial to compare ipilimumab with interferon alfa in stage III or IV melanoma.

Reference: N Engl J Med. 2016 Nov 10;375(19):1845-1855.

Abstract

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Independent Commentary by Dr Helena Collgros and Associate Professor Pascale Guitera.

Dr Helena Collgros (MD) completed her Dermatology and Venereology specialisation in Barcelona in 2014. Afterwards she worked as a dermatologist in the public university hospital *Germans Trias i Pujol* in Barcelona (2014-2016). Her fields of expertise and research interests include pigmented lesions, melanoma, skin cancer and imaging techniques. She is currently working in the Sydney Melanoma Diagnostic Centre at the Royal Prince Alfred Hospital in Sydney, covering an Area of Need Position attending patients at high risk for developing melanoma and skin cancer.

Associate Professor Guitera is currently Director of the Sydney Melanoma Diagnostic Centre (SMDC) and academic dermatologist at the Melanoma Institute Australia (MIA), with a position of Associate Professor at the University of Sydney. She undertook her dermatology fellowship in Saint Louis hospital in Paris. She was awarded the highest distinction for her PhD at the Curie Institute and SMDC on the application of instrumental techniques for the diagnosis of skin tumours. She has lived in Sydney since 2005, where she has achieved global recognition as one of the top 10 researchers of *in vivo* confocal microscopy. Dr Guitera was awarded the 2013 Wildfire Premier's award by the Cancer Institute NSW for outstanding research. She organises courses in imagery for the diagnosis of skin cancer on a yearly basis

Sunscreen use and subsequent melanoma risk: A population-based cohort study

Authors: Ghiasvand R, et al

Summary: This team used data from a Norwegian prospective population-based study of 143,844 women age 40 to 75 years with 1,532,247 person-years of follow-up and 722 cases of melanoma. They reported SPF ≥ 15 sunscreen use was associated with significantly decreased melanoma risk compared with SPF < 15 use (hazard ratio, 0.67; 95% CI, 0.53 to 0.83). The estimated decrease in melanoma with general use of SPF ≥ 15 sunscreens was 18% (95% CI, 4% to 30%).

Comment: It is reasonable to think that the use of sunscreen reduces the risk of melanoma, as UV radiation has proved to be strongly linked to melanoma development, however some initial studies failed to prove it. This was probably due to lack of adjustment for potential confounding factors and use of low SPF sunscreen. There are still few high-quality studies that prove that melanoma incidence decreases by sunscreen use. The Australian study conducted in Nambour is the only randomised controlled trial to date (Green AC et al, J Clin Oncol 2011 Jan 20;29(3):257-63). It found a decrease in melanoma incidence among adults who used daily SPF>15 compared to those with only discretionary use. Conversely, the present study conducted in Norway assesses a different type of population, as in northern Europe there is low ambient solar radiation with people receiving high UV exposure mainly on intentional sunbathing in summer holidays. Besides the differences in study population, these results also favour the use of sunscreen SPF ≥ 15 to decrease melanoma risk compared with SPF < 15 use.

Reference: J Clin Oncol 2016 Sep 12. pii: JCO675934
Abstract

An independent validation of a gene expression signature to differentiate malignant melanoma from benign melanocytic nevi

Authors: Clarke LE, et al

Summary: This 23-gene signature measures the expression of 14 genes involved in melanoma pathogenesis as well as 9 housekeeper genes, and applies an algorithm that produces a numerical diagnostic score ranging from –16.7 to +11.1. Scores from –16.7 to –2.1 were reported as likely benign, scores from –2.0 to –0.1 were reported as indeterminate, and scores from 0.0 to 1 11.1 were reported as likely malignant. The sensitivity and specificity was quite high (91.5 and 92.5% respectively). Most false-positives occurred in dysplastic nevus and false-negatives were most common in lentigo maligna. The later could be related to a small volume of malignant melanocytes.

Comment: Histopathology remains the gold standard for melanoma diagnosis, however evidence suggests that about 15% of lesions may have an ambiguous diagnosis even by experienced dermatopathologists, therefore there is a need of other complementary tests to assess difficult cases. In the area of non or minimal invasive diagnosis techniques, there is still a lack of genetic testing that allows differentiation between melanocytic nevi and melanoma. Genetic testing could not only be useful for complicated cases that are not clear cut when examined with histopathology, even using immunostaining, moreover it could allow minimal micro biopsies to obtain some cells and determine if a lesion needs to be excised or not.

Although the samples analysed in this study were obtained from samples prospectively submitted for gene expression testing in routine clinical practice, discordant cases that were assessed differently by the study dermatopathologists or given other diagnosis than benign or malignant were not included. This was needed to validate the test, but because of this, the study may not be completely representative of the real clinical setting where controversial lesions are seen.

Reference: Cancer. 2016 Oct 21 doi: 10.1002/cncr.30385
Abstract

Prevalence and gross morphologic features of perianal melanocytic nevi

Authors: Socik A, et al

Summary: This study at an outpatient dermatology clinic in Chicago, Illinois, included 236 adults (138 men and 98 women, ages 23 to 84 years) presenting for melanoma and/or skin cancer screening or surveillance. Of the participants, 219 were non-Hispanic white; 4, Hispanic white; and 13, nonwhite. Perianal nevi of any size were evident in 48.9% (107 of 219) of non-Hispanic whites; 50.0% (2 of 4) of Hispanic whites; and 38.5% (5 of 13) of nonwhites. The authors noted perianal melanocytic nevi were associated with prominent and atypical nevi elsewhere.

Comment: There are some areas of the body, such as genitalia, scalp and soles, that are frequently missed even in patients that present for skin cancer and melanoma screening. This study shows that about 50% of white patients have melanocytic nevi in perianal area (including anal margin, gluteal cleft and perineum). Although melanoma in perianal area is rare (accounting for 2-4% malignant anorectal neoplasms and about 1% of all melanomas), it is associated with a poor prognosis, with a 5-year survival of 3 to 22%. This poor prognosis is related to diagnosis delay because this area is not seen by the patient and often ignored during cutaneous routine examination. In light of the relatively high prevalence of nevi in this area we may consider exploring this area or at least asking the patients if they or a partner can have a look and report to the doctor if they can see any pigmented lesion.

Reference: JAMA Dermatol 2016 Nov 1;152(11):1209-1217
Abstract

An exploratory study investigating the metabolic activity and local cytokine profile in patients with melanoma treated with pazopanib and paclitaxel

Authors: Thurneysen S, et al

Summary: Seventeen patients with BRAF wild-type melanoma were treated with pazopanib orally from days 1 to 10 and from days 14 to 70 and an intravenous infusion with paclitaxel on days 14, 35 and 56. The group reported 5 of 14 evaluable patients had a partial metabolic response at day 10 under pazopanib monotherapy, while the response rate at day 70 under combined pazopanib-paclitaxel treatment was 0%. Overall, the median progression-free survival was 70 days, which did not differ significantly between responders and nonresponders. There were 67 adverse events, of which nine (13%) were grade 3 or 4. Immunohistochemistry evaluation found an increase of M2-like macrophages in nonresponders compared with responders. A significant upregulation of five cytokines (CXCL1, CXCL2, CXCL13, CCL22 and SPP1) in responding vs. nonresponding lesions was also observed.

Comment: Several drugs have been developed for BRAF mutated metastatic melanoma, but there is still a need for new drugs for BRAF and NRAS wild-type melanoma. Some studies conducted in the 90s estimated that 17% of advanced melanoma responded to paclitaxel. Sorafenib, a tyrosine kinase inhibitor, showed initial promising results but was not successful in randomised clinical trials.

Increased expression of VEGF and other tyrosine kinases leads to disease progression in melanoma; therefore treatment with pazopanib (tyrosine kinase inhibitor with antitumour and antiangiogenic activity) has been tried. However, pazopanib either alone or with paclitaxel showed limited efficacy. The median progression-free survival in the local responders was longer (148 days) than in nonresponders (70 days), but this was not significant. Resistant tumours showed high numbers of tumour-associated M2-like macrophages, these might protect the melanoma cells from the drug growth inhibition and cell death. Therefore, strategies to inhibit tumour-associated macrophages are needed and they are already in clinical trials.

Reference: Br J Dermatol 2016 Nov;175(5):966-978
Abstract

Paired comparison of the sensitivity and specificity of multispectral digital skin lesion analysis and reflectance confocal microscopy in the detection of melanoma in vivo: A cross-sectional study

Authors: Song E, et al

Summary: Study patients (n = 36) with atypical-appearing pigmented lesions (n = 55) underwent imaging by both reflectance confocal microscopy (RCM) and multispectral digital skin lesion analysis (MDSLA). Lesions were biopsied and analysed by histopathology. The authors concluded RCM exhibited superior sensitivity and specificity compared with MDSLA.

Comment: Nowadays several tools have been developed to aid in melanoma diagnosis in vivo. Dermoscopy is already established and recommended with a grade A evidence in the guidelines. Additionally, several other technologies have been developed, some are operator-dependent and require training, such as RCM and optical coherence tomography (OCT), and others are based on an algorithm that creates a classifier score, as with MDSLA and electric impedance spectroscopy (Nevisense®). Each of these uses a different technology and has its advantages and disadvantages. The present study compares MDSLA and RCM, showing that RCM is superior in both sensitivity (71.4% vs 85.7%) and specificity (25% vs 66.7%). Previous studies showed higher sensitivity up to 98% for MDSLA but very low specificity (10%), meaning that based only on this score several benign lesions would be unnecessarily excised (false positive rate 75%). Conversely, RCM false-positive rates are much lower (33%). Regarding RCM, several algorithms for melanoma diagnosis have been proposed, all with high sensitivity (87.6-86.1%) and specificity (70.8-95.3%), (Xiong YD et al, J Eur Acad Dermatol Venereol 2016 Aug;30(8):1295-302).

Both devices are not designed to be used for screening purposes, but as tools to give additional information. The interpretation of it will vary depending on the user, thus sensitivity and specificity of the device itself may increase in the hands of a dermoscopy-trained dermatologist. Both devices may reduce the number of unnecessary biopsies, but their use in daily clinical practice is limited by time, availability, cost and training.

Reference: J Am Acad Dermatol 2016 Dec;75(6):1187-1192.e2
Abstract

A comparison of current practice patterns of US dermatologists versus published guidelines for the biopsy, initial management, and follow up of patients with primary cutaneous melanoma

Authors: Farberg AS, et al

Summary: This cross-sectional study surveyed dermatologists (540 respondents) to assess preferred biopsy methods for lesions suspicious for melanoma, margins used for excision, and recommended follow-up intervals. The authors reported shave biopsy (35%) was the most commonly used method followed by narrow excisional biopsy (31%), saucerisation/scoop shave (12%), punch (11%), and wide excision (3%).

Comment: This online survey conducted in the USA aimed to evaluate to what extent dermatologists follow clinical guidelines. Surprisingly, only 31% of dermatologists used narrow excisional biopsy (<5mm margins) as a preferred excision method for suspicious cutaneous melanoma, while in most of the guidelines (American Academy of Dermatology (AAD), and National Comprehensive Cancer Network (NCCN)) this is the recommended method. Shave biopsy and saucerisation/scoop shave accounted for about half of the methods used (45%). This may reflect a low suspicion of melanoma, or biopsies for lentigo maligna, in which shave is appropriate, however this seems unlikely given the extent of usage. It is most likely due to time constraints, which should not be more important than patient care. The use of punch biopsy may be justified to confirm the diagnosis of a melanocytic lesion versus non-melanocytic, knowing that the complete excision will be performed if it is melanocytic; in facial or acral lesions without a clear clinical diagnosis of melanoma, or in large lesions such as congenital nevi, targeting the area of concern. There is less controversy in melanoma excision margins, however strikingly 14% of respondents used <1cm margins for excising melanomas >1 mm thick.

The most commonly recommended follow-up interval was 6 months for the first 5 years (49%), extending to yearly reviews afterwards (64%). This is consistent with the recommendation of the guidelines that stay quite vague: every 3 to 12 months. The authors highlight that the deviation noted from the guidelines may indicate that there is a need for continuous education of dermatologists, but also that clinical guidelines should be reassessed and updated frequently. To ensure a homogeneous quality of care, guidelines should be followed.

Reference: J Am Acad Dermatol 2016 Dec;75(6):1193-1197
Abstract

Melanoma-associated leukoderma and vitiligo cannot be differentiated based on blinded assessment by experts in the field

Authors: Lommerts JE, et al

Summary: This study aimed to assess whether experts in the field can distinguish between melanoma-associated leukoderma (MAL) and vitiligo. Four experts assessed photographs and medical history of 11 patients with MAL and 33 with vitiligo. They misdiagnosed 72.7% of MAL cases and marked 80.0% of them as typical vitiligo. No discriminative features were found.

Comment: We wonder if MAL and vitiligo are truly 2 separate entities, as clinical and histological data do not support this fact or data from published studies are contradictory. Some studies found differences in clinical appearance between MAL and vitiligo, presenting as mostly hypopigmented macules with irregularly shaped borders and confetti-like in MAL, as opposed to the well-demarcated white macules in vitiligo. Conversely, in other studies and the present one, no significant differences in clinical presentation (morphological pattern and extent of depigmentation) were identified. Histologically, no differences could be identified. The main difference between them resides in the causes or triggering factors. Vitiligo is related to genetic and environmental factors, while MAL is triggered by melanoma. Although both have a similar pathogenesis with an immune attack against melanocytes, in MAL cases there is an antibody response against the melanoma-associated antigen recognised by T cells (MART-1 Ag) that is not present in vitiligo. Therefore MAL cannot be classified as a subtype of vitiligo, but both may be subtypes of the same disease with different provoking factors. The authors propose to use the term "melanoma-associated vitiligo" instead of MAL and highlight the importance for clinicians to be aware that skin depigmentation may be a sign for an arising melanoma, especially in higher age at onset with no family history of vitiligo. A thorough skin check is of course necessary but the research of occult melanoma with PET scan is more controversial.

Reference: J Am Acad Dermatol 2016 Dec;75(6):1198-1204
Abstract

Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial

Authors: Hodi FS, et al

Summary: The combination of targeted therapies for melanoma (anti-BRAF + anti-MEK) has already been proven more effective than each drug alone. Currently there are many trials assessing the results of combining immunotherapy drugs (anti-CTLA4 + anti-PD1). This study assesses long-term results. They included 142 eligible patients, 76% BRAF wild-type and 23% BRAF V600 mutated. 22% of patients in the combination group achieved complete response, while no patients in the ipilimumab group did. Progression-free survival at 1 year was 52.5% in the combination group and 16% for ipilimumab alone. These percentages were very similar at 2 years (51.3% and 12%), indicating that after 1 year, those who responded were most likely to maintain that response. Overall survival was 73.4% at 1 year and 63.8% at 2 years in the combination group and 64.8% and 53.6% respectively in the ipilimumab. This 2-year overall survival in the ipilimumab group was much higher than expected, as previously reported values were between 25-29%. This could be explained by the fact that 57% of ipilimumab treated patients crossed over to receive nivolumab while on study. Of note overall survival is not a good end point anymore and progression-free survival is better to compare drugs and regimen efficacy. BRAF mutation status made no difference in the overall survival. In a phase 3 study (Checkmate 066), nivolumab showed 2-year overall survival of 58%. At a median 2 year follow up, those who responded had a durable response, with 80% of ongoing responses in each group.

Reasons for treatment discontinuation were disease progression (18% in the combination vs 41% in ipilimumab) and toxicity (49% in the combination vs 22% in ipilimumab). Nearly all patients in both groups presented a treatment-related adverse event of any grade; however, grade 3-4 were more common in the combination group (54%) than in the ipilimumab (20%).

Comment: The present study analyses the tumour PD-L1 expression status in the combination group, and found that responses were not related to a low or high expression, which differed from previous studies of anti-PD1 monotherapy findings. As toxicity is much higher in the combination, it would be interesting to identify response biomarkers to predict which patients would benefit from the combination and which would respond to the ipilimumab alone and could spare the increased toxicity of the combination. Further investigation of drug combinations are needed to better assess the risk-benefit profile.

Reference: Lancet Oncol 2016 Nov;17(11):1558-1568
Abstract

The influence of postoperative lymph node radiation therapy on overall survival of patients with stage III melanoma, a National Cancer Database analysis

Authors: Danish HH, et al

Summary: These researchers analysed patients (n=912) with stage III melanoma with pathologically involved nodes and compared survival outcomes of adjuvant radiation and no-radiation treatment. Five-year overall survival was 69.0, 51.1, and 30.6% for stage IIIA, IIIB, and IIIC, respectively. Adjuvant radiation was found to have no statistically significant impact on overall survival (OS). The researchers also noted age older than 60 years, number of nodes, increasing pathologic stage, and absence of immunotherapy correlated with worse OS.

Comment: For patients with high-risk nodal recurrence after lymph node dissection, adjuvant radiation is recommended to improve loco-regional control; however the benefit on OS has not been shown. Our guidelines recommend consideration of adjuvant radiation if >=3 lymph nodes are positive, if there is extra-capsular spread, for any node of >3 cm, matted nodes or clinically involved nodes. There is only one prospective trial (ANZMTG/TROG 02.01) that assessed the benefit of adjuvant radiation in node-positive stage III melanoma but it was not powered to assess OS. This study retrospectively confirmed that there is no significant improvement in OS. The aim of radiation is to avoid or delay loco-regional recurrence and the subsequent morbidity of further surgeries. It improves disease-specific survival. The ANZMTG/TROG 02.01 trial found a 15% difference in the 5-year incidence of lymph node field relapse (18% for adjuvant radiation vs 33% for observation).

Obviously, radiotherapy is a localised treatment compared to immunotherapy or targeted therapies that are now proposed in adjuvant setting and eventually patients will succumb to their metastases, meaning no change in OS. But one of the future and interesting developments is the synergy possible with the combination of radiotherapy and immunotherapy. Radiation may enhance the response to immunotherapy as it can increase antigen presentation and CTLA 4 and PD1/PDL-1 expression in radiated tissue.

Reference: Melanoma Res 2016 Dec;26(6):595-603
Abstract

