Skin Cancer Research Review™

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Issue 7 - 2021

In this issue:

Abbreviations used in this issue:

AJCC = American Joint Committee on Cancer; **BCC** = basal cell carcinoma; **CI** = confidence interval; **CRT** = chemoradiotherapy; **HCTZ** = hydrochlorothiazide; **HR** = hazard ratio; **MCC** = Merkel cell carcinoma; **OR** = odds ratio; **ORR** = overall response rate; **OS** = overall survival; **PD-L1** = programmed death-ligand ; **PFS** = progression-free survival; **PNI** = perineural invasion; **RCM** = reflectance confocal microscopy; **SCC** = squamous cell carcinoma; **UV** = ultraviolet; **WTP** = willingness to pay.

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Welcome to the latest issue of Skin Cancer Research Review.

While the strategy of adjuvant immunotherapy following standard chemoradiotherapy (CRT) has shown success in unresectable non-small cell lung cancer with durvalumab extending survival in the PACIFIC trial, results from the phase 3 JAVELIN head and neck 100 trial published in *The Lancet Oncology* demonstrate that concurrent CRT with avelumab is not beneficial in locally advanced head and neck squamous cell carcinoma (SCC) with the combination failing to confer a benefit in disease progression. The results bring into question the viability of combining immunotherapy with radiotherapy with not only no advantage to the combination but also an antagonist effect seen with survival curves favouring the placebo trial arm. These results follow the negative results for avelumab maintenance following chemotherapy in the JAVELIN gastric 100 trial where no survival advantage was found in unresectable advanced HER2-negative stomach or gastroesophageal junction cancer, even in a programmed death-ligand 1 (PD-L1)-positive population. For the moment, immune checkpoint inhibitor use in head and neck SCC will remain limited to the recurrent/metastatic setting. In other research, a randomised trial concludes that despite the advantages a non-invasive test like reflectance confocal microscopy offers, the significantly reduced accuracy for the diagnosis of aggressive basal cell carcinoma (BCC) subtypes compared to standard 3 mm punch biopsy prevent its routine use, longer-term follow-up from the KEYNOTE-017 trial demonstrates durable three-year responses to front-line pembrolizumab in Merkel cell carcinoma (MCC) and a US Surveillance, Epidemiology and End Results database study finds inferior survival in nodular versus superficial spreading melanoma when matched for Brelow depth and TNM stage.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,

Dr David Simpson

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Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial

Authors: Lee N et al.

Summary: Results from a pre-planned interim analysis of the JAVELIN Head and neck 100 trial (ClinicalTrials.gov Identifier: NCT02952586) published in *The Lancet Oncology* failed to demonstrate any efficacy for the addition of the immune checkpoint inhibitor avelumab to a standard chemoradiotherapy (CRT) regimen in patients with advanced head and neck cancer and the trial has been prematurely terminated. The Pfizer sponsored, phase 3 trial accrued a total of 697 adult patients with histologically confirmed, previously untreated locally advanced SCC of the oral cavity, oropharynx, hypopharynx or larynx eligible for definitive CRT with curative intent from 196 treatment centres across North America, Europe and Australasia. PD-L1 status was not a study entry criterion. Patients were randomised to treatment with either standard concurrent CRT plus placebo (100 mg/m^2 cisplatin every three weeks plus intensity-modulated radiotherapy with standard fractionation of 70 Gy; n=350) or CRT plus avelumab (single 10 mg/kg lead-in dose plus two-weekly maintenance for 12 months; n=347). At a median of 14.7 months follow-up, the addition of avelumab to CRT did not elicit any improvement in the primary efficacy outcome of progression-free survival (PFS) compared to CRT alone (not reached vs not reached; stratified hazard ratio [HR] 1.21; 95% confidence interval [CI], 0.93-1.57; one-sided p=0.92) and the lower limit of the 95% CI favoured the CRT alone arm (23 vs 16.9 months).

Comment: Immune checkpoint inhibitors have been shown to be successful in a variety of cancers since their initial use in melanoma. Avelumab is best known for treatment of metastatic MCC but is also indicated in urothelial and renal cell cancers. This study is the first to investigate whether concurrent therapy with avelumab and standard CRT might result in improved PFS in locally advanced oropharyngeal SCC. Unfortunately, there was no benefit found although there was a possible improvement in a subgroup with strong PD-LI expression. It might be interesting to see whether pre-treatment with CRT followed by immune checkpoint therapy might be more effective by utilising the abscopal effect whereby the treatment of one area of tumour enhances subsequent immune destruction of untreated deposits of cancer.

Reference: Lancet Oncol 2021;22(4):450-62

Abstract

Independent commentary by Dr David Simpson

Dr David Simpson is a skin cancer doctor on the Sunshine Coast in Queensland. He has a masters degree in Skin Cancer Medicine from the University of Queensland and is a teaching assistant on the MMed program.

Three-year survival, correlates and salvage therapies in patients receiving first-line pembrolizumab for advanced Merkel cell carcinoma

Authors: Nghiem P et al.

Summary: Paul Nghiem and colleagues report longer-term follow-up results from the phase 2, single-arm Cancer Immunotherapy Trials Network-09/Keynote-017 trial of front-line pembrolizumab monotherapy for unresectable advanced MCC. A total of 50 systemic therapy naïve patients (median age 70.5 years; 64% Merkel cell polyomavirus–positive tumours) were administered up to two-years of 2 mg/kg pembrolizumab every three weeks. At a median follow-up of 31.8 months the overall response rate (ORR) was 58% with a complete response in 30%. The median duration of response was not reached at three-years. The median PFS was 16.8 months and median overall survival (OS) not reached (three-year OS, 59.4% for the entire cohort and 89.5% in responders). A survival benefit to salvage chemotherapy or immunotherapy was observed.

Comment: This study in non-resectable locally advanced MCC investigated the longer-term benefits of pembrolizumab over a period of 30 months. MCC is a highly immunogenic tumour and immune checkpoint therapy has been shown to be of benefit in previous studies. The majority of patients who would benefit showed a good response in the first 12 weeks of treatment. The ORR was 58% and in these patients 72% remained in response after three years. Initial response rate was far more important than tumour burden. Previously the PFS in advanced MCC using cytotoxic chemotherapy was only 90 days whereas immunotherapy is leading to durable responses over at least three years. Re-treatment with pembrolizumab or alternative immunotherapies in those who relapsed led to further survival benefits.

Reference: J Immunother Cancer 2021;9(4):e002478
Abstract

Eight years of experience with vismodegib for advanced and multiple basal cell carcinoma patients in the Netherlands

Authors: Verkouteren B et al.

Summary: This retrospective cohort study evaluated the efficacy of vismodegib for BCC in a Dutch population. A total of 78 adult patients administered vismodegib between 2011 and 2019 for a histologically-confirmed BCC (locally advanced, n=48; metastatic, n=11; basal cell nevus syndrome, n=19) were included in the study. The median PFS for locally advanced, metastatic BCC and basal cell nevus syndrome were 10.3, 11.7 and 19.1 months, respectively. A positive relationship was found between risk of non-response to vismodegib therapy and size of locally advanced lesion (HR 0.77 per 1 cm increase; p=0.02).

Comment: Locally advanced and metastatic BCC are fortunately rarely encountered in routine dermatological and skin cancer practice but when they occur can be fatal. Vismodegib acts as an inhibitor of the Smoothened protein in the Hedgehog signalling pathway and thus inhibits tumour progression in BCCs. This retrospective study showed that 98% of patients experienced adverse reactions with vismodegib and this often led to discontinuation with treatment. PFS was 10.3 months for locally advanced BCC and 11.7 months for metastatic BCC. Patients with basal cell naevus syndrome and multiple BCCs had a median 19.1 months PFS. Treatment breaks and repeat courses have been used to mitigate adverse reactions. Patients with basal cell nevus syndrome (Gorlin's Syndrome) tended to be younger and several had been treated successfully several times with vismodegib. Despite the high discontinuation rates due to adverse reactions, this group of patients can benefit by reducing their disease burden and morbidity from other interventions such as repeated surgeries.

Reference: Br J Cancer 2021;124(7):1199-1206
Abstract

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

Authors: El Sharouni M-A et al.

Summary: This study of two cohorts – one Dutch and one Australian - analysed the prognostic value of histologic regression in stage 1 and 2 primary, invasive cutaneous melanoma. Population-based data on 17,271 patients from the Netherlands were extracted from PALGA, the Dutch Pathology Registry with matched follow-up data at a median time of 4.5 years obtained from the Netherlands Cancer Registry. The Australian cohort was comprised of 4,980 patients treated between 2000 and 2014 at a specialised melanoma treatment centre with a median follow-up of 11.1 years. In both cohorts, multivariable Cox proportional hazard analyses found favourable survival in the presence of histologic regression including a 45% and 39% reduced risk of regression-free survival in the Dutch and Australian cohorts, respectively (HR 0.55; 95% CI, 0.48-0.63 and HR 0.61; 95% CI, 0.52-0.72, both p<0.001) and 13% and 27% reduced risk of death (HR 0.87; 95% CI, 0.79-0.96 and HR 0.61; 95% CI, 0.64-0.84; both p<0.01). Analysis of subgroups revealed a recurrence-free survival advantage with regression in thin and intermediate Breslow thickness melanomas (≤4.0 mm) whereas regression in superficial spreading melanoma correlated with an advantage in both recurrence-free survival and OS.

Comment: Regression in melanoma is a fairly common finding and is a feature of host immunological response directed at the tumour. Its prognostic significance has been uncertain with studies showing both positive and negative results possibly due to non-standardised definitions of regression, small studies and inadequate length of follow-up. Using data from a Dutch cohort over four years and from the Melanoma Institute Australia over 11 years, the authors showed improved recurrence-free survival and OS in patients with histologic regression, particularly with superficial spreading melanoma. With the advent of successful immunotherapies, it makes sense that a strong natural immunologic reaction would be beneficial and this study appears to add weight to considering regression as a favourable prognostic histologic feature.

Reference: JAMA Dermatol 2021;157(2):166-73
Abstract

Treatment of early-stage mycosis fungoides

Authors: Quaglino P et al.

Summary: Results from the PROspective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study from the Cutaneous Lymphoma International Consortium regarding early-stage mycosis fungoides were published by Quaglino et al in *British Journal of Dermatology.* Analysis was based on 395 patients from around the globe with newly diagnosed, early-stage (stage 1A-2A) disease identified between 2015 and 2018. Front-line therapy predominantly comprised skin-directed treatments (81.5%) with systemic treatment used in the front-line setting in 11.1% of patients and observation in 7.3%. Physicians were more likely to prescribe systemic therapy in cases of more severe disease or clinical stage (quantified using the modified Severity Weighted Assessment Tool; stage 1A, 6% vs stage 2A, 20%;), when plaques were present and in cases of folliculotropic variants (24% vs 12%; all comparisons p<0.01). A significantly improved ORR was achieved with front-line skin-directed versus systemic treatments (73% vs 57%; p=0.027). Patients with both responsive and stable disease had improvements in health-related quality of life.

Comment: Mycosis fungoides is the most common form of cutaneous T cell lymphoma and diagnosis is often delayed due to initial misdiagnosis. It may resemble dermatitis or psoriasis and progresses from a patch phase to a plaque stage and then a tumour phase. Treatments may be skin-directed or systemic. The most common initial therapy was topical corticosteroids followed by ultraviolet (UV) B and psoralen with UVA phototherapies. This study found that most centres followed guidance to treat thinner patch lesions with narrowband or broadband UVB and thicker lesions and plaques with the deeper penetrating UVA (UVA – with psoralen). Skin directed therapies appeared to be associated with both better outcomes and better patient quality of life even when stage of disease was taken in account

Reference: Br J Dermatol 2021;184(4):722-30
Abstract

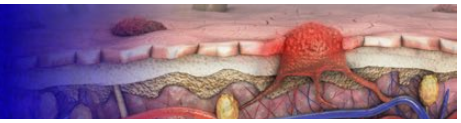
Biopsy outperforms reflectance confocal microscopy in diagnosing and subtyping basal cell carcinoma

Authors: Woliner-van der Weg W et al.

Summary: Results and experiences from a randomized controlled multicentre trial find that reflectance confocal microscopy (RCM) has a significantly reduced accuracy for the diagnosis of aggressive BCC subtypes compared to punch biopsy and cannot therefore be used in clinical practice for this indication. The trial enrolled a total of 288 patients with clinical suspicion of BCC from four Dutch hospitals and randomised them to undergo diagnosis by either non-invasive imaging of the lesion using *in vivo* RCM (n=145) or by histological examination after punch biopsy sampling (n=143) in comparison to conventional excision or clinical follow-up. There was no difference between the two modalities for the diagnostic sensitivity (both 99%) but RCM had a lower specificity (59.1% vs 100%; p<0.001). RCM also showed lower sensitivity for subtyping (aggressive subtype, 33.3% vs 77.3%; p=0.003)

Comment: RCM is a non-invasive tool which allows examination of lesions at the cellular level without the need for anaesthetic, pain, scarring and delays awaiting assessment of biopsy material in a laboratory. It also allows examination of the whole lesion whereas biopsies only provide a small sample and could potentially be vulnerable to sampling errors. This study compared RCM with standard 3 mm punch biopsies for the diagnosis of BCCs in a hospital population. Despite having high and similar sensitivity, RCM had a much lower specificity and ability to distinguish between aggressive and non-aggressive BCC subtypes. Whilst being inferior for establishing subtypes RCM might be useful for analysing difficult lesions such as eyelid margin tumours and mapping large lesions.

Reference: Br J Dermatol 2021;184(4):663-71
Abstract



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NEW treatment option for advanced cutaneous squamous cell carcinoma (CSCC)[1]

Candidates for LIBTAYO[1]

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- Nodal metastasis
- Distant metastasis

Locally advanced CSCC[1]

- Locally advanced CSCC patients who are not candidates for curative surgery or curative radiation

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Response rates[*†]
Primary end point ORR, with an ORR of 49.2% for the group with the longest duration of follow up (Group 1)[1]

Time to response
Median time to response was at the first assessment for Groups 1-3 (time of first assessment was 8 or 9 weeks, depending on dosing group)[1]

Duration of response[*]
Median duration of response was not reached for Groups 1-3[1]

*Data cut-off was Sep 20, 2018 for Groups 1 and 3 patients, and Oct 10, 2018 for Group 2 patients.[1]

†Median duration of follow up for Group 1: 16.8 months (mCSCC), Group 2: 9.3 months (laCSCC), Group 3: 8.1 months (mCSCC)[1]

Demonstrated acceptable risk/benefit profile with LIBTAYO[1]

LIBTAYO demonstrated an acceptable risk/benefit profile in clinical studies of 591 patients with advanced solid malignancies, including 219 advanced CSCC patients who received LIBTAYO monotherapy.[1]

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▼This medicinal product is subject to additional monitoring in Australia due to provisional approval. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

Abbreviations: CSCC, Cutaneous Squamous Cell Carcinoma; **ORR,** overall response rate.

References: 1. LIBTAYO® (cemiplimab) Approved Product Information. July 2020.

Sanofi and Regeneron are collaborating in the global development and commercialisation for LIBTAYO (cemiplimab).

SANOFI GENZYME

Five-year survival in patients with nodular and superficial spreading melanomas in the US population

Authors: Allais B et al.

Summary: This population-based cross-sectional study analysed data from the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database to compare survival differences between superficial spreading and nodular melanoma subtypes. Analysis of two cohorts of patients with the same Brelow depth and TNM stage of disease, diagnosed in the time period 2004-2009 or 2010-2015 consistently showed inferior five-year relative survival in patients with the nodular melanoma subtype with an approximate 30% lower five-year survival rate than patients with superficial spreading melanoma (53.7% vs 87.3%; z score -41.35 and 61.5% vs 89.7%; z score -2.7078; both $p<0.01$). The authors concluded that treatment recommendations need to consider melanoma subtype.

Comment: Histological subtype is not included in the American Joint Committee on Cancer (AJCC) guidelines when staging melanoma and yet we know from clinical practice that nodular tumours appear to be more aggressive. This has been assumed to be partly due to their greater Breslow thickness at diagnosis and more rapid growth but this study examined five-year survival data comparing nodular melanoma and superficial spreading melanoma cases matched for TNM status. Nodular melanoma cases were more likely to be older, male and present with metastases but when subgroup analysis was performed nodular melanoma patients with T1b, T2a and T2b tumours had a significantly worse prognosis compared to superficial spreading melanoma patients. Previous studies have shown an increased risk of sentinel lymph node biopsy positivity and local recurrence in nodular compared to superficial spreading melanoma and nodular melanoma tumours are more likely to have gene expression for tissue invasion, proliferation and adhesion. Thin nodular melanomas need to be considered as a higher risk tumour and this information will help in decision making when dealing with thin tumours.

Reference: J Am Acad Dermatol 2021;84(4):1015-22
Abstract

Association between hydrochlorothiazide and the risk of in situ and invasive squamous cell skin carcinoma and basal cell carcinoma

Authors: Adalsteinsson J et al.

Summary: This Icelandic population-based case-control study assessed the risk of keratinocyte skin cancers with hydrochlorothiazide (HCTZ) exposure. Conditional logistic regression analyses were performed to compare the odds of keratinocyte carcinoma with HCTZ use in a patient cohort comprised of all Icelandic BCC, invasive SCC and SCC *in situ* diagnosed between 2003 and 2017 (n=6,880). A 69% increased odds of invasive SCC was found with a cumulative HCTZ dose >37,500 mg (odds ratio [OR] 1.69; 95% CI, 1.04-2.74). HCTZ use also associated with a significantly greater risk for *in situ* SCC and BCC (OR 1.24; 95% CI, 1.10-1.52 and OR 1.14; 95% CI, 1.02-1.29). The authors acknowledged the inherent limitations in their study including the inability to adjust for UV exposure, Fitzpatrick skin type and comorbidities.

Comment: There is increasing evidence that HCTZ use is associated with increased rates of skin cancer. The postulated mechanism being increased production of free radicals and reactive oxygen species on exposure to UV light. This study looked at data from Iceland where the population is almost entirely white and has low ambient UV exposure but enjoys sunbed use and overseas holidays. A statistically significant association was found for invasive SCC, SCC *in situ* and BCC with HCZ use. Age over 50 years and male sex were strongly linked and cumulative HCTZ dose linked to subsequent BCC risk. In Australia and New Zealand, we have extremely high ambient UV exposure, both occupational and recreational and an ageing population and it is may be wise to consider patients skin cancer history and current lifestyle before opting for thiazide diuretics to treat their hypertension.

Reference: J Am Acad Dermatol 2021;84(3):669-75
Abstract

A histopathologic scoring system for perineural invasion correlates with adverse outcomes in patients with cutaneous squamous cell carcinoma

Authors: Totonchy M et al.

Summary: In order to refine staging of cutaneous SCC Totonchy et al examined the prognostic significance of features of perineural invasion (PNI) beyond its binary presence/absence. The retrospective study included 45 patients (median age 74 years) who underwent a surgical excision (Mohs micrographic surgery or wide local excision) of primary cutaneous SCC with PNI at the US Yale Dermatologic Surgery between 2013 and 2016. Thirteen patients received adjuvant radiotherapy. The researchers assessed five histopathologic features of malignant nerve involvement to assess the extent and severity of PNI: the diameter of the affected nerves, the number of distinct nerve structures affected, the depth of nerve involvement (dermis vs subcutis and muscle/fascia), intra-versus extratumoral nerve involvement and focal versus circumferential PNI. At two-year follow-up six patients had an adverse outcome: local recurrence (n=2), metastasis (n=4) or death (n=2). The median number of PNI-impacted nerves was 4 (range, 1-17) and the median affected nerve diameter was 0.13 mm (range, 0.02-0.55 mm). Larger nerve diameter and increased number of affected nerves were both identified as negative prognostic factors. Finally, the group created a composite PNI score that considered all five features of PNI malignant nerve involvement that accurately predicted adverse outcome ($p=0.020$).

Comment: Cutaneous SCC is a common malignancy in Australia and causes over 600 deaths annually. PNI is a known risk factor for adverse outcomes and in the AJCC guidelines PNI involving a nerve greater than 0.1 mm is used as part of the staging process. The authors of this paper examined 45 cases of cutaneous SCC with PNI and used five histological features of PNI to develop a reproducible scoring system. The factors were the size of the largest nerve affected, the number of nerves affected, anatomic depth of the nerve affected (dermis or subcutis), intra versus extra tumoral and focal versus circumferential involvement. Whilst all five features were associated with adverse outcomes only nerve size and number of nerves reached statistical significance. Combining the five features into a scoring system produced a composite PNI scoring system that was significantly associated with adverse outcomes. This should help when selecting patients who will benefit from adjuvant radiotherapy.

Reference: Dermatol Sur 2021;47(4):445-51
Abstract

Willingness to pay for surgical treatments for basal cell carcinoma: A population-based cross-sectional study

Author: Kantor J

Summary: According to results from an internet-based age-, sex-, and race-stratified cross-sectional survey in the US the willingness to pay (WTP) threshold for surgical treatment of BCC is highest for Mohs micrographic surgery, especially for facial or trunk carcinomas. Questionnaires completes by 425 people representing the US general population found that the median WTP was US$1000 for electrodesiccation and curettage, US$1,503 for excision and US$3,006 for Mohs micrographic surgery. Participants were willing to spend up to US$3,989 for Mohs micrographic surgery when it was presented as the best treatment option for BCC but were less willing to spend money on BCC when it was located on the back with the median WTP dropping by 12%.

Comment: Paying for skin cancer treatments varies between patient groups with some refusing to contribute a cent and others opting for the most expensive option available. In the US patients are used to paying and have also been exposed to large rates of Mohs micrographic surgery whereas in Europe and Australasia we achieve similar outcomes with standard excisions and electrodessication/curettage techniques. In this US study Mohs surgery was stated to have the highest cure rate but cosmetic outcome was not discussed. Patients were willing to pay a large premium for Mohs surgery, particularly on the face and when it was claimed to be the "Gold Standard" they were willing to pay even more. Patients seem more interested in efficacy than cost and the willingness to pay more for facial lesions suggests than cosmesis is also a factor. When presenting options to patients we shouldn't be afraid to offer more expensive treatment – such as surgery – when the cure rate is higher. Opting for the Pharmaceutical Benefits Scheme funded skin cream or electrodesiccation and curettage may be cheaper but less desirable when the patient is fully informed.

Reference: Dermatol Surg 2021;47(4):467-72
Abstract

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