

EDUCATIONAL REVIEW ARTICLE

Current Trends and Controversies in Cutaneous Melanoma

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Introduction

The progressive rise of melanoma in Scotland continues unabated, and globally, incidence rates of cutaneous melanoma are increasing more rapidly than any other cancer.¹ Treatment of metastatic melanoma remains highly unsatisfactory, despite significant research investment and heightened public and professional awareness of the condition. Cutaneous melanoma is thus a serious and growing public health issue.

In this article we aim to provide an overview of current areas of interest and highlight some controversies in melanoma research and management.

Incidence and Mortality

Incidence rates for cutaneous melanoma have more than doubled over the last twenty years in the UK.² Rates in Scottish men have trebled in 25 years.³ Similar increases have been seen in most Caucasian populations. In Scotland cutaneous melanoma is the ninth most common malignant tumour in men and the seventh most common in women.⁴ In the USA in 1935 one in 1500 people were diagnosed with melanoma, by 2010 it is predicted to be one in 50.⁵ Cutaneous melanoma is predominantly a disease of the Caucasian population. In the USA it is approximately ten times less prevalent in the black population and in this population incidence has remained stable for 20-30 years.⁵

Mortality rates have increased along with incidence rates suggesting that at least part of the increased incidence is due to aggressive invasive disease. In the UK mortality figures for men have increased from 1.2/100,000 in the early 1970's to 3.1/100,000 in 2006, ie more than doubling (1.3/100,000 in early 1970's and 2.0/100,000 2006 for women).⁶ Annually in the UK there are over 8,000 cases of melanoma diagnosed and approximately 1700 deaths.⁶ Melanoma is one of the most common causes of cancer death in 20 to 35 year olds.⁷

Sunlight and Melanoma

The aetiology of melanoma is complex. Most authors accept that ultraviolet (UV) light plays an important role in causation. Particular risks include sunburn, especially in early life. This is demonstrated in migration studies which find that earlier or longer exposure in areas of higher natural sunlight lead to increased melanoma formation⁸ and in human xenograft studies.⁵ There are a number of studies demonstrating increase in incidence of melanoma with decreasing latitudes and thus higher average UV levels.^{9,10} Case control studies have demonstrated positive associations with intermittent exposure, childhood sunburn and lifetime sunburn.^{11,12} Patients with xeroderma pigmentosum, a condition in which DNA repair of UV damage is impaired, have up to an 8,000 times increased

risk of melanoma further indicating a key role for UV induced damage. In addition to this it is known that UVB can directly damage DNA and a number of signature UVB mutations are found in melanoma. UV (mainly UVB) exposure in animal models has been shown to induce melanoma in a variety of conditions. The role of UVA in mutagenesis is less well understood.

Although the evidence for the role of sunlight in causation of melanoma is substantial, there are a number of unanswered questions. Melanoma occurs at sites other than the skin (although much less commonly). Acral melanoma is a form of cutaneous melanoma, which occurs principally on the soles of the feet (and is more common in non-caucasians). These facts indicate that UV exposure alone is probably only part of a complex interaction of environmental and host susceptibility factors responsible for the development of melanoma.

Since the suggestion of a link between melanoma and sun exposure, there have been attempts throughout the world to reduce incidence of melanoma by attempting to modify sun exposure behaviour. This is a long term strategy as the lag time between exposure and development of melanoma may be many decades. Therefore it is perhaps not unexpected that prevention programmes to date have not resulted in dramatic reductions in incidence. There is some evidence that prevention programmes in Queensland have resulted in a reduced incidence of melanoma in younger age groups (under 35).²

Modification of sun exposure behaviour is challenging. Sun exposure habits in Britain have changed considerably in the last 30-40 years. In 1971, British citizens took 4.2 million trips abroad, in 1994 this figure was 27 million.¹³ In addition to this, tanning is still popular with 70% of 16-24 year olds seeking a tan whilst on holiday.¹³ Thus as a long term strategy there is clear need for education aimed at prevention. In the UK the principle awareness programme is the "Sunsmart" campaign run by Cancer Research UK and commissioned by the Health Department in 2003. The benefits of this programme are likely to take some time to become apparent, and may be obscured by continuing excessive sun exposure opportunities and behaviours.

The role of vitamin D deficiency in a number of conditions is beginning to emerge, and indeed vitamin D may help prevent metastasis from primary melanoma. There is therefore, concern amongst some that sun protection may potentially be harmful. Further studies are required into the health benefits of UV induced vitamin D synthesis. We would suggest that avoidance of burning and excessive tanning is important, and that great caution should be applied when providing public health messages, as there is considerable scope for confusion. There is a role for oral vitamin D supplements in those receiving low levels of UVB, particularly darker skinned individuals during winter months.

Melanoma Genetics

Around 85% of cutaneous melanomas are sporadic. The CDKN2A, CDKN4 group of genes are of most importance in familial melanoma, and genes controlling types of pigmentation are also important. New technologies, such as comparative genomic hybridisation and genome wide association studies have allowed insight into key cell signalling pathways which offer the possibility of new treatments. The control of cell proliferation, growth and cell death is highly sophisticated and there are many cellular pathways which interact at various levels. This cross-talk between pathways further complicates understanding of these processes and potentially creates therapeutic obstacles.

There has been extensive work into putative regulatory pathways in melanoma and some key areas are now sufficiently well understood to have provided new experimental clinical therapies. Four pathway systems are of particular interest: mitogen-activated protein kinase pathway (MAPK), a cell cycle regulator, the Bcl-2 family of apoptosis related proteins, PTEN, a tumour suppressor and c-Kit, which is an important tyrosine kinase pathway.

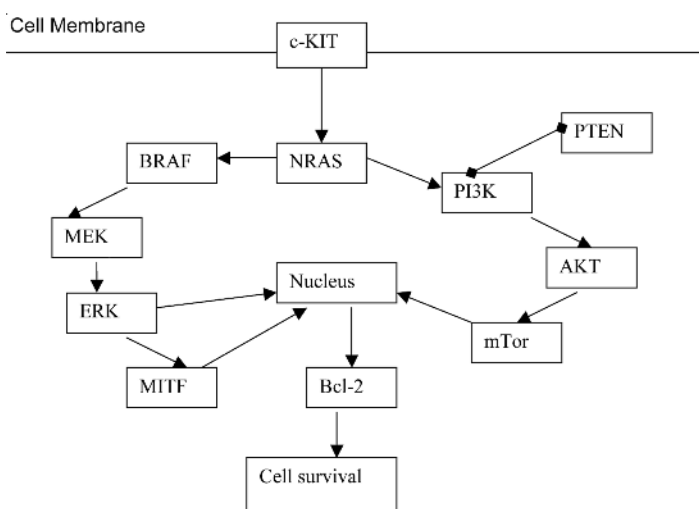
The MAPK pathway (Ras/Raf/Mek/Erk) is found in numerous cell types and is an important regulator of cell growth and survival (see Figure 1). Mutations resulting in activation of the MAPK pathway are found in as many as 90% of melanomas, and usually occur in the oncogenes BRAF and NRAS.¹⁴ Aberrant signalling through the MAPK pathway is thus implicated in melanoma development and progression.

NRAS can activate the MAPK pathway or the PI3K pathway (necessary for survival signals). Mutations may be more common in chronically sun-exposed sites.¹⁵ NRAS mutations are also common in benign naevi¹⁶ and so NRAS seems to stimulate melanocyte proliferation but how this becomes malignant transformation remains to be elucidated. NRAS can be inhibited by farnesyl transferase inhibitors, drugs which inhibit small GTP binding proteins central to cell cycling.

BRAF is also found in many benign lesions¹⁷ and it is suggested that a concomitant p53 deficiency may also be required to result in tumourigenesis.¹⁴ BRAF plays an important role in signal transduction and downstream effectors include MEK (which influences Bcl activity) and ERK (which stimulates proliferation and MITF). BRAF is thus also a target for inhibition eg sorafenib which has been developed as a BRAF inhibitor. Early trials have not shown significant efficacy for sorafenib as monotherapy in melanoma.¹⁸ Results with sorafenib in combination with chemotherapy agents, for example, carboplatin and paclitaxel have been more hopeful.¹⁴ Sorafenib may also act by inhibiting angiogenesis.¹⁹ There is recent evidence that sorafenib can activate glycogen synthase kinase-3β (GSK-3β) and that this reduces sorafenib antitumour activity,²⁰ thus it may be possible to increase efficacy by inhibiting this process with a GSK-3β inhibitor. This is another example of the complex cross-talk which occurs in cell control and melanoma pathways. It is hoped that more specific anti-BRAF inhibitors currently entering trials may be more efficacious.

Dysfunctional apoptosis may be an important reason underlying chemoresistance in melanoma. The Bcl-2 family are believed to be a key controlling influence over melanoma apoptosis. This family consists of a number of pro-apoptotic and anti-apoptotic genes. Normal control of apoptosis requires an equilibrium between pro-apoptotic (eg BAX, BAK, NOXA) and anti-apoptotic members (eg Bcl-2, Bcl-xL, Mcl-1).²¹ Oblimersen is an oligonucleotide which has been shown to cleave Bcl-2 mRNA and suppress activity. In a large clinical trial with dacarbazine, it demonstrated some therapeutic activity to improve melanoma response rate and with possible prolonged survival.²² Mcl-1 (anti-apoptotic) is inhibited by obatoclax which is currently in phase II clinical trials for leukaemia, lymphoma and some solid tumour malignancies. Gossypol is an inhibitor of Mcl-1/Bcl-2/Bcl-xL and is in phase II trials for a number of other malignancies. Gossypol has given some promising results in mouse melanoma models when combined with bortezomib (a proteasome inhibitor which induces anti-apoptotic Mcl-1 and pro-apoptotic NOXA).¹⁴

Figure 1
Overview of the MAPK pathway and some key interactions



Overview of the MAPK pathway and some key interactions

◆ —◆ Inhibitory
 —> Stimulatory

The tumour suppressor gene, PTEN has multiple activities including cell adhesion, migration and apoptosis. PTEN alterations have been demonstrated in a variety of human cancers. It strongly influences and reduces activity in the PI3K pathway (which is activated in up to 60% of melanomas and which results in cell proliferation).²³ PTEN loss increases activity in this pathway. PTEN mutations have been found in melanomas and in metastases.¹⁵ Restoration of PTEN to PTEN-deficient melanoma cells has been shown to reduce metastases and tumorigenicity.²⁴ It is thought epigenetic events may also reduce PTEN activity without a mutation being present in PTEN itself.²⁵ In tumours with PTEN reduction or loss, at present the downstream Phosphoinositide 3-kinase (PI3K) pathway offers a target.

PI3K signals through Akt3 (V-akt murine thymoma viral oncogene homolog 3). When Akt3 is activated a number of enzymatic substrates are released which contribute to tumour proliferation and survival eg mTOR. Inhibition of Akt3 alone at present is not possible. Therefore attempts to modulate some of the downstream effectors have been made. Currently there are several mTOR inhibitors. In the small clinical studies carried out so far responses have not demonstrated significant efficacy.¹⁴ The results of a study underway combining sorafenib (MAPK pathway inhibition) and CCL-779 (PI3K pathway inhibition) are awaited. It may be that combination approaches blocking multiple pathways will be required, as tumours in vivo often can survive using default or escape pathways.

C-Kit encodes the stem cell factor receptor tyrosine kinase found on melanocytes (and multiple other cells). C-Kit regulates the MAPK pathway. Mutations in c-Kit are heterogeneous and seem to occur more frequently in acral and mucous membrane melanoma.^{26,27} Imatinib mesylate is an oral tyrosine kinase receptor inhibitor. It has demonstrated efficacious c-Kit inhibition in gastrointestinal stromal tumours and is the only licenced adjuvant for a rare skin tumour, dermatofibrosarcoma protuberans. A phase II trial of 26 patients with metastatic melanoma revealed no response; however the c-Kit status of the tumours was not investigated.²⁸ There is a trial underway to investigate the response in metastatic acral and mucosal melanomas. Although effective use of this drug, if proven, would only apply to 1% of all melanomas, it gives hope to clinicians looking for successful translational research in melanoma.

Epigenetics

The study of epigenetic phenomena is a potentially important direction for future melanoma therapies. There are two main types of epigenetic event, alterations to the packaging of DNA or alterations to DNA itself. The most researched changes so far are in the methylation of DNA which can modify gene expression. So far in melanoma there are at least 50 identified genes shown to be silenced during melanoma development by hypermethylation of promoter sequences.²⁹ Silenced genes may include tumour suppressor genes. There are a number of other complex and poorly understood mechanisms which may result in epigenetic events. It seems likely that this area of research will become increasingly important as understanding improves and may provide therapeutic targets.

Assessment and Monitoring of Pigmented Lesions

Thinner melanoma has a better prognosis and earlier detection of these lesions is likely to provide a reduction in mortality earlier

than prevention programmes. The key to earlier diagnosis is public and clinician awareness. In practice there is a difficult balance between not missing melanoma and not excising every pigmented lesion seen. Thus any device or system which can assist in the decision making process is potentially useful. There are a number of advances in the field of diagnosis.

An important technical advance is the hand held dermoscope, which resembles an otoscope and requires oil or gel to be placed on the lens to reduce diffraction. A newer device uses cross-polarisation to achieve a similar effect and is thus more practical to use.

contact dermoscopy



- immersion -light emitting diode using liquid interface

non-contact dermoscopy



- dermoscope with cross polarization lens

This allows a combination of illumination and magnification which enables the skin surface to be assessed in close up and allows the subsurface anatomic structures of the epidermis and papillary dermis to be visualised. Dermoscopy is a skill and requires training, practice and an appreciation of its limitations. It should only therefore be performed by those with sufficient training and supervision. It depends on the recognition of pigment patterns which have been shown to have a high sensitivity and specificity in detecting melanoma. Dermoscopy has been found to improve sensitivity and specificity of diagnosis compared with the naked eye in several meta analyses.³⁰ In a retrospective study, Carli et al demonstrated improvement in the benign/malignant excision ratio from 18:1 pre dermoscopy to 4:1.³¹ Dermoscopy may be combined with standardised clinical photography to aid follow up. A progression from this has been computerised analysis of digital images. These systems are expensive and as yet have not replaced clinical assessment in the management of pigmented

lesions. These "mole map" systems are becoming more widely available in the private sector with notably some supermarkets now offering this service, but clinical decisions still require to be taken by experienced clinicians. The role of these systems is therefore debatable. In the future we are likely to see more sophisticated versions of these computerised scanning devices.

A number of other imaging technologies are becoming available eg reflectance-mode confocal microscopy, but many of these remain research tools at present.

Surgical Management and the Sentinel Node Debate

The management of suspected melanoma is surgical excision. Suspicious lesions should be referred to an appropriate specialist. The current SIGN guidelines on cutaneous melanoma provide a well researched and clear pathway for management of melanoma and are readily available³² (www.sign.ac.uk). Skin cancer surgery is performed by a range of specialties including dermatology, plastic surgery, ENT, ophthalmology and maxillo-facial surgery.

Sentinel lymph node biopsy (SLNB) forms part of SIGN and AJCC (American Joint Committee on Cancer) recommendations. However, despite being well established in clinical practice the procedure continues to polarise opinion.

The involvement of lymph nodes is a key predictor of outcome in melanoma. The sentinel node is the first node encountered in the regional node basin draining from a lesion. Locating the node involves use of a blue dye, radiocolloid and a hand held gamma probe. Thus it requires significant technical and surgical expertise. The technique was first developed in the late 1970's and became well established in the early 1990's.

For intermediate and poor prognosis primary tumours, many centres will consider sentinel lymph node biopsy.³² This is prompted by the fact that 15-20% of intermediate thickness lesions will have microscopic metastases at the time of presentation.³³ Currently, it is recommended that a positive SLNB is followed by a radical node dissection, a negative sentinel node means no complete lymph node dissection (CLND). A study of the effects of observation of positive sentinel node basin is underway.

The procedure provides more accurate prognostic information than Breslow thickness alone^{34,35} but no randomised controlled trial has yet demonstrated a survival benefit for elective lymph node dissection.³⁶ It is argued however that there is little real patient benefit from the slight improvement in accuracy of prognosis in most cases. There is also the possibility of a false negative result (more worrying) and of false positives. The question of survival benefit has, as yet perhaps not been fully answered and longer term follow up results are awaited which may further illuminate this issue.

Detractors also argue that the hypothesis of lymphatic spread on which the technique is based may be flawed and, for example, takes no account of the possibility of haematogenous spread. Some suggest that micrometastases may not necessarily progress to clinical metastases, therefore questioning the role of SLNB.

Thus, in many quarters the debate regarding SLNB continues. Ongoing research may help to clarify some areas of contention. SLNB is an entry criteria for many melanoma clinical trials and so, whilst SLNB remains controversial in some quarters, it is likely to remain an important and valuable technique until it is surpassed by a technological breakthrough.

Chemotherapy and Immunotherapy

The prognosis for metastatic melanoma remains poor with five year survival for treated patients between 3-14%.³⁷ Dacarbazine (DTIC) remains the standard chemotherapy agent of choice, despite low response rates of only up to 15%.³⁸ An oral formulation of DTIC, temozolamide, appears to be at least as efficacious as DTIC³⁹ and it may have promise in treating cerebral metastases as it has improved cerebral bioavailability. There have been numerous studies of various chemotherapy agents and combinations of agents but so far there are none with clear benefit over DTIC. Thus, especially when compared to other cancers, chemotherapy remains very disappointing for cutaneous melanoma.

The role of the immune system in controlling melanoma is clearly important and is illustrated by the fact that melanoma may, rarely, spontaneously regress. The presence of tumour antigen specific antibodies and tumour specific cytotoxic T cells in peripheral blood provides further good evidence of immunomodulation. The CD8 T-cell response appears important with presence of infiltrating CD8 cells in tumours correlating with improved prognosis.⁴⁰ The two most studied treatments so far are interferon-alpha (IFN- α) and interleukin 2 (IL-2).

IFN- α has been extensively studied and after promising early results subsequent analyses have been less encouraging. High dose regimens are associated with considerable toxicity.

A recent meta-analysis has demonstrated an overall survival benefit of 3% when compared to no treatment.⁴¹ Pegylated interferon aroused interest as it may be given sub-cutaneously and may be less toxic. A recent study demonstrated improved relapse free survival but no overall survival benefit compared to observation.⁴² After more than a decade of well designed large scale adjuvant studies with interferon, it appears that the overall clinical benefit is slight, at best, and energies might now be better placed investigating newer therapies.

It is thought that IL-2 may exert anti-tumour activity by increasing activity of immune cells and cytotoxic cytokines. Clinical studies have however demonstrated low response rates.⁴³ Combination with IFN- α has not given survival benefit, and IL-2 is associated with significant toxicity.⁴⁰ Combination of IL-2 and chemotherapy (biochemotherapy) has improved response rates but not survival, and increases toxicity. New approaches may prove more fruitful in the future eg an antibody to CTLA4, ipilimumab, theoretically reinstalls the anti tumour immune response and is now in clinical trials.

Attempts at various vaccination strategies such as immunisation with melanoma associated peptides, although initially very exciting, have been disappointing and inconsistent.

Summary

Cutaneous melanoma is an emerging and complex health problem. Management may require the expertise of multiple specialties. Although the outlook for advanced disease remains very poor, there are major advances in the understanding of melanoma. The heterogeneous nature of melanoma is more apparent and as such it is becoming evident that in the future we will probably utilise multiple approaches to treat disease and treatments may be tailored to individual needs. We can anticipate that as technology improves and information continues to accrue, our increased understanding of melanoma will lead to improved treatment of advanced disease.

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