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REVIEW ARTICLE

Advances in Treatment for Patients with Unresectable or Metastatic *BRAF* V600 Mutated Melanoma

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ABSTRACT

*Melanoma is widely prevalent among western populations and is a relatively rare malignancy in the local Chinese population. In local Chinese patients, clinicians should be wary of suspicious pigmented lesions over the extremities, such as the soles, palms, nail beds, or mucous membrane because up to 60% of cases of melanoma in Chinese people are of acral lentiginous type, compared with only 2% in Caucasians. The pigmented type of basal cell carcinoma is the most common subtype of basal cell carcinoma in Hong Kong. Thus, differential diagnoses of pigmented skin lesions in local Chinese should include pigmented basal cell carcinoma in addition to melanoma. The standard treatment of advanced and metastatic disease is chemotherapy with agents such as dacarbazine, with immunotherapy (e.g. interleukin-2) providing an alternative option. However, both treatment modalities are associated with modest effectiveness in terms of response and survival, and with potentially serious side-effects. A phase III clinical trial in patients with metastatic melanoma showed that treatment with the novel immunotherapy ipilimumab — an intravenous, fully humanised immunoglobulin monoclonal antibody — was associated with a response rate of 10.9% and median overall survival of approximately 10 months; however, there were marked immune side-effects. Recently, advances in the knowledge of cell signalling pathways in melanoma — particularly with regard to the role of the serine/threonine kinase v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) — have led to the development of targeted biological agents. Vemurafenib is a potent oral small molecule that inhibits the activated form of the oncogenic* BRAF *V600E mutant. In a recent phase III clinical trial comparing vemurafenib with dacarbazine, treatment with vemurafenib was associated with improved overall survival (median, 13.6 months vs. 9.7 months with dacarbazine), progression-free survival (median, 5.3 months vs. 1.6 months with dacarbazine), and confirmed objective response rate (57.0% vs. 8.6% with dacarbazine) in patients with advanced melanoma at a median follow-up of 12.5 months. This article provides an overview of the features of melanoma in Chinese patients, and the current treatment options for advanced metastatic melanoma. At the time of crossover in 2012, subjects receiving vemurafenib showed higher objective response rate (57.0% vs. 8.6%), complete remission rate (5.6% vs. 1.2%), and partial response rate (51.3% vs. 7.4%), versus those receiving dacarbazine.*

Key Words: *Immunotherapy, adoptive; Melanoma; Oncogenes; Skin neoplasms*

中文摘要

不能切除或轉移性帶*BRAF* V600E突變黑色素瘤的治療發展

應志浩

黑色素瘤在西方人口中較普遍，而在華籍人口當中則仍屬相對罕見的惡性腫瘤。與白種人的2%相比，華籍人口中有60%的黑色素瘤病例屬肢端雀斑樣痣（acral lentiginous）型，因此在本港的華籍患者中，臨床醫生應對出現於四肢 如腳底、手掌、指甲床，或黏膜的可疑色素病變加以警惕。在

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香港，最常見的基底細胞癌亞型是色素型基底細胞癌。因此，對本地華籍人皮膚色素病變的鑑別診斷，除黑色素瘤外，亦應包括色素型基底細胞癌。在晚期和轉移性疾病的治療方面，採用例如達卡巴（dacarbazine）的化療藥物是標準治療，而免疫治療（例如白細胞介素-2）則是另一選擇。然而，這兩種治療方案在治療反應及存活方面的療效只屬一般，並有嚴重的潛在副作用。一項轉移性黑色素瘤三期臨床試驗採用了新型的免療治療ipilimumab，一種靜脈注射完全人源化免疫球蛋白單克隆抗體，相關的反應率為10.9%、總存活中位數約10個月，但有顯著的免疫副作用。最近在黑色素瘤細胞信號傳導途徑——尤其對於絲氨酸-蘇氨酸激酶（serine/threonine kinase）v-raf鼠肉瘤病毒癌基因同源物B1（*BRAF*）的知識進展——造成了標靶生物製劑的研發。一項近期的三期臨床試驗在晚期黑色素瘤患者中，採用了一種抑制致癌*BRAF* V600E突變活化形的強效口服小分子藥物vemurafenib；在跟進12.5個月（中位數）後，與達卡巴相比，vemurafenib改善了相關的總存活率（中位數為13.6個月比9.7個月）、無惡化存活率（中位數為5.3個月比1.6個月）及客觀反應率（57.0%比8.6%）。本文概述了華籍患者黑色素瘤的特點，以及目前對晚期轉移性黑色素瘤的治療選擇。2012年的數據顯示，與達卡巴相比，vemurafenib有較高的客觀反應率（57.0%比8.6%）、完全緩解率（5.6%比1.2%）和部分反應率（51.3%比7.4%）。

INTRODUCTION

Melanoma most commonly affects white western populations, with the highest incidences found in Australia and New Zealand.[1-3] In Caucasians, the incidence of melanoma is actually increasing at a faster rate than that of any other neoplasm, with the exception of female lung cancer. However, the prevalence of melanoma in Hong Kong is lower than that in western countries.[4] From 2001 to 2010, there were 542 new cases of cutaneous melanoma in Hong Kong, with the median age of patients being 63 years.

Melanoma is a highly lethal skin cancer. Incidence and mortality curves for melanoma often follow a similar trend, and melanoma-associated skin cancer mortality is approximately 30 times greater than that for non-melanoma, a problem that is compounded by the fact that patients often present late. This article discusses the global and special local features of cutaneous melanoma, and recent advances in the treatment of advanced melanoma.

SPECIAL FEATURES OF CUTANEOUS MELANOMA IN HONG KONG CHINESE SUBJECTS

The distribution sites of melanoma differ between Caucasian and Chinese individuals. In Caucasian men, it usually presents on the trunk, and in Caucasian women, on the lower extremities. In Asians, however, melanoma commonly presents on the soles, palms, nail beds or mucous membrane. Melanoma lesions on the feet may initially appear like minor black bruises, which do not heal over time and, gradually, become larger.

Acral lentiginous-type melanomas are far more common in Asian patients, accounting for 40 to 60% of cases, but are only found in approximately 2% of cases in Caucasians. Acral lentiginous lesions are least likely to be associated with sun exposure and, in general, cutaneous melanoma appears to be a very different disease in Chinese people compared with that in Caucasians.[5-9] Hutchinson's sign, which describes the presence of pigmentation in the periungual skin and around the posterior nailfold, is a useful tool for diagnosing nail-bed melanoma. Although not exclusive to melanoma, the presence of Hutchinson's sign necessitates a biopsy.[10] Basal cell carcinoma (BCC) is more common than melanoma in Chinese people and should be distinguished in the differential diagnoses, particularly as up to 60% of BCC in Chinese patients are pigmented and resemble melanoma clinically. Once again, there is a clear differentiation in skin cancers between Chinese and Caucasian populations — in Caucasians, the classical nodulo-ulcerative subtype is the most frequent BCC, while the pigmented BCC is very rare.

TREATMENT

Chemotherapy

In the past, monotherapy with a chemotherapeutic agent was the mainstay of treatment for metastatic melanoma, but this was largely ineffective.[11] Response rates to single-agent therapy, such as dacarbazine, temozolomide and paclitaxel, typically ranged from 5 to 28%, with little additional improvement gained with combination chemotherapy.[12-19]

Dacarbazine is the most commonly used chemo-

therapeutic agent for metastatic carcinoma in clinical practice, and is the only one approved by the US Food and Drug Administration (for stage IV metastatic melanoma). However, dacarbazine has not been shown to improve progression-free or overall survival. Side-effects of dacarbazine vary depending on the individual patient and the dose of drug used, and may include allergic reactions; decreased bone marrow function and haematologic problems; nausea, vomiting, diarrhoea or loss of appetite; temporary hair loss; and flu-like symptoms.

Immunotherapy

Immunotherapy, such as interferon or interleukin-2 (IL-2), provides an alternative option to chemotherapy but, again, only modest response rates have been reported.[11,20-23] Until the availability of ipilimumab, high-dose IL-2 was the only approved immunotherapy for use in patients with metastatic melanoma.[23-25] In a small proportion of patients, IL-2 was shown to induce prolonged complete response.[23] Median survival was 11.4 months in all patients (n = 270), median progression-free survival was 13.1 months in responders (n = 43), and median duration of response was 8.9 months in responders (n = 43). However, treatment efficacy was offset by the incidence of serious side-effects, including cardiovascular, gastrointestinal, neurological, pulmonary, hepatic, renal and haematological side-effects.[23]

Ipilimumab is an intravenous, fully humanised immunoglobulin monoclonal antibody, which activates the immune response against cancer cells.[26] Specifically, this novel agent inhibits the activity of cytotoxic T-lymphocyte antigen 4. Numerous phase II and III studies of ipilimumab have been completed in metastatic melanoma, either as monotherapy or in combination with other treatments. In one phase III clinical trial of metastatic melanoma, ipilimumab was associated with a response rate of 10.9% and median overall survival of around 10 months, although marked immune side-effects were noted.[27] This agent is approved for use in metastatic melanoma in the USA since March 2011, but is currently not available in Hong Kong.

BRAF AS A THERAPEUTIC TARGET IN METASTATIC MELANOMA

In the past few years, key signalling pathways that are important in melanoma have been identified, which have led to the development of novel targeted therapies.[28] These agents, and the discovery of novel targets, have greatly expanded a therapeutic field that was previously very limited. Among these potential therapeutic targets, the serine/threonine kinase v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) has probably generated the most interest, because it is present in 7% of all cancers, and it is the first intracellular signalling molecule activated by point mutations for which single-agent therapy appears to be effective.[29]

As such, *BRAF* is one of the RAF kinases of the rat sarcoma–rapidly accelerated fibrosarcoma (RAS-RAF) pathway, which acts in a series to transmit signals to control cell proliferation, differentiation, and survival.[29,30] *BRAF* is expressed predominantly in neuronal tissues and melanocytes (both of neural crest origin), as well as in testis and haematopoietic cells.[29] Under normal physiological conditions, the RAS-RAF signalling pathway is controlled by mitogenic signals.[30] However, *BRAF* mutations lead to RAS-independent activation of the RAS-RAF pathway. The most common oncogenic mutation of *BRAF* is the T1796A point mutation, which results in substitution of valine (V) for glutamic acid (E) at position 600 of the amino acid sequence (the 'V600E' substitution). Notably, mutated *BRAF* is highly prevalent in melanoma, with reported prevalence ranging from 30 to 70%.[29]

Vemurafenib in Metastatic Melanoma

Vemurafenib is a potent, oral small molecule that inhibits the activated form of the oncogenic *BRAF* serine-threonine kinase enzyme, thereby suppressing downstream signalling of the RAS-RAF pathway.[31] In *BRAF* mutation-positive melanoma cell lines, vemurafenib was shown to inhibit extracellular signal-regulated kinase activation, arrest the cell cycle, selectively inhibit cell growth and proliferation, and induce apoptosis.[32-35]

Phase I through phase III clinical trials have demonstrated the efficacy of vemurafenib in melanoma patients with the *BRAF* V600E mutation.[36-38] Phase I clinical trials showed that vemurafenib had a manageable safety profile, with the majority of side-effects found to be mild or moderate in intensity (grade 1 or 2). Importantly, the response rate with vemurafenib in these early studies was high (56%) and it was also possible to achieve an early response within 2 weeks of initiating treatment in some cases.[36,37] Subsequently, the phase II BRIM trial of previously treated patients with metastatic melanoma positive for *BRAF* V600E mutation not only confirmed the response

rate and duration results from phase I studies, but the longer follow-up period provided critical additional information on survival. Specifically, median overall survival of patients in BRIM was 15.9 months, and median progression-free survival was 6.8 months.[37]

In 2010, a phase III clinical trial was conducted to compare the efficacy of vemurafenib with dacarbazine in 675 patients with previously untreated metastatic melanoma with the *BRAF* V600E mutation.[38] Patients were randomised to receive either vemurafenib 960 mg orally twice daily or dacarbazine 1000 mg per square metre of body surface area intravenously every 3 weeks. The co-primary endpoints were rates of overall survival and progression-free survival; secondary endpoints included response rate, response duration, and safety.

At 6 months, the overall survival in the vemurafenib arm was 84% (95% confidence interval [CI], 78-89) compared with 64% (95% CI, 56-73) in the dacarbazine arm. In the interim analysis for overall survival and final analysis for progression-free survival, vemurafenib was associated with a 63% relative risk reduction in death and 74% relative risk reduction in either death or disease progression compared with dacarbazine ($p < 0.001$ for both comparisons). Following this interim analysis, a recommendation was made to crossover patients in the dacarbazine group to the vemurafenib group. At this time point of 12.5 months, subjects receiving vemurafenib showed significantly longer progression-free survival (median, 5.3 months vs. 1.6 months; hazard ratio [HR] = 0.38; 95% CI, 0.32-0.46, $p < 0.001$), and overall survival (median, 13.6 months vs. 9.7 months; HR = 0.70; 95% CI, 0.57-0.87; $p < 0.001$) than those receiving dacarbazine. Moreover, the survival benefit with vemurafenib was observed in all pre-specified subgroups (age, sex, Eastern Cooperative Oncology Group performance status, tumour stage, lactate dehydrogenase level, and geographic region).

At the time of crossover in 2012, subjects receiving vemurafenib showed higher objective response rate (57.0% vs. 8.6%), complete remission rate (5.6% vs. 1.2%), and partial response rate (51.3% vs. 7.4%), versus those receiving dacarbazine. Of note, the response rate with dacarbazine was somewhat lower than that reported in previous phase III trials suggesting that, perhaps, melanomas with the *BRAF* V600E mutation are more aggressive, and less sensitive to chemotherapy, than *BRAF* wild-type melanomas. Furthermore, 10 patients in the vemurafenib group who were responders to this treatment were later identified to have the *BRAF* V600K (valine to lysine) mutation, not the V600E mutation. This raises the question of whether this *BRAF* variant may also be sensitive to inhibition with vemurafenib.

The most common adverse events in the vemurafenib group were cutaneous events, arthralgia, fatigue and photosensitive skin reactions; in the dacarbazine group, these included fatigue, nausea, vomiting, and neutropenia. Cutaneous squamous-cell carcinoma, keratoacanthoma, or both developed in 18% of patients receiving vemurafenib, which were treated by simple excision. At the time of the study's publication, pathological analyses of skin-biopsy specimens were underway. In view of these potential adverse events, patients receiving vemurafenib therapy should be advised to take strict measures for avoiding sun exposure. Vemurafenib-treated patients should be monitored for suspicious skin lesions and those who develop cutaneous squamous-cell carcinoma should be managed according to the current standard of care — any such lesions should be excised and sent for dermatopathological evaluation. It is recommended to continue treatment with vemurafenib without dose adjustment in patients who develop cutaneous squamous cell carcinoma.

CONCLUSION

Melanoma is a very aggressive form of skin cancer associated with significant mortality. Despite the low prevalence of melanoma in Hong Kong compared with Caucasian populations, a high degree of clinical suspicion is required as significant mortality is associated with advanced disease. Chemotherapy with dacarbazine, the standard treatment, or immunotherapy with IL-2, is associated with very modest response rates and any benefit may be offset by serious side-effects. The discovery of cell signalling pathways important for melanoma has opened up a new field of treatment with targeted biologic therapy; in particular, *BRAF* mutations are highly prevalent in melanoma and represent an attractive therapeutic target. In phase I, II, and III clinical trials, the oral small molecule vemurafenib, which inhibits the activated form of oncogenic *BRAF*, was associated with improved rates of overall and progression-free survival, as well as objective response, in patients with previously untreated melanoma with *BRAF* V600E mutation. As such, vemurafenib represents a new viable option for these patients, for whom treatment options were previously very limited.

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