Welcome to the fifth issue of Melanoma Research Review

We lead this issue with a study assessing the effects of treatments on health-related quality of life in the COMBI-v study. The group found a significant and clinically meaningful difference in favour of the dabrafenib plus trametinib combination compared with vemurafenib monotherapy. A study of ipilimumab toxicity showed approximately one-third of ipilimumab-treated patients required systemic corticosteroids, and almost one-third of those required further immune suppression with anti-TNFα therapy. An Australian retrospective cohort study compared cutaneous toxic effects of BRAF inhibitor monotherapy and CombiDT therapy in a large cohort of patients. The study highlights the differences in the cutaneous toxicity profile of different BRAF targeted therapies and provides practical information on the prevalence of toxicity to guide surveillance of patients on these agents.

A meta-analysis specifically examining the relationship between regression and sentinel node status, found that regression was associated with a significantly lower risk of sentinel node positivity. Another study found early sentinel-node biopsy is associated with worse survival in patients with cutaneous melanoma.

An important study from Sydney demonstrated oral nicotinamide was safe and effective in reducing the rates of new nonmelanoma skin cancers and actinic keratoses in high-risk patients. This study has significant implications as a public health primary prevention strategy, however compliance may be an issue.

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,

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Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): Results of a phase 3, open-label, randomised trial

Authors: Grob JJ, et al

Summary: This exploratory analysis prospectively assessed the health-related quality of life of 704 patients with metastatic melanoma with a BRAF Val600 mutation randomly assigned to dabrafenib plus trametinib (n=352) or vemurafenib (n=352). Questionnaire completion rates were high for both groups. The authors found a significant and clinically meaningful difference in favour of the dabrafenib plus trametinib combination compared with vemurafenib monotherapy. A study of ipilimumab toxicity showed approximately one-third of ipilimumab-treated patients required systemic corticosteroids, and almost one-third of those required further immune suppression with anti-TNFα therapy. An Australian retrospective cohort study compared cutaneous toxic effects of BRAF inhibitor monotherapy and CombiDT therapy in a large cohort of patients. The study highlights the differences in the cutaneous toxicity profile of different BRAF targeted therapies and provides practical information on the prevalence of toxicity to guide surveillance of patients on these agents.

Comment: These results confirm what is seen in clinical practice; that combined BRAF and MEK inhibition is better tolerated than single agent BRAF inhibition. In practice, many patients on this treatment have excellent quality of life. Advantages of this study include the comprehensive assessment tools utilised and the high completion rate. Caveats to the data are that it is collected in an un-blinded cohort of study patients, potentially a more motivated (and optimistic) cohort than the average patient. A previous analysis of quality of life data from the COMBI-d study showed very similar findings (Schadendorf et al, EJC 2015). Combined BRAF and MEK inhibition is already standard of care given the improved efficacy and the fact that its also well tolerated is an added bonus.


Abstract

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Effect of time to sentinel-node biopsy on the prognosis of cutaneous melanoma

Authors: Tejera-Vaquerizo A, et al

Summary: This observational, retrospective study included 1963 patients in four tertiary referral hospitals. The group assessed the prognostic implications of a time delay between excisional biopsy of the primary tumour and sentinel-node biopsy (SNB). They showed a delay time of 40 days or less increased Breslow thickness, ulceration and sentinel-node metastasis. They also found primary melanoma localised in the head or neck were independently associated with worse melanoma-specific survival.

Comment: The findings of this study are unexpected and provocative, that is a delay of <40 days between excisional biopsy of primary melanoma and subsequent SNB was independently associated with worse melanoma-specific survival. This finding was significant on multivariate analysis only in the cohort with a negative sentinel node. Although patients who underwent an “early” sentinel node biopsy were more likely to have other poor prognostic features, the time to SNB remained significant even after adjusting for factors such as Breslow thickness and ulceration. There does not seem to be any good biologic rationale for these findings, although the authors do hypothesise that this may be related to the immune response to primary melanoma. At present these findings provide reassurance that a delay to SNB did not worsen the prognosis, however further research is warranted.

Reference: Eur J Cancer 2015 Sep;51(13):1780-93
Abstract

Association of histologic regression in primary melanoma with sentinel lymph node status: A systematic review and meta-analysis

Authors: Ribero S, et al

Summary: Histologic regression has been suggested to represent evidence of an immune response against primary cutaneous melanoma, although there have been conflicting studies regarding the prognostic significance of this finding. This meta-analysis specifically examined the relationship between regression and sentinel node status, with a pooled analysis of approximately 10,000 patients from 14 studies finding that regression was associated with a significantly lower risk of sentinel node positivity.

Comment: There are limitations to the data, including the quality and heterogeneity of the available studies, and the authors also comment on the need for a worldwide consensus on the definition and assessment of regression. However, these findings may form part of a comprehensive assessment of an individual patients likelihood of having a positive sentinel node, allowing informed discussion and decision making regarding whether this procedure is performed.

Reference: JAMA Dermatol 2015 Sep 2
Abstract

Immune-related adverse events, need for systemic immunosuppression and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Centre

Authors: Horvat TZ, et al

Summary: This team retrospectively reviewed the medical records of 298 patients with melanoma who had received treatment with ipilimumab. Eighty five per cent of patients experienced an immune-related adverse event with 19% discontinuing therapy because of an immune-related adverse event, most commonly diarrhoea. The estimated median time to treatment failure was 5.7 months (defined as starting a new treatment or death). They also reported 12% of patients experienced long-term disease control without receiving additional antimelanoma therapy.

Comment: This real-world, although single-institution, study of ipilimumab toxicity shows a higher rate of grade 3 or higher toxicity than reported in clinical trials. This is not unexpected in a non-trial cohort of patients with potentially more comorbidities and concomitant medications, although it’s worth noting that this cohort had good performance status, with 98% ECOG 0-1. A higher proportion of patients required systemic corticosteroids (35%) and additional immunosuppressants (10%) and this may in part reflect earlier use of these treatments based on the investigators prior experience with managing these toxicities. The question has been raised by previous small studies (with conflicting results) as to whether the occurrence of immune-related toxicities correlates with response or survival. In this cohort neither the occurrence of adverse events or use of corticosteroids was associated with overall survival or time to treatment failure.

Reference: J Clin Oncol 2015 Oct 1;33(28):3193-8
Abstract

Acute skin reaction suggestive of pembrolizumab-induced radiosensitisation

Authors: Sibaud V, et al

Summary: This paper reports a case suggestive of acute skin radiosensitisation induced by pembrolizumab, supported by the time relationship between the completion of ionising radiation, drug administration, and rapid onset of the skin reaction. The group hypothesise that radiation therapy may also interact rapidly with anti-programmed-death 1 antibodies.

Comment: Combining radiotherapy and immunotherapy is an attractive proposition given previous reports of an “abscopal effect” and the theory that by inducing local tumour cell destruction radiotherapy may increase exposure and presentation of tumour antigens and this may enhance the immune response. However currently there is little data available on the safety of this approach. This short communication reports a possible case of acute cutaneous radiosensitisation in the setting of initiation of pembrolizumab within days of palliative radiotherapy. Another series reported at ESMO this year (Linker et al) found that anti-PD-1 therapy and extra-cranial radiotherapy was generally well tolerated although cases of cerebral oedema and neurocognitive decline were seen with anti-PD-1 and whole brain radiotherapy. Clearly controlled clinical trials are required to further address the questions of both safety and efficacy, and in fact there are a number of trials currently underway.

Reference: Melanoma Res 2015 Dec;25(6):555-8
Abstract
YERVOY NOW TGA APPROVED FOR FIRST-LINE

Start first with YERVOY® (ipilimumab), the metastatic melanoma treatment with proven durable long-term survival

1In a phase III trial of previously-treated metastatic melanoma patients, there was a 34% reduction in the risk of death with YERVOY 3 mg/kg monotherapy vs. gp100 (HR=0.66 [95% CI: 0.51–0.87], p=0.003; median follow-up 27.8 months). Objective responses maintained beyond 44 months in some patients.1,2 YERVOY is now approved for first-line treatment of adult unresectable/metastatic melanoma patients.1

PBS Information: Section 100 Authority Required. Refer to PBS Schedule for full authority information

WARNING: IMMUNE-MEDIATED ADVERSE EVENTS
YERVOY therapy should be administered and monitored under the supervision of physicians experienced in the treatment of cancer. YERVOY can cause severe and life-threatening immune-related adverse reactions (irARs), including enterocolitis, intestinal perforation, hepatitis, dermatitis (including toxic epidermal necrolysis), endocrinopathy (which may not be reversible), neuropathy, as well as irARs in other organ systems [see PRECAUTIONS and DOSAGE AND ADMINISTRATION]. Early diagnosis and appropriate management are essential to minimise life-threatening complications.

Please refer to Approved Product Information for a full list of adverse events. DOSAGE AND ADMINISTRATION: Clinical chemistries (e.g., electrolytes, liver and thyroid functions) must be assessed before initiation of YERVOY at baseline and before each dose of YERVOY. Additionally, any signs or symptoms of immune-related adverse reactions, including diarrhoea and colitis, should be assessed during treatment with YERVOY. YERVOY must not be administered as an IV push or bolus injection. Patients should be monitored for the signs and symptoms of irARs during and after cessation of therapy. The recommended induction regimen of YERVOY is 3 mg/kg administered intravenously (IV) over a 90-minute period every 3 weeks for a total of four doses. Patients should receive the entire induction regimen (4 doses) as tolerated, regardless of the appearance of new lesions or growth of existing lesions. Assessments of tumour response to YERVOY should be conducted only after completion of induction therapy. Additional treatment with YERVOY (re-induction with 4 doses) may be considered for patients who develop progressive disease after prior CR, PR or SD for ≥3 months. The recommended re-induction regimen of YERVOY is 3 mg/kg administered IV over a 90-minute period every 3 weeks for a total of four doses as tolerated, regardless of the appearance of new lesions or growth of existing lesions. Management of immune-related toxicity may require withholding of a dose and initiation of corticosteroid or other immunosuppressive therapy or permanent discontinuation of YERVOY therapy. Please refer to full Product Information for a full description of guidelines. Please refer to full Product Information for preparation and administration instructions. Each vial of YERVOY is for single use in one patient only. Store in a refrigerator (2°C to 8°C), do not freeze, protect from light.

REFERENCES:
A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention

Authors: Chen AC, et al
Summary: These researchers randomly assigned 386 participants (1:1) who had at least two nonmelanoma skin cancers in the previous 5 years to receive 500 mg of nicotinamide twice daily or placebo for 12 months. They found the rate of new nonmelanoma skin cancers was lower by 23% in the nicotinamide group than in the placebo group at 12 months. They also reported oral nicotinamide was safe with no significant difference in the number or types of adverse events between the two groups.

Comment: Non-melanoma skin cancers are a significant cause of morbidity and health care costs in Australia. This important study run out of Sydney demonstrated a significant reduction in the rate of non-melanoma skin cancers and actinic keratosis with nicotinamide (vitamin B3) — a simple, oral, non-toxic therapy. This study has significant implications as a public health primary prevention strategy. However as with other preventative strategies, particularly use of sunscreen, compliance with long-term therapy may be an issue.


Repeated isolated limb perfusion in melanoma patients with recurrent in-transit metastases

Authors: Deroose JP, et al
Summary: This paper reports on repeat tumour necrosis factor-α and melphalan-based isolated limb perfusion for locoregional recurrence after isolated limb perfusion in 32 patients. The overall response rate was 86% during a median follow-up of 20 months. Complete response was recorded after 24 perfusions (65%). They also reported complete response after first perfusion was a strong predictor for successful repeat perfusions in terms of clinical response and local recurrence. The local recurrence rate was 59% and the five-year overall survival was 35%. Local toxicity was mild.

Comment: In-transit metastases are a unique manifestation of melanoma in which metastases develop within regional dermal and subdermal lymphatics draining from the primary site to the regional nodes. In-transit disease is associated with significant morbidity and often remains a locoregional problem for which localised therapy may be appropriate. Administration of chemotherapy to the affected limb by isolated limb perfusion can result in good responses and local control, and this study demonstrates that retreatment can also be effective in select cases. However in the era of effective and generally well-tolerated systemic therapies for melanoma the place of local treatments is not well established, particularly given the significant risk of patients eventually developing distant metastatic disease. Such treatment may be reserved for cases of failure of systemic therapy or in patients for whom systemic therapy is not felt to be an option.


Multiple primary melanomas among 16,570 patients with melanoma diagnosed at Kaiser Permanente Northern California, 1996-2011

Authors: Moore MM, et al
Summary: This team examined the incidence of and risk factors associated with multiple primary melanomas. The study cohort included 15,448 patients with a single melanoma and 1122 with multiple primary melanomas. The team found those at highest risk of multiple primary melanomas were older, male, white, and partnered. The risk of multiple primary melanomas was highest in the first year after diagnosis (2%) and remained stable thereafter (1%).

Comment: It is well known that a personal history of melanoma is associated with a higher risk of developing a second primary cutaneous melanoma. This is one reason why ongoing dermatologic surveillance is so important in such patients, irrespective of the perceived risk of recurrence of the original melanoma. In this very large cohort ~7% had multiple primary melanomas and identified risk factors included male gender and older age. The risk of a subsequent melanoma was highest in the first year after diagnosis. The finding that subsequent melanomas were thinner and more likely to be in-situ may reflect early detection due to these patients being surveyed more closely, as is appropriate.


Cutaneous toxic effects of BRAF inhibitors alone and in combination with MEK inhibitors for metastatic melanoma

Authors: Carlos G, et al
Summary: This Australian retrospective cohort study included 185 patients with unsegregable stages IIIC and IV melanoma. Of these, 119 patients received dabrafenib; 36, vemurafenib; and 30, CombiDT therapy. The most common cutaneous adverse effects seen in patients receiving the single-agent BRAF inhibitor dabrafenib or vemurafenib included Grover disease, plantar hyperkeratosis, verrucal keratosis and cutaneous squamous cell carcinoma. Compared with dabrafenib, CombiDT therapy showed a higher frequency of folliculitis and a significant decrease of cutaneous squamous cell carcinoma, verrucal keratosis and Grover disease.

Comment: This study highlights the differences in the cutaneous toxicity profile of different BRAF targeted therapies and provides practical information on the prevalence of toxicities to guide surveillance of patients on these agents. As has been previously shown in clinical trial settings, the addition of a MEK inhibitor to BRAF inhibitor therapy reduces toxicities caused by paradoxical activation of the MAPK pathway, particularly cutaneous squamous cell carcinoma. However combination therapy is still associated with some cutaneous toxicity and these may still warrant dermatologic assessment.