Chapter 11
Topical Treatment of Skin Cancers and the Risks of 'Fighting Fire with Fire'

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Background

While surgical excision remains the mainstay of managing non-melanoma skin cancers, many authors have published successful topical or non-surgical options for treating non-melanoma skin cancers [1]. A recent review article compared the efficacy of topical 5-fluorouracil (5FU), topical imiquimod 5 % cream, intralesional 5FU, intralesional methotrexate (MTX), intralesional bleomycin, and intralesional interferon (IFN) for non-melanoma skin cancers [2].

5-fluorouracil has been around since the 1960s and it acts as an antimetabolite, interfering with DNA synthesis [3]. Imiquimod was then approved in 1997 for the treatment of genital warts and this nucleoside analogue will be discussed in greater detail in this case study. Diclofenac, an NSAID, acts

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by down regulating cyclooxygenase enzymes and increasing apoptosis. Topical diclofenac 3 % gel in 2.5 % hyaluronic acid (which delivers and retains the drug in the epidermis) is approved by the US Food and Drug Administration for the treatment of actinic keratosis. Diclofenac acts by reducing dysplastic keratinocytes in cancerous lesions, including AKs, by stimulating programmed cell death via COX-2 inhibition and may inhibit angiogenesis [4]. Ingenol mebutate, a macrocyclic diterpene-ester, is a recently marketed natural extract from Euphorbia peplus. The sap of this plant has long been used as a topical traditional remedy for common skin lesions, such as warts and neoplasms – and has a dual action: the induction of rapid cellular death in the treated area, followed by an inflammatory response within days of application, able to eliminate residual cells [5, 6]. Other emerging topical therapies include Piroxicam, Betulinic acid, Resiquimod or calcium/potassium dobesilate [7].

Imiquimod belongs to the class of 1H-imidazo-[4,5-c] quinolones – a group of drugs that was originally developed as nucleoside analogues with the aim to find new potential antiviral agents [8]. Indeed, Imiquimod was first released as treatment for genital warts before its actions against skin cancer were studied. Imiquimod is a relatively small sized molecule (Mr = 240.3). The molecular size, as well as it being hydrophobic, allow it to penetrate the skin epidermal barrier and therefore make it suitable for topical formulations [9]. In many studies Imiquimod has shown itself effective against skin cancers and pre-cancerous lesions, especially basal cell cancers and actinic keratosis [10, 11]. There have also been reports of Imiquimod being used as topical treatment against cutaneous metastases of melanoma and some authors have reported its use as first-line therapy against melanoma in situ [12, 13].

We report a case of an invasive malignant melanoma arising de novo at the specific site of application of Imiquimod (Aldara™ Cream 5 %) for a biopsy-proven superficial BCC. Therefore while Imiquimod has added to our topical armamentarium with respect to skin cancer management,

care must be exercised in prescribing this treatment and it is especially important to follow-up patients regularly.

In recent years, Imiquimod has become widely used as topical treatment for skin cancers. Its tumouricidal activity is based mainly on activating the innate immune system, for which dendritic cells seem primarily responsible. These dendritic cells initiate a tumour-directed cellular immune response [14]. Researchers have noted that dendritic cells respond to much lower concentrations of imiquimod than many other cell types [15]. At higher, but therapeutically relevant concentrations, Imiquimod exerts some pro-apoptotic activity against tumour cells.

Toll-like Receptors (TLR), especially TLR 7 and TLR 8 are important receptors of this innate immune system. It is generally felt that Imiquimod is an agonist of TLRs 7 and 8 [16]. However, while these innate immunity-related actions are well known, there are some findings which cannot be explained easily by TLR-dependent mechanisms – for example Imidazoquinolines like Imiquimod can stimulate the proliferation of B cells in vitro, even in the absence of other immunocytes [17].

However, in recent times Imiquimod has been shown to paradoxically cause tumors, or more precisely tumors have been reported at bodily sites of treatment. In 2006, two cases of invasive SCC arising after treatment of squamous carcinoma-in-situ with 5 % imiquimod cream were reported [18]. While the exact mechanism of tumor-induction by Imiquimod is unclear, presumably it is due to its local alteration and stimulation of an exuberant immune response. Keratoacanthomas have also been reported as arising after treatment with topical Imiquimod [19].

Some authors have used Imiquimod ‘off-label’ and have reported resolution of primary melanoma-in-situ (lentigo maligna) and recurrent lentigo maligna with 5 % Imiquimod cream [20, 21]. Some authors have also noted Imiquimod inhibits melanoma development by promoting pDC cytotoxic functions and impeding tumor vascularization [22], and there have been many reports where researchers have used Imiquimod topically to treat melanoma metastases [23].

In this context, we believe our case report to be noteworthy and worth reporting as in our patient, 5 % Imiquimod was used as topical treatment for a biopsy-proven BCC and the patient ended up developing an invasive melanoma over the site. While, as discussed earlier, keratoacanthomas have been known to develop at the precise site of a treated superficial BCC -- an invasive melanoma arising in this situation is unusual and to our knowledge, not been reported previously. In the case of our patient, the area on his back was marked for treatment, which was then undertaken for 6 weeks with 5 % Imiquimod (Aldara™ cream) with two treatment-free days each week as per usual protocol. At 8 weeks, when the patient was reviewed, he had a complete clearance of the BCC noted earlier; however, he had developed a new pigmented lesion over the site of topical application of Imiquimod which both on dermoscopy and clinical examination was suspicious for melanoma. Histopathological analysis has confirmed this to be an invasive melanoma. While many authors are advocating the use of Imiquimod for melanoma, we would like to present this case, where an invasive melanoma has arisen at the precise site of application of Imiquimod (Aldara™ Cream 5 %) for a superficial BCC.

Case History

A 60 year old white male presented to our skin cancer center with superficial BCC areas on his mid back. Given he had three to four sBCCs present within a 10 cm area, it was decided to treat these lesions topically using Imiquimod (Aldara™ Cream 5%). A biopsy was undertaken initially to confirm sBCC. We used the standard protocol recommended by the manufacturers i.e., the cream was applied to the affected area once a day at bedtime for five consecutive days per week (Monday to Friday) for 6 weeks. The patient was reviewed at 8 weeks and it was noted that the patient had developed a de novo pigmented lesion over the site

of application of Imiquimod. Given the clinical impression was that of a malignant melanoma, this lesion was excised. The approximate area within which the treatment was undertaken is shown in Fig. 11.1. The image clearly shows the de novo pigmented lesion arising within the field of treatment.

HISTOPATHOLOGY
Specimen:
EXCISION SKIN LESION BACK

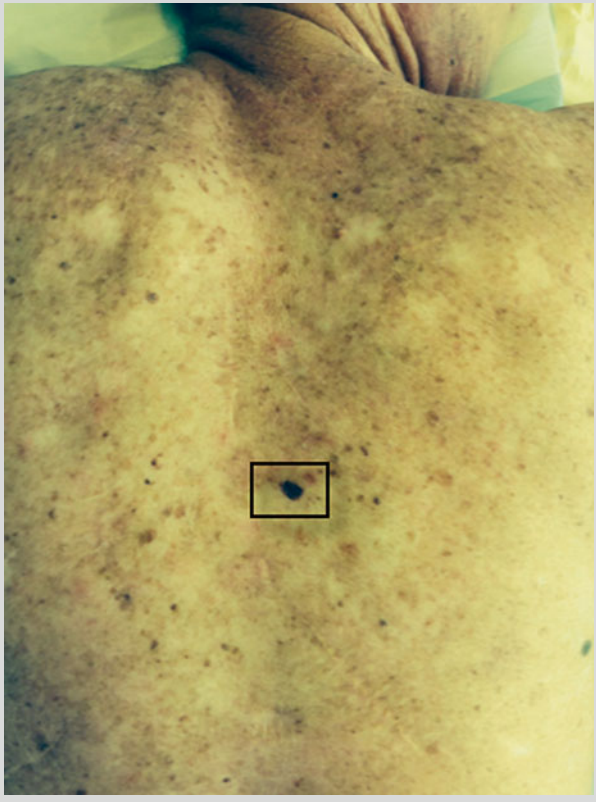

FIGURE 11.1 *Box* shows area of application of Aldara for s BCC

Gross Description:
The specimen consists of a skin ellipse 15 mm × 10 mm ×5 mm bearing a central dark brown irregular lesion approximately 9 mm ×7 mm. 3r 6l
Microscopy:
SYNOPTIC REPORT FOR INVASIVE MALIGNANT MELANOMA
SUMMARY DIAGNOSIS:
INVASIVE MALIGNANT MELANOMA, CLARK LEVEL 3, BRESLOW THICKNESS 0.8 MM, CLOSEST SIDE MARGIN 1.25 MM. OTHER SIDE MARGIN 2.5 MM. CLOSEST DEEP MARGIN 4.1 MM.
Tumor Type: Invasive malignant melanoma arising in an area of melanoma in-situ
Ulceration: Nil
Tumor Infiltrating Lymphocytes: Mild
Regression: Nil
Lymphovascular Invasion: Nil
Perineural Spread/Neurotropism: Nil
Mitotic Rate: 0 per sq mm
Microscopic Satellitosis: Nil
Radial Margin of Excision: Closest side margin 1.25 mm. Other side margin 2.5 mm.
Deep Margin: Closest deep margin 4.1 mm.
Associated Nevus: Nil
The case has also been viewed by Dr F.O. who agrees with the diagnosis. Reported By: Dr. H T. Anatomical Pathologist
Office Data: nl/lm/as
Ordered by: SHARAD PAUL
Observation date: 16-Aug-2014

Histological report is detailed above – which reveals a non-ulcerated tumor of 0.8 mm Breslow thickness, Clark Level 3 invasive melanoma, arising in an area of melanoma-in-situ. A compete skin and lymph node

examination revealed no other abnormalities. After reviewing the histopathology, this patient was managed with a wide local excision with 1 cm margins in keeping with standard guidelines for management of Stage 1A melanoma of skin.

Discussion

Dermatologists, surgeons and skin cancer doctors are faced with an epidemic of skin cancer in Australia and New Zealand. Actinic Keratoses and Squamous Cell Carcinomas share multiple genomic mutations that suggest common origins [24]. It is well known that increases in p53 mutations are seen in sun-damaged skin, AK, and SCC [25]. Given the need to reduce unnecessary surgery as well as associated costs, researchers have turned their focus to topical applications to deal with skin cancer. Some prevailing topical treatments include 5-fluorouracil, diclofenac sodium, topical photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) Imiquimod and few others discussed earlier.

Given the clinical interest for TLR agonists in metastatic melanoma and indeed skin cancer, it is essential to determine the mechanism of action of Imidazoquinolines such as Imiquimod. Imiquimod has many cellular effects that stimulate Th-1 innate immunity. The drug's effects is mediated after binding to TLR 7, the receptor that is found on dendritic cells and monocytes. TLR-7 is also involved in regulation of cellular apoptosis. Following Imiquimod treatment, 'immunologic memory' is established, and this differentiates this drug from other topical agents [26]. From Imiquimod's early use for genital warts, it was noted that a significant proportion of patients ended up 'non-responders.'

Some authors have been enthusiastic about the 'field clearance' effects of Imiquimod – the concept of lymphatic transport of immune cells and factors with subsequent immu-

nological curing of tumors, not only in the treated area, but also those in 'field' around the treatment site. Akkilic-Materna and colleagues suggest that their observations on the actions of Imiquimod support the concept of lymphatic transport of immune cells and factors with subsequent immunological curing of tumors, not only in the treated area, but also those in the area between the imiquimod application site and the regional lymph nodes – what they term the "lymphatic field clearance" [27] Others have raised concerns about recurrence after Imiquimod use and whether Imiquimod may select more aggressive tumor cells or may just convey a natural course of tumor recurrence as we see with other treatment modalities [28].

Recurrence aside, there have been several reports of Imiquimod triggering keratoacanthomas and indeed infiltrating or aggressive SCC [29]. There has been also a report of a pulmonary embolism occurring after Imiquimod use [30]. The exact mechanism of inducing tumors remains unknown, although the exuberant immunological response is blamed – a sort of fighting 'fire with fire' when utilizing immune-modulating agents that stimulate apoptosis.

There are now several reports that have supported the use of Imiquimod in amelanotic lentigo maligna [31], peri-ocular lentigo maligna [32], facial lentigo maligna [33] and even in large lentigo malignas prior to staged excision [34]. However given the reports of Imiquimod causing aggressive SCC, or in our case, an invasive melanoma arising at the site of topical Imiquimod use, I would like to stress the importance of follow up after Imiquimod use.

Schön and others have discussed that more pleiotrophic antitumoral responses have to be considered when studying imidazoquinolines. They demonstrated that imiquimod is able to act not only as synthetic adjuvant but also as direct inducer of apoptosis for melanoma cells in vitro and in vivo. They concluded that cell death was exerted by apoptosis rather than necrosis and that this pro-apoptotic signal is selectively activated in melanoma cells, but *not* in primary human melanocytes [35].

Of course, in this case report, it is impossible to prove causal effect – other than to say that the melanoma arose at the exact Imiquimod treatment site. However, I believe it is prudent, given this case-study, to undertake ongoing surveillance of patients after Imiquimod use.

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