CANCER FORUM

FORUM

Skin Cancer

AUSTRALIA'S MOST COMMON MALIGNANCY: SKIN CANCER IN FOCUS

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The problem of skin cancer in Australia began over 200 years ago when the first fair-skinned Europeans settled on the shores of Sydney Harbour in 1788. Australians are more than five times as likely to develop a skin cancer as any other form of cancer, and two of every three will have developed some form of skin cancer by the time they reach 70 years of age.[1]

Non-melanoma skin cancer

Non-melanoma skin cancer (NMSC) is so common in Australia that reporting of this form of malignancy to state and national cancer registries is not a legal requirement, whereas reporting all other forms of cancer is mandatory. For NMSC, the amount of data would simply overwhelm existing systems, and the vast resources that would be required for its collection and processing would be extremely difficult to justify. As a result, accurate incidence data state by state and nationally are not available. Nevertheless, estimates that are likely to be reliable indicate that approximately 430,000 new cases of NMSC were diagnosed in 2008, 296,000 of them basal cell carcinomas (BCCs) and 138,000 of them squamous cell carcinomas (SCCs).[2] The enormous magnitude of the problem of NMSC in Australia is reflected by the huge sums in the national health expenditure budget that are spent on its diagnosis and treatment. Treatment of NMSC in Australia currently costs upwards of $340 million per year.[3]

For the majority of the Australian population the most common forms of NMSC, ie. SCC and BCC, are a cosmetic and economic burden and cause considerable inconvenience, but are not a threat to life. For some however, the risk is much greater. Transplant recipients for example, have a substantially increased likelihood of developing SCC, with a risk that is much higher still than that of the predominantly Caucasian general population in Australia. Comprehensive and highly accurate information is available from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), which has collected cancer incidence data for all renal transplant recipients and dialysis patients since 1963.[4] The data collected by the ANZDATA registry indicates that the risk of a renal transplant recipient developing an SCC is approximately 100 times the risk for the general population. Not only is the risk of developing SCC drastically higher in immunosuppressed transplant recipients, but the chance of metastasis to regional lymph nodes and systemic sites is much greater, and the risk of mortality much higher. Patients who are immunosuppressed for other reasons, eg. because they are receiving immunosuppressive drugs, or because they have an immunodeficiency state that is not drug-induced, (notably resulting from HIV infection but also in association with chronic haematological malignancies),[5] are likewise at high risk of developing SCC and dying as a result.

While the risk of metastasis and death from cutaneous SCC is much higher in immunosuppressed individuals, a small proportion of immune competent individuals also develop potentially life-threatening metastatic disease from SCC, BCC and other forms of NMSC, notably Merkel cell carcinoma (MCC). Overall, there were 448 reported deaths from NMSC in Australia in 2007.[2]

In this edition of *Cancer Forum*, several aspects of the investigation and management of patients with metastatic NMSC are addressed.

Emmett and Ho discuss the appropriateness of present-day imaging techniques for patients with NMSC and melanoma.[6] The more readily available access to sophisticated imaging technologies including CT scans, PET scans and MRI scans in recent years, has had an enormous impact on the staging and management of patients with all forms of skin cancer. However, it has also resulted in expensive tests sometimes being ordered inappropriately, subjecting patients not only to possible financial hardship, but also to unnecessary and potentially harmful radiation. It is important for all medical personnel who deal with patients with skin cancer to be aware of the current indications and contraindications for each of the modern imaging modalities. Emmett and Ho explore these matters in detail.

Guminski discusses the management of locally advanced and metastatic BCC that is not able to be dealt with by surgical excision or radiotherapy.[7] Although BCC is very

common, the great majority of patients are able to be cured using simple measures including surgery, radiotherapy, cryotherapy, topical imiquimod or photodynamic therapy. However, BCCs are occasionally more aggressive and recur locally, or metastasise to regional lymph nodes or distant sites, rendering successful treatment with surgery or radiotherapy difficult or impossible. Until recently no effective systemic treatments were available for metastatic BCC. But understanding of the "hedgehog" signalling pathway, which is active in both sporadic BCC and in the basal cell naevus (Gorlin's) syndrome, has led to the development of hedgehog signalling pathway inhibitors. These have provided a new treatment option both for patients with locally advanced or extensive BCCs, and for those with metastatic disease. Guminski discusses the role of these new agents in the treatment of patients with advanced BCC, and explains why the three hedgehog genes that have been identified in mammals were given the curious names desert hedgehog, Indian hedgehog and sonic hedgehog!

The role of radiation therapy in the management of skin cancers is discussed by Stevens.[8] Radiotherapy is widely used in the treatment of BCCs and SCCs, and in many patients is a better treatment option than surgical excision, as it provides a more satisfactory cosmetic outcome and avoids the risks inevitably associated with surgery. Stevens also discusses the role of radiotherapy for MCC, and its value as adjuvant and palliative treatment for patients with melanoma. He points out that radiotherapy plays an important role in the management of all the common skin cancers, but emphasises that the role of radiotherapy varies between the different cancers. He concludes by stressing the importance of individualising treatment and managing patients in a multidisciplinary setting whenever possible.

Gee and Hruby discuss present-day management of MCC, an aggressive but relatively uncommon form of NMSC that is frequently misdiagnosed and often managed inappropriately. It is only 40 years since this tumour type was first described,[9] and even today there is uncertainty about the origin and function of the cells from which they originate, first recognised by Friedrich Sigmund Merkel. He called them 'Tastzellen' or 'touch cells', and subsequent studies have confirmed that they appear to be involved in the process of touch, by which fine spatial details are appreciated. Although MCC is sometimes referred to as primary cutaneous neuroendocrine carcinoma, recent studies suggest an epidermal rather than a neural crest origin.

MCC is predominantly a disease of older people, with a median age at diagnosis of around 65 years. Exposure to solar ultraviolet radiation appears to be the major risk factor for developing MCC, but it has recently been shown that a polyoma virus can be identified in MCC in the majority of cases (although it is not clear whether it is causative). In their review, Gee and Hruby consider the epidemiology, diagnosis, staging and management of MCC and provide guidelines for patient management. Prompt referral to an experienced specialist centre for definitive management is recommended, because treatment delays are associated with a significantly worse outcome.

Melanoma

The other form of skin cancer that is of enormous significance in Australia is melanoma. Although the number of incident cases in the nation is much lower than the number of cases of NMSC, the proportion of patients who die from the disease is much higher. The most recent figures available from the Australian Institute of Health and Welfare indicate that 10,342 patients developed melanoma in 2007 (making it the fourth most common cancer), and 1279 patients died of the disease.[10]

Rational management of both primary and metastatic melanoma is entirely dependent on the accuracy of histopathological assessment. This is becoming even more important in the era of personalised therapy that we have now entered. In this edition of *Cancer Forum*, Scolyer and colleagues provide a comprehensive review of contemporary melanoma pathology, and explain how recent insights into the molecular pathogenesis of melanoma have allowed traditional histological assessment to be supplemented and enhanced by molecular pathology testing, providing more accurate classification and better estimates of prognosis, and allowing eligible patients to be selected for specifically targeted therapies.[11] Molecular testing has already found its way into everyday clinical use, for example by identifying patients who have a mutation in the BRAF oncogene. This is important, because if their melanoma is BRAF positive, they are likely to respond to therapy with a BRAF inhibitor. Scolyer and colleagues provide guidelines for molecular testing in patients with melanoma, and give practical advice on when and how to arrange testing, and which specimens to test, based on knowledge of the advantages and disadvantages of the various testing methodologies. They also explain that as well as the long-established melanoma prognostic indicators such as Breslow thickness and the presence or absence of ulceration, recent studies have demonstrated that other histopathological features also have prognostic significance. These include tumour mitotic rate, the extent of ulceration, tumour-infiltrating lymphocyte grade and the presence, extent and distribution of metastatic disease in sentinel lymph nodes.

Melanoma has a particularly adverse effect on years of productive life lost, because it is one of the most common cancers in young people.[12] Until recently, the treatment of systemic melanoma metastases with drugs was almost invariably unsuccessful. The most commonly used systemic agent was dacarbazine, but complete responses were rare and the partial response rate was less than 20%. The situation has now changed dramatically, and recent clinical trials have shown that signal pathway inhibitors (eg. the BRAF inhibitors vemurafenib and dabrafenib) and immunological modulators (such as the anti-CTLA-4, anti-PD-1 and anti-PD-L1 antibodies) can achieve much more impressive complete and partial response rates. Early results of clinical trials of these new agents are reported and discussed by Menzies,[13] and future prospects for effective combination therapies are outlined. Menzies summarises recent advances in the understanding of the molecular biology of melanoma that have led to the development of these new agents. He points out that although the signal pathway inhibitors

and new immunotherapeutic agents produce results that are vastly superior to previous chemotherapy regimens, they all have potentially serious side-effects, and durable long-term responses are rarely achieved. He explains that there are ongoing clinical trials of new agents and various combinations of existing agents, and also trials of some of these agents as adjuvant therapy in melanoma patients identified as being at high risk of recurrence. The results of these studies are keenly awaited.

Finally, the particular problem of management of locoregional melanoma recurrence, i.e. local, in transit and nodal metastasis, is considered by Geere and Barbour.[14] They explain that local and in transit recurrences are best treated by surgical excision whenever possible, but for patients with extensive disease other options exist. These range from topical therapy (such as the contact sensitiser diphencyprone),[15] to intratumoural injection therapy (such as with Rose Bengal).[16]

RT is sometimes useful for advanced localised disease, while for unresectable local and in transit recurrences confined to a limb, regional chemotherapy with vascular isolation (isolated limb perfusion or isolated limb infusion) is the current standard of care.[17]

Regional lymph node recurrence is best managed by surgical lymphadenectomy. Adjuvant post-operative radiotherapy has been shown in a recent Australian multicentre trial to significantly reduce the risk of regional recurrence in patients with surgically resected high risk stage III melanoma.[18]

Conclusion

The management of all forms of skin cancer is becoming increasingly complex and new therapeutic options are becoming available at an ever-increasing pace. As a result, patients with high risk, locally advanced or metastatic disease are best managed in specialist treatment centres, where treatment recommendations can be made on the basis of multidisciplinary team assessment. Such multidisciplinary teams now exist in most major population centres in Australia, and it is to be hoped that ready access to such facilities will improve the outcome for the large and ever-increasing number of Australians who are affected by skin cancer.

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