

Treatments for melanoma are advancing, with two drugs recently gaining approval. Its rising incidence means general nurses are likely to see patients with the condition

Causes and treatment of malignant melanoma

In this article...

- › Causes and prevalence of malignant melanoma
- › Treatment methods for different stages
- › The role of nurses in assessment and during treatment

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Abstract Hodgetts J (2013) Causes and treatment of malignant melanoma. *Nursing Times*; 109: 28, 12-15.

The incidence of melanoma is rising faster than any other malignancy. As more cases are diagnosed, it is likely that general nurses will come into contact with melanoma patients. This article discusses the identification, treatment and prognosis for this group of patients.

Cutaneous melanoma is the most aggressive form of all skin cancers. Worldwide, it is expected that over 132,000 people will be diagnosed with the disease each year and more than 37,000 people are expected to die of it annually (World Health Organization, 2013).

The incidence of melanoma is rising faster than that of any other malignancy, and it is now the sixth most common cancer in the UK (Cancer Research UK, 2011).

While the majority of patients will be cured with surgery, 20% of cases will be fatal. In the past 40 years, the median survival time for patients with metastatic or unresectable melanoma has been short – approximately only 6-9 months from the time of diagnosis. Only 10-15% of patients with this type of melanoma will be alive after three years (Balch et al, 2009).

Melanoma is the second most common cancer in the 15-34 age group and studies suggest that more years of life and lifetime earnings are lost to it than to any other cancer (Mouawad et al, 2010).

Much has changed in the treatment

landscape of melanoma over the past year. Two new treatments have been given regulatory approval, and have demonstrated their ability to significantly increase survival rates in well-controlled phase III trials (Chapman et al, 2011).

Pathophysiology

Malignant melanoma is a tumour that arises from cutaneous melanocytes in the basal layer of the epidermis (Fig 1). These skin cells produce the protective pigment melanin, which gives a tan or brown colour to the skin and helps protect the deeper layers of the skin from the harmful effects of the sun.

A number of molecular alterations have been identified in melanoma. Mutations, affecting genes responsible for proliferation (cell division), differentiation (cells changing) and apoptosis (cell death), are generally believed to transform normal cells to cancer cells and lead to angiogenesis (the formation of new blood vessels), tumour invasion and metastases. Genetic analysis of melanoma tumours and precancerous lesions point to alterations in genes involved in cell signalling (the process by which a cell is instructed to divide) and cell cycle regulation pathways, which cells go through before they divide (Platz et al, 2008). One of the above mentioned treatments specifically targets one of these genetic abnormalities – the BRAF gene – and is discussed later in the article.

Causes of melanoma

Sun exposure, in the form of UVB and UVA light, is a potential cause of melanoma. Evidence suggests that several episodes of sunburn due to intense, intermittent sun exposure significantly increase the risk of

5 key points

1 Malignant melanoma arises from the cutaneous melanocytes in the basal layer of the epidermis

2 The incidence of melanoma is rising faster than that of any other malignancy, making it the sixth commonest cancer in the UK

3 Sun exposure and sun bed use are thought to increase risks

4 Primary melanomas should be treated with an excision biopsy, followed by the excision of a good margin of healthy tissue from around the tumour

5 Around 20% of cases are fatal, and treatment for later-stage melanoma is usually palliative, so education on the risks is paramount



“Be proud of the nursing profession”

Angela Wallace ▶ p24

developing a melanoma later in life (Gandini et al, 2005).

There is emerging evidence that exposure to ultraviolet radiation through the use of sun beds also increases the risk of melanoma. In 2009, the International Agency for Research on Cancer raised the classification of ultraviolet-emitting tanning devices to “carcinogenic to humans” in the highest-risk category. This is based on evidence that people who regularly use sun beds have a substantially higher risk of developing cutaneous melanoma. The most recent meta-analysis concluded that the use of sun beds increases the risk of melanoma by 75%, especially when used before the age of 35 (IARC, 2007).

Ultraviolet radiation appears to induce melanoma through many mechanisms, including suppression of the immune system of the skin, induction of melanocyte cell division and free radical production. Free radicals are highly reactive molecules that are produced in the body naturally as a byproduct of metabolism, and as a result of exposure to toxins in the environment such as tobacco smoke and ultraviolet light.

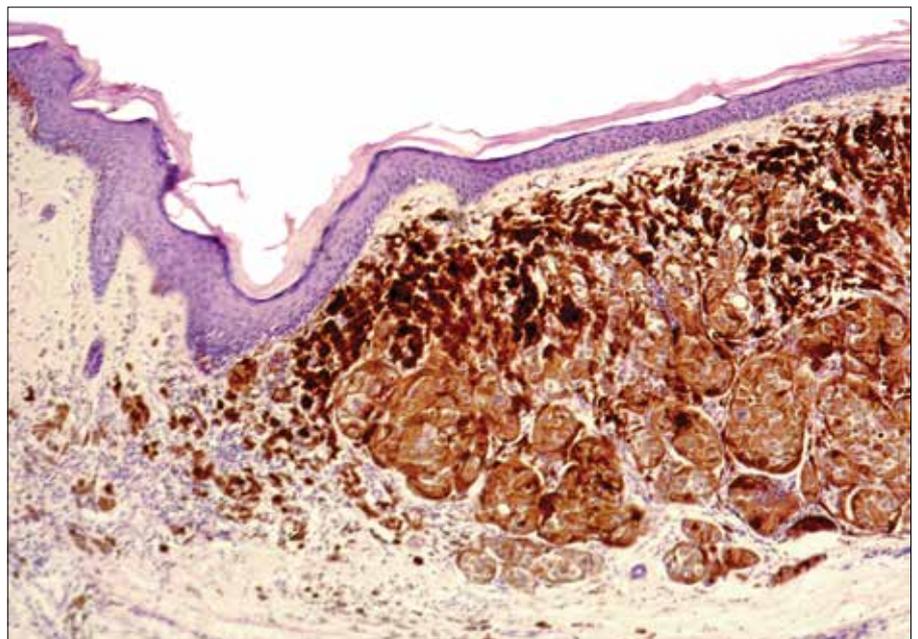
Free radicals contain an unpaired electron. In essence, they are in a constant search to bind with another electron to stabilise themselves – a process that can damage DNA and other parts of human cells. This damage may play a role in the development of cancer and other diseases, as well as accelerating the ageing process (Niki, 2012).

Diagnosis of malignant melanoma

The majority of melanomas are visible on the skin and nurses should be familiar with the clinical signs and symptoms so they can advise patients with suspicious skin lesions.

A spot, freckle or mole that displays one

FIG 1. **MALIGNANT MELANOMA**



Melanoma cells (brown) arise from melanocytes in the basal layer of the epidermis

of the major signs or three of the minor signs (Table 1) or a combination of both could be a melanoma and should be checked by a doctor as soon as possible.

Health professionals can use the ABCD system as a guide for assessing skin lesions (Box 1). Once a melanoma has been diagnosed, it is important to identify which stage it has reached (Table 2) – the higher the stage, the greater the burden of disease and consequently the poorer the prognosis. The stage of the tumour depends on:

- » The thickness of the primary tumour measured by Breslow thickness, which is measured from the granular layer of the epidermis down to the deepest point of invasion (Breslow, 1970);
- » Ulceration of the primary tumour. This has been confirmed as a strong

prognostic indicator of survival (Cochran et al, 2000) and is associated with a worse survival outcome. It is felt that if the tumour is ulcerated, it is more likely to have invaded the blood vessels, increasing the risk of metastatic spread;

- » The proliferation of the primary tumour, which is defined by the mitotic rate. This has recently been identified as a powerful, independent predictor of survival (Balch et al, 2009). A higher mitotic rate indicates that the cells are growing more rapidly and are therefore more likely to invade and spread;
- » The site of distant metastases. This is the most significant predictor of survival in stage IV. Common sites of metastases are lung, liver, brain and subcutaneous tissue, but melanoma can metastasise to any area in the body. Patients with metastases in visceral

TABLE 1. SIGNS OF MELANOMA

Major signs

- Change in size – the mole may become lumpy or spread outwards over the skin
- Change in shape – most moles have a smooth, regular outline, but a melanoma is more likely to have an irregular, ragged edge
- Change in colour – the mole may develop a reddish edge. It may become darker or appear to have different shades of colour, usually a mixture of brown and black
- Melanomas can also be red, due to inflammation, or have a blue-white tinge due to partial clearing in the centre

Minor signs

- Diameter – most normal moles are smaller than the blunt end of a pencil (7mm)
- Inflammation – many early melanomas are inflamed or have a reddish edge
- Crusting or bleeding – slight oozing is a common symptom and causes the melanoma to stick to clothing
- Sensory change – itching

BOX 1. ABCD SYSTEM

- **A**symmetry – the two halves of the area differ in shape
- **B**order – the edges of the area may be irregular or blurred, and sometimes show notches
- **C**olour – this may be uneven. Different shades of black, brown and pink may be seen
- **D**iameter – most melanomas are at least 6mm in diameter

TABLE 2. STAGING

There are four main stages of melanoma

Stage I	<2mm thickness with or without ulceration
Stage II	>2mm thickness with or without ulceration
Stage III	Lymph node involvement or microsatellites (small metastases around the primary site)
Stage IV	Metastatic disease

For more details about staging and staging investigations, see www.bad.org.uk

Source: Balch et al (2009)

organs have a poorer prognosis than those with metastases in skin or distant lymph nodes. The prognosis in stage IV disease is very poor, with median survival at 7-9 months and five-year survival in the 6-9% range (Balch et al, 2009);

- » Involvement of the regional lymph nodes. This is associated with a poorer prognosis, as is the number of lymph nodes involved and whether the tumour has spread outside the capsule of the lymph node (Balch et al, 2009).

Poor prognostic indicators for nodal disease are:

- » A high number of lymph nodes involved – the higher the number, the worse the prognosis;
- » If the lymph node is palpable or evident on a CT, ultrasound or MRI scan (macroscopic);
- » If the tumour has spread outside the capsule of the lymph node.

Treatment at stages I, II and III

Primary melanoma (Fig 2) should be treated with an excision biopsy; this is the only way in which Breslow thickness can be evaluated. Other biopsy techniques, such as wedge or punch biopsy, are less accurate and should not be used. Tumour depth cannot be calculated from a shave biopsy that contains only a portion of the tumour as it will lead to an underestimation.

The biopsy should be followed by wide excision with a good margin of healthy tissue. The recommendations for extent of further excision depend on the thickness of the primary tumour (Marsden et al, 2010). Following initial diagnosis, depending on the thickness of the primary tumour, patients may be offered a “sentinel” lymph node biopsy, which is a diagnostic test to see if the draining lymph nodes are affected.

If the regional lymph nodes are involved, a radical lymph node dissection is necessary. This procedure may be followed by preventive radiotherapy if a large number of the nodes contain tumours or if

the tumour has broken through the capsule of the lymph gland.

Treatment of stage IV

Until very recently, the standard treatment for stage IV disease was dacarbazine chemotherapy. This treatment has very poor response rates, in the region of 7-12%, with median overall survival of 5.6-7.8 months after treatment is started (Chapman et al, 2011). However, two new drug treatments have recently become available.

Vemurafenib

Vemurafenib (Zelboraf) has recently been approved by the National Institute for Health and Care Excellence (2012) and is now a valuable treatment option for patients with metastatic melanoma who have the abnormal BRAF gene. The treatment has been shown to have significantly better response rates, progression-free survival and overall survival rates than dacarbazine (Chapman et al, 2011).

One of the most important developments for decades has been the discovery that some melanoma patients have genetic mutations within their tumours. Over 40% harbour mutations in the v600E BRAF gene. This gene is involved in cell signalling and leads to abnormal cell proliferation. Vemurafenib works by targeting these genetic mutations thereby disrupting abnormal signals.

Vemurafenib is a twice-daily oral treatment and is taken by patients as long as they are responding to treatment. Its toxicity profile can vary from mild to extreme and includes:

- » Skin rashes;
- » Extreme photosensitivity, involving both UVA and UVB light;
- » Arthralgia;
- » Fatigue;
- » Raised liver enzymes;
- » New skin lesions;
- » Squamous cell carcinoma of the skin (usually non-serious and only requiring excision);
- » Headache;

- » Gastrointestinal disturbances.

It should be noted that the side-effects of vemurafenib differ greatly from those experienced with cytotoxic chemotherapy.

Patients often have dramatic responses even within hours of starting the drug. Unfortunately, despite this promising data, tumours eventually develop a resistance to the drug and patients relapse as a result.

There are many ongoing trials looking at similar approaches, targeting different genes or combining more than one targeted treatment.

Ipilimumab

It has been understood for some time that the immune system plays a part in controlling melanoma. The monoclonal antibody ipilimumab can be given to patients in stage IV. This works by encouraging the production of T cells (Hodi et al, 2010); essentially, it deactivates the “brake” on the production of T cells, thereby heightening the immune system. Ipilimumab is given by intravenous infusion for a total of four treatments. The drug’s toxicities are all immune-mediated and include:

- » Skin rash;
- » Diarrhoea, including potentially fatal colitis;
- » Hepatitis;
- » Inflammation of the endocrine glands including pituitary, thyroid and adrenal glands;
- » Neuritis;
- » Uveitis.

Many of these toxicities can be serious and patients require careful monitoring and active side-effect management. There are very clear algorithms advising how to deal with specific toxicities. Approximately 30% of patients will have some response to this drug and often this can be long term (Hodi et al, 2010).

Since ipilimumab works by enhancing the immune system, tumours may appear to enlarge following treatment; this may not necessarily be disease progression but “pseudo progression” caused by the tumours swelling due to the immune response. Because of the possibility of this pseudo progression, the disease is not evaluated until all four treatments have been completed. A new set of guidelines are being developed for response criteria. These are based on modified World Health Organization criteria and new immune-related response criteria (irRC) (Wolchok, 2012).

The specialist nature of both vemurafenib and ipilimumab and their complicated side-effect profiles means patients

should only be treated in specialist oncology units by experienced staff.

Despite this major progress in the clinical management of metastatic melanoma, there are drawbacks to both these treatments. The use of ipilimumab is limited due to its severe immune-mediated toxicities and slow response rate. The efficacy of vemurafenib is limited by the onset of resistance. It is believed that combination therapies of targeted agents can improve the likelihood of survival currently achieved with single-agent ipilimumab and vemurafenib (Eggermont and Robert, 2011). Many clinical trials are investigating this.

Nursing care and the role of the specialist nurse

The roles of skin cancer clinical nurse specialists are many and varied. Their scope of practice will depend on which area they work in, for example dermatology, plastic surgery or oncology. Some will have a caseload that covers all these disciplines.

There are, however, core roles that will be practised throughout the patient journey. These are coordinating treatment and services, personalising care throughout the patient pathway, ensuring complex information is understood, and offering support for patients and their families. Nurses are also well placed to assess patients for holistic care needs and provide psychosocial support.

Some patients with melanoma will require disfiguring surgery and, following lymph node dissection, lymphoedema is a possible permanent complication. Patients' psychological adjustment to scarring and disfigurement will vary depending on personality, ability to cope, amount of social and family support, degree of pain, length of hospital stay, loss of occupation, levels of anxiety and concern about physical appearance. Their ability to cope can be enhanced by giving good preoperative information, which gives a sense of control and helps to

FIG 2. PRIMARY MELANOMA



reduce anxiety and prepare patients for the presence of a scar (Bowers, 2008).

Since metastatic melanoma has such a poor prognosis, emphasis should be placed on primary prevention and early diagnosis. Many skin cancer nurses are involved in prevention projects, going into schools to educate children about the importance of sun protection and arranging awareness events in the local community. All nurses have a responsibility to be familiar with the causes of melanoma and encourage sensible sun exposure. Nurses are in a unique position of regularly viewing patients' skin and by being familiar with the signs of melanoma, can actively aid early detection.

With the advancement of novel therapies, knowledge of toxicities is evolving and cancer nurse specialists are involved in developing protocols for managing these effectively to ensure patients have an optimal quality of life while undergoing palliative treatments.

Summary

These are exciting times in the treatment of melanoma. However, treatments for metastatic disease are palliative and all nurses have a responsibility to educate their patients about the dangers of excessive UV exposure and the use of sun beds.

They should also be familiar with the signs of melanoma as many lesions are picked up incidentally by staff. **NT**

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