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EDUCATIONAL SERIES

Treating Advanced Basal Cell Carcinoma in NZ

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This review is intended as an educational resource for health professionals. It discusses the incidence, prevalence, burden, diagnosis and treatment of advanced basal cell carcinoma (BCC) in New Zealand. Peer-reviewed clinical trial evidence is presented with accompanying expert commentary that is intended to inform readers about advancing clinical practice in the treatment of this cancer.

What is advanced basal cell carcinoma?

Predominantly affecting Caucasians, basal cell carcinoma (BCC) is a slow-growing, invasive malignant epidermal skin tumour, which infiltrates tissues in a three-dimensional fashion.[1] BCC is the most common of all human malignancies and comprises the majority of non-melanoma skin cancers.[2,3] According to a meta-analysis, the 3-year cumulative risk of developing a subsequent BCC after an index BCC is 44%.[4]

Occasionally, untreated BCCs or those that are not cured after surgical excision may become locally invasive and infiltrate other structures (eyes, brain, vital structures and organs), or they may very rarely metastasise to lymph nodes or distant organs (it is estimated that metastatic BCCs account for 0.0028-0.55% of all cases).[3] Together, locally advanced and metastatic BCCs comprise a disease group termed `advanced BCCs'. Aggressive subtypes of BCC include micronodular, infiltrative, adenoid and morphoeic forms.[2,5]

Burden of disease

Worldwide, the incidence of BCC has been rising in recent decades.[6,7] New Zealand incidence estimates suggest that BCC affects 1120 individuals per 100,000 population[6]; however, accurate incidence data are not available. The New Zealand Cancer Registry collects data on malignant tumours first diagnosed in New Zealand from laboratories, but it excludes BCCs and squamous cell carcinomas (SCCs). Many BCCs are treated without obtaining histology, particularly superficial BCCs that may undergo cryotherapy or topical therapy. Furthermore, incidence statistics underestimate the burden of disease because large numbers of patients present with multiple primary BCCs, sometimes hundreds over a period of time.

Advanced BCCs can be very difficult to treat and carry considerable physical, psychological, psychosocial and economic burden.[3,8,9]

Epidemiology and aetiology of advanced BCC

BCC is more common in men than women and the average age for developing this cancer is 60 years; however, there is a rising incidence of BCC in younger women.[2,6] A number of genetic diseases (see below) are associated with an increased incidence of BCC, but the majority of BCCs occur sporadically.[2] Genetic predisposition (including fair skin that burns easily and does not tan well) and exposure to ultraviolet radiation (particularly a history of sunburn in early life) appear to be the most significant aetiological factors for BCC.[2,10,11]

Individuals presenting with advanced BCC generally have experienced a delay in medical treatment or have disease that has recurred, or is refractory to treatment.[3] While surgery is curative for most patients with BCC, around 3-4.5% of patients treated via surgical excision will experience a recurrence after 5 years; the rate is lower for those treated with histologically-guided serial excision (Mohs surgery) at around 0.3-2.5%.[12-15] Most recurrences can be re-treated successfully, but recurrent tumours of the head and neck, and particularly of the eyelids, nose and ears may be challenging to excise.

A number of risk factors for metastatic BCC have been identified and include male gender, primary tumour located in the head-and-neck region (especially the ear and face), recurrence following surgery and/or radiation, large and locally invasive lesions (e.g.T4 lesions), and immunosuppression.[2] A review of published cases of metastatic BCC between 1981 and 2011 revealed a median duration of 9 years between primary tumour diagnosis and the first sign of metastasis.[16] Metastases occur more commonly in the regional lymph nodes, followed by bone, liver and lung, and carry a poor prognosis.[2,17] In a recent review of 100 cases of metastatic BCC between 1981 and 2011 (50 with regional metastases and 50 with distant metastases) including seven from Australia and New Zealand, the median survival after metastatic BCC diagnosis was 54 months; 24 months for those with distant metastases and 87 months in those with regional metastases (93 cases were treated with radiation, surgery and/or chemotherapy and 36 patients received >1 type of treatment).[18]

Genetic syndromes associated with BCC

The genetic syndromes associated with BCC are rare causes of skin cancer, but are important in terms of genetic counselling and early identification. Minimising the functional and aesthetic morbidity of surgery and timing of radiotherapy (where indicated) is an additional challenge, given that there are usually multiple tumours. Genetic syndromes associated with BCC include the following:

Gorlin syndrome (also known as basal-cell nevus syndrome) is the best-known genetic disorder associated with BCC.[2,19] This syndrome is characterised by multiple BCCs (see **Figure 1**), palmar pits, jaw cysts, rib abnormalities, calcification of falx cerebri, characteristic facies (frontal bossing, hypoplastic maxilla, broad nasal root and ocular hypertolerism). BCCs may develop early in life.

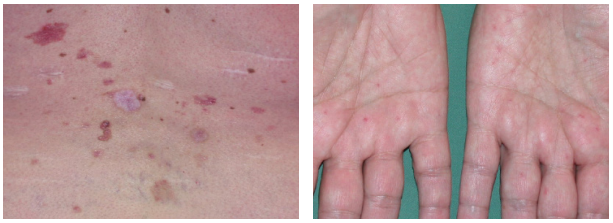

Figure 1: Multiple BCCs on the back in a patient with Gorlin syndrome and palmar pits associated with the disease.

Bazex-Dupré-Christol syndrome, also known as Bazex syndrome or follicular atrophoderma-basal cell carcinoma, is a disorder of the hair follicles. It is characterised by follicular atrophoderma of the extremities, multiple BCCs on the face, milia, hypotrichosis and localised and generalised hypohidrosis. Skin neoplasms can occur at a young age, but usually occur after the first decade.[2,19]

Rombo syndrome is characterised by acral erythema, vellus hair cysts, vermiculate atrophoderma and hypotrichosis.[19] BCCs may develop in adulthood.

Rothmund-Thomson syndrome is an autosomal recessive disorder characterised by widespread swelling, erythema and blistering in the first 6 months of life.[19] In young individuals the prevalence of BCCs and SCCs is estimated at 2-5%.[19]

Xeroderma pigmentosum is caused by a defect in DNA repair and synthesis and is associated with a significantly increased risk of BCC, SCC and melanoma.[19,20] Clinical features include sun sensitivity, severely damaged skin and ocular involvement. BCCs develop at an average age of 8 years in these individuals.

Clinical evaluation and diagnosis of advanced BCC

Locally advanced BCC is mainly located on the head and neck, and may involve the eye or ear canal, and extend into vital organs such as the sinuses, oropharynx and brain. In advanced BCC where bony involvement, nerve, gland or organ invasion is suspected, computed tomography or magnetic resonance imaging are indicated to determine the extent of disease.[21] These cases should be managed by a Head and Neck or Cutaneous Oncology multidisciplinary team. Several examples of advanced BCC are shown in **Figure 2**.

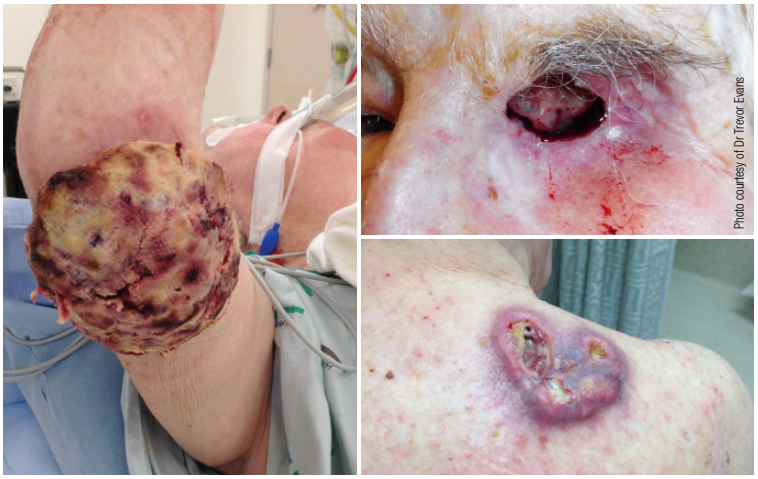

Figure 2: Several examples of advanced BCCs

Treatment options for advanced BCC

The goals of BCC treatment are tumour clearance, tissue preservation and optimal cosmetic outcome.[22] Cryotherapy, photodynamic therapy and topical therapy (e.g. imiquimod cream) may be used for small, low-risk superficial BCCs, but these treatments are unsuitable for larger or thicker forms of BCC.[6,22] Treatment options for advanced BCC have been limited to surgery, radiotherapy and traditional chemotherapy (such as cisplatin-based regimens) and there have been few randomised controlled trials comparing their efficacy.[3,23] More recently, the hedgehog pathway inhibitors vismodegib [Erivedge®; Roche] and sonidegib [Novartis] have joined the limited armamentarium against advanced BCC; vismodegib received FDA approval for this indication in 2012 and sonidegib is currently undergoing clinical trials.[24] In April 2014, vismodegib was registered in New Zealand for use in adults with metastasised BCC or locally advanced BCC who are not candidates for surgery or radiation.[25] This agent is not PHARMAC funded.

Surgery

Treatment of the majority of BCCs is surgical and usually involves excision with 3-4 mm clinical margins or wider depending on the size and invasiveness of the BCC.[22] Recurrent tumours or tumours in high-risk sites such as the eyelids and nose may be excised using microscopic control of margins (Mohs surgery, frozen section margin control or two stage procedures).[21] Surgical removal of advanced BCC tumours may be associated with excessive morbidity or disfigurement and major surgical resections often require complex reconstruction with microvascular free flaps.[26] In some cases, surgery is untenable due to potential loss of function.[9]

Radiotherapy

Radiation has demonstrated efficacy in the treatment of high-risk disease and has been the treatment of choice for many patients unable to tolerate surgery.[21] Radiotherapy may be used in an adjuvant role following incomplete excision of high-risk BCCs.[21] This therapy is not considered to be helpful in some cases of locally advanced BCC arising either from earlier untreated lesions or recurrence of aggressive BCCs.[21,27] In some cases, radiotherapy may be untenable due to the potential loss of function, and may be inappropriate for patients with metastatic disease.[9]

Chemotherapy

For patients with metastatic disease, systemic therapy may be appropriate. While earlier studies of metastatic BCC showed a lack of significant response to most systemic chemotherapeutic agents (methotrexate, bleomycin, 5-fluorouracil, cyclophosphamide, toyomycin and dactinomycin), more recently, platinum-based regimens have shown significant tumour responses in large numbers of patients with metastatic and non-metastatic BCC.[2,6] A review of 53 patients receiving platinum-containing therapy for progressive BCC showed a response rate of 83% (complete remission in 17%) with a median time to disease progression of 24 months.[28] While platinum-based chemotherapy has shown good efficacy, it is associated with significant toxicity and may not be administered in many elderly patients.[2] A recent study found considerable variation in the treatment of metastatic BCC, with only 20% of cases receiving chemotherapy.[18]

Newer treatment options - targeted therapy

BCC is a cancer that is associated with mutations in components of the hedgehog-signalling pathway and dysregulation of this pathway is the pivotal molecular abnormality in this type of cancer.[2,29] In fact, mutations in the *PTCH* gene (patched hedgehog) are found in up to 90% of sporadic cases, and almost all cases associated with Gorlin syndrome.[30,31] The hedgehog pathway was first discovered in mutant fruit flies, the larvae of which resembled hedgehogs.[32] This pathway plays a significant role in the development of tissues and organs during embryonic and postnatal development. The hedgehog pathway is kept inactive in adult tissues through inhibition by the Patched-1 receptor (*PTCH-1*), but becomes activated via the binding of hedgehog ligand to *PTCH-1*.[33] This activation allows the transmembrane protein, Smoothened homolog (SMO) to transfer signals downstream via various proteins. In most BCCs, mutations in the hedgehog gene inactivate *PTCH-1* (loss of function), or less commonly activate SMO (gain of function). The constitutively activated hedgehog pathway then mediates unrestrained basal cell proliferation.

Targeted inhibition of the hedgehog pathway holds exciting new prospects in the treatment of BCC and other cancers, and a number of systemic inhibitors of SMO, including oral vismodegib and topical and oral sonidegib (LDE225) are being investigated, as is topical vitamin D_3, which has been shown to inhibit SMO *in vitro*.[34-36] Preclinical work is also focusing on developing inhibitors of downstream targets in the hedgehog pathway, such as GLI transcription factors.[36]

Vismodegib which targets the hedgehog signalling pathway by binding to and inhibiting SMO, is the first US FDA-approved oral, small molecule pathway inhibitor for this indication.[3,9,34] This agent has shown proven efficacy and an acceptable safety profile in advanced BCC.[34,37,38] As with other molecularly targeted anti-cancer drugs, acquired resistance to vismodegib has been observed.[2]

In a pivotal Phase II clinical trial (ERIVANCE BCC), vismodegib resulted in objective response rates of 30% (95% CI 16-48%; p = 0.001) among 33 patients with metastatic BCC and of 43% (95% CI 31-56%; p = 0.001) among 63 patients with locally advanced disease; 20.6% with locally advanced BCC exhibited a complete response.[34] 30-month follow-up data from this trial have confirmed the agent's efficacy and shown consistent safety.[37] Discontinuation of vismodegib after achieving tumour stabilisation did not appear to lead to rapid tumour recurrence, with patients maintaining their response for >1 year.[38] Furthermore, patients appeared to benefit from retreatment with vismodegib for disease progression.[38]

Another trial investigating the efficacy of vismodegib in 41 patients with basal-cell nevus syndrome, showed the agent to reduce BCC tumour burden and to block the growth of new BCCs.[29]

The safety and efficacy of vismodegib is further being assessed in the single-arm, open-label, multi-centre STEVIE study in adult patients with locally advanced or metastatic BCC.[39] In this trial patients receive the agent until disease progression or unacceptable toxicity.

Phase II trials are currently underway to investigate the use of vismodegib in conjunction with radiotherapy for advanced head/neck BCC, and to evaluate its use for reducing tumour size in operable advanced BCC, allowing for a lower surgical stage, the preservation of function and optimal aesthetic appearance (VISMONEO, MIKIE and NICCI studies).[40-42]

As systemic therapy in advanced BCC is not curative and long-term use is necessary, it is recommended that such therapy not be used in place of curative procedures and that evaluation for the possibility of curative/definitive surgery with or without radiation be undertaken before the initiation of any systemic therapy.[17] However, there are some cases that would benefit from targeted therapy with vismodegib that are not suitable for surgery or radiotherapy.

EXPERT COMMENTARY ON DRUG TRIALS TARGETING THE HEDGEHOG PATHWAY IN ADVANCED BCC

Efficacy and safety of vismodegib in advanced basal-cell carcinoma[34]

Authors: Sekulic A et al.

Summary: Outcomes are reported from this Phase II study (ERIVANCE BCC) that evaluated the efficacy and safety of vismodegib in 33 patients with metastatic BCC and 71 patients with locally advanced BCC who had inoperable disease or for whom surgery was inappropriate (because of multiple recurrences and low likelihood of surgical cure, or substantial anticipated disfigurement). Oral vismodegib (150 mg/day) was administered for 13 months or until disease progression (20% increment or new lesion) or toxicity was observed. The primary end point was the objective response rate, which was expected to be >10% for metastatic BCC and >20% for locally advanced BCC. Objective response rates were 30% and 43% in the metastatic and locally advanced BCC cohorts, respectively. In an efficacy analysis of 63 patients with locally advanced BCC, 13 (21%) attained a complete response. The median duration of objective response was 7.6 months for both cohorts. Adverse events (AEs) occurring in >30% of patients included muscle spasms, alopecia, dysgeusia (taste disturbance), weight loss and fatigue. Serious AEs were reported in 26 patients (25%), including fatal AEs in 7 patients (the deaths were considered to be unrelated to vismodegib).

A recent update presented at ASCO 2014, of 30-month data from the trial confirmed the agent's efficacy and showed long-term consistent safety data.[37]

Comment: Eighteen-month follow-up data confirmed prolonged responses and consistent safety in vismodegib-treated patients with advanced BCC. Unfortunately, many patients were unable to tolerate the drug, most often because of severe muscle cramps. It is likely that the best use of hedgehog inhibitors is in the neoadjuvant setting whereby inoperable tumours become resectable and clinical trials are underway.

Expanded access study of patients with advanced basal cell carcinoma treated with the hedgehog pathway inhibitor, vismodegib[9]

Authors: Chang AL et al.

Summary: This open-label, multicentre study involving 119 patients with advanced BCC inappropriate for surgery or radiotherapy assessed the efficacy and safety of vismodegib 150 mg/day administered until disease progression or intolerable toxicity (median duration of treatment 5.5 months). An objective response (evaluated via Response Evaluation Criteria for Solid Tumours version 1.0) was observed in 46.4% of those with locally advanced BCC and in 30.8% of those with metastatic BCC. In patients with locally advanced BCC, prior systemic therapy was negatively associated with response ($p = 0.002$). During a mean follow-up period of 6.5 months, the most common adverse events were muscle spasms (experienced by 70.6% of patients), dysgeusia (70.6%), alopecia (58.0%) and diarrhoea (25.2%).

Comment: The response rates are good, given that there is no other treatment, but the benefits are often limited by unacceptable side effects that occur with targeted therapy drugs, and by cost.

Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome[29]

Authors: Tang JY et al.

Summary: This randomised, double-blind, placebo-controlled trial tested the efficacy of vismodegib 150 mg/day for the treatment of BCC in 41 patients with basal-cell nevus syndrome. After a mean of 8 months (range 1-15), the mean per-patient rate of new surgically eligible BCCs was significantly ($p < 0.001$) lower with vismodegib than placebo (2 vs 29 cases/year). Vismodegib also significantly ($p = 0.003$) reduced the size of existing clinically significant BCCs (mean percentage change from baseline in the sum of the longest diameter -65% vs -11% with placebo). In no case was there evidence of existing tumour progression during treatment with vismodegib. Hedgehog target-gene expression by BCCs measured after 1 month of vismodegib therapy showed a reduction of 90% ($p < 0.001$). Adverse events resulted in treatment discontinuation in 54% of patients; most adverse events were mild to moderate and included hair loss, muscle cramps, dysgeusia and weight loss.

Comment: Gorlin syndrome is a devastating, albeit rare disease. Hedgehog inhibitors clearly have a clinical role to play in the management of these patients and the efficacy of vismodegib looks promising.

Checklist for managing advanced BCC

1. Referral to Cutaneous Surgical Oncologist or Head and Neck surgeon
2. Clinical, pathological and radiological assessment
3. Management via multidisciplinary team
4. Utilisation of multi-modality treatments including surgery, radiation and hedgehog inhibitors.

Case reports of three patients with advanced BCC

Case 1: A 65-year-old woman presented with a history of having hundreds of basal cell carcinomas excised from her body, head and neck (see **Figure 3**). Forty years ago she had had problems with odontogenic cysts causing pain that needed surgical correction in keeping with a diagnosis of Gorlin Syndrome. The patient's father and sister had a similar history of medical problems. On examination she had frontal bossing, plantar pits and multiple BCCs scattered all over her body in both sun exposed and non-sun exposed areas. Many were very small; others were larger measuring up to 1 cm in diameter. She had extensive scars all over her face, scalp, trunk, arms and legs from prior surgical excisions of BCCs. Many years ago she developed BCC that extended into the left orbit. Extensive Mohs surgery was undertaken to remove the tumour; however, it was not technically possible to remove it completely. Residual tumour in the orbit was treated with adjuvant radiotherapy. She also had prior major operations on the nose and paranasal sinuses to remove locally aggressive invasive BCC. These operations necessitated a prosthesis for the glabella and nasal regions and a left eye prosthesis. Based on the extensive nature of her condition, and locally aggressive BCC, a decision was made to commence vismodegib at a dose of 150 mg per day.

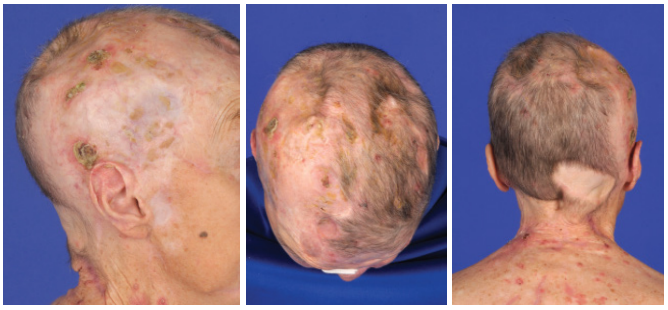

Figure 3: A 65-year-old woman with Gorlin syndrome and multiple BCCs on her head and neck.

Case 2: A 35-year-old woman had a lesion on her scalp for many years, which was treated as dermatitis with no histological diagnosis. As the lesion grew and did not respond to steroid creams the young lady sought a second opinion. A biopsy was taken immediately, which showed a morphoeiform BCC (see **Figure 4**). A radical excision was performed with 10 mm margins down to the periosteum and this was temporarily reconstructed with a split skin graft. Pathology showed a completely excised morphoeiform BCC with greater than 5 mm clear margins. The patient was referred on to a plastic surgeon for tissue expanders and scalp rotation flap reconstruction.

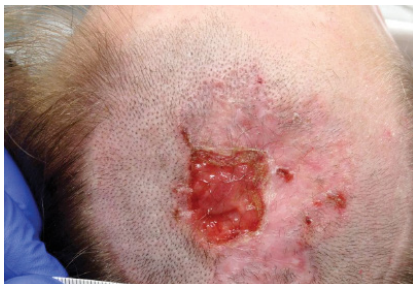

Figure 4: A 35-year-old woman with a morphoeiform BCC on her scalp. This lesion was subsequently completely excised.

Case 3: A reclusive 65-year-old woman presented to clinic with a neglected scalp BCC. She was severely anaemic as the tumour bled at the slightest trauma. Pathology showed a BCC. CT staging revealed invasion of the cranium and underling cerebrum. She had no neurological deficits. The multidisciplinary team concluded that the tumour was inoperable and the radiation oncologist felt radiotherapy was futile. Vismodegib was started, resulting in rapid shrinkage of the tumour, and, amazingly, regrowth of cranial bone under the tumour. While only a partial response was achieved, the patient was adequately palliated for 9 months until progression to unconsciousness and death.

Concluding remarks and take home messages

We are entering a new era of targeted therapy for advanced BCC. The hope is that new developments will lead to safer, better-tolerated and effective medical treatments that will stabilise tumours and shrink them enough to enable curative surgery. It is likely that long-term drug therapy will be required for some patients. Multidisciplinary patient care is essential, particularly for patients with basal cell naevus syndrome and advanced BCCs.

A significant number of patients discontinue vismodegib therapy due to adverse effects, such as muscle cramps. While most of the adverse effects are mild to moderate and resolve upon discontinuation of the agent, vismodegib should be used with caution in women of childbearing age. Vismodegib may impair fertility and may cause embryo-fetal death or severe birth defects when administered in pregnant women.[25] Male patients are also advised to use appropriate contraceptive measures.

As the safety data of targeted therapies matures, we are moving to using these drugs in the neoadjuvant and adjuvant setting. If the side effects can be tolerated, then this is where surgical oncologists believe the greatest increases in overall survival will occur. Phase III trials are warranted to ascertain the long-term safety and efficacy of these agents.

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