Cutaneous Melanoma: Taiwan Experience and Literature Review

John Wen-Cheng Chang, MD

Malignant melanoma is a rare disease in Taiwan with an incidence rate of 0.65/100,000. Excessive exposure to ultraviolet radiation is not associated with most Taiwanese melanoma cases. Acral lentiginous melanoma comprises 58% of cutaneous melanoma. Advanced disease is seen in 50% of cases. Surgery, including resection of the primary melanoma, sentinel lymph nodes that may harbor microscopic metastasis, clinically abnormal lymph nodes, and selected distant metastases, is the most important treatment. Lymphatic mapping and sentinel lymph node biopsy has changed the clinical stage in 22.2% of our patients. Adjuvant high-dose interferon significantly prolongs progression-free survival. However, its use in Taiwan is limited by its substantial toxicity. The prognosis of metastatic disease remains poor with a median survival of 12 months. In the past, chemotherapy alone was the most common treatment modality for metastatic disease. Recently biochemotherapy has been more commonly utilized to treat patients with metastatic melanoma. *(Chang Gung Med J 2010;33:602-12)*

Dr. John Wen-Cheng Chang

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Incidence rate of melanoma

Incidence rates of melanoma show substantial variation worldwide.[1] The incidence of invasive melanoma in Auckland, New Zealand is the highest in the world, with an age-standardized rate of 40.2/100,000 and similar rates for males and females.[2] The cumulative risk of developing melanoma in this population over a lifetime is 5.7%. Other high rates are reported in Australia, with rates of 37.7/100,000 among males and 29.4/100,000 among females.[3] In the United States, 68,720 new diagnoses and 8,650 deaths from invasive melanoma were reported in 2009.[4] A low incidence rate (approximately 1/100,000) has been reported in Asian populations incuding China, India, Japan, and Singapore.[5] In Taiwan, the 2006 age-adjusted rate for invasive melanoma was 0.65/100,000, 0.71/100,000 for males and 0.58/100,000 for females.[6]

Etiology of melanoma

Ultraviolet light exposure has been implicated as a major etiologic factor in the development of melanoma.[7] However, the lesions of acral lentiginous melanoma (ALM) and mucosal melanoma, which comprise more than 60% of melanoma in Taiwan, are generally not a result of exposure to ultraviolet irradiation. The etiology is yet to be deter-

From the Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan.
Received: June 2, 2010; Accepted: Aug. 25, 2010
Correspondence to: Dr. John Wen-Cheng Chang, Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou. 5, Fusing St., Gueishan Township, Taoyuan County 333, Taiwan (R.O.C.)
Tel.: 886-3-3281200 ext. 2524; Fax: 886-3-3286697; E-mail: wen1902@hotmail.com

mined. Guo et al. conducted an ecological study in 243 townships in Taiwan and assessed the correlation between arsenic exposure and skin cancers.[8] A total of 2369 patients were registered. The results indicated that squamous cell carcinoma and basal cell carcinoma appear to be associated with chronic ingestion of arsenic contaminated water, but no association between arsenic exposure and melanoma was observed. In an etiologic study of acral melanomas from Australia, an increased risk was associated with penetrating injury of the feet or hands (relative risk, RR, 5.0) and with heavy exposure to agrichemicals (RR, 3.6).[9] These risk factors could also be important in acral melanoma in Taiwan. Further etiologic studies to identify the risk factors, including occupation, in Taiwanese melanoma are warranted.

Patient characteristics and prognosis of melanoma in Taiwan

Chang et al. retrieved a total of 221 cases of malignant melanoma at Chang Gung Memorial Hospital (CGMH) in Taiwan.[10] Forty cases (18%) were located at sites other than skin. The authors analyzed the other 181 cases of cutaneous melanoma to determine their characteristics and clinical outcome. The male to female ratio was 1:1.13. The most common age at onset was the sixth decade. The median age of onset was 61 years (range 2-95 years). There were 105 (58%) cases of ALM (Fig. 1), 55 (30.4%) of nodular melanoma (NM), 19 (10.5%) of superficial spreading melanoma (SSM) and two (1.1%) of lentigo maligna melanoma (LMM). The median survival of the 181 patients was 3.71 years, and the 5-year survival rate was 45.63%. Of the 168 cases with complete staging information, the incidence of stages I, II, III and IV was 47 (27.5%), 23 (13.5%), 58 (33.9%) and 43 (25.1%), respectively. The median survival of stage IV disease was 12 months. Five-year survival rates of patients with stages I, II, III and IV disease were 84.39%, 56.03%, 34.7% and 0%, respectively. Sex, Breslow thickness, Clark level, pathological type and age were signifi-

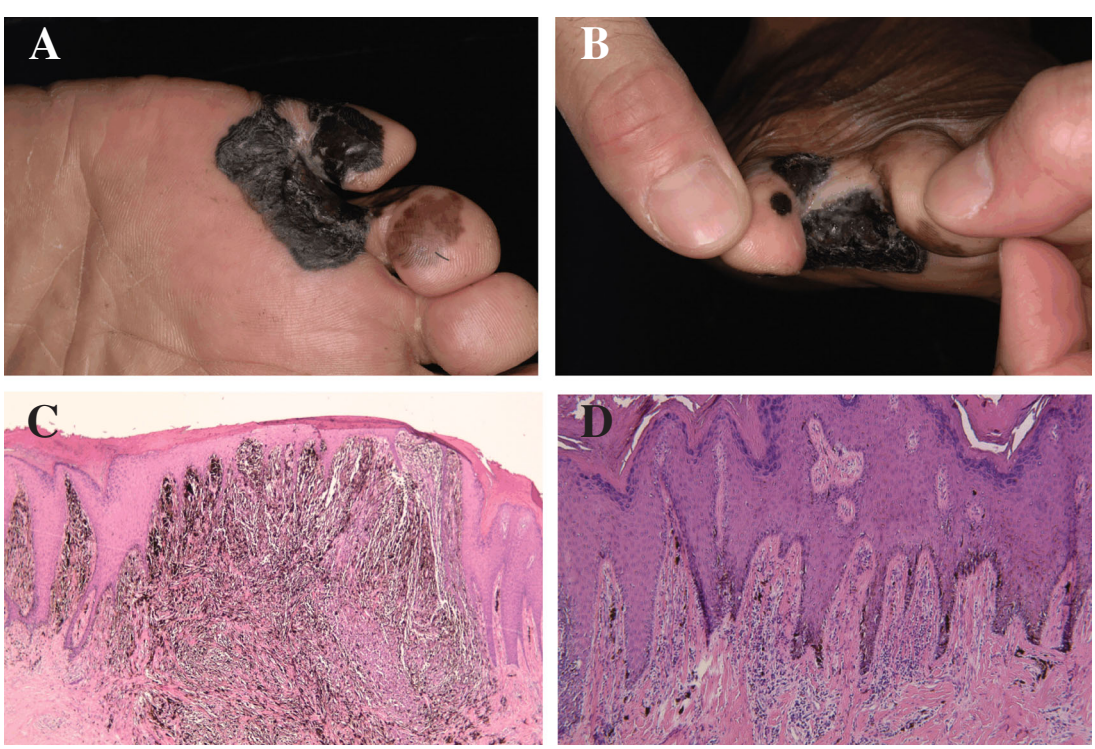

Fig. 1 Acral lentiginous melanoma (ALM) on the 4th and 5th toes (A) and the web with ulceration (B). Microscopically, there are prominent junctional activity and atypical melanocytes with hyperchromatic nuclei scattered along the basal layer of an acanthotic epidermis. Junctional nests are present at the tips of the rete. Invasive tumor cells are present in the papillary dermis (C, x 100; D, x 200). (Courtesy of Chih-Hsun, Yang, MD)

cant prognostic factors. There were no survival differences between ALM and NM. Both ALM and NM were associated with a worse prognosis than SSM.

Soong et al. studied 22 cases of malignant melanoma registered at Tri-Service General Hospital, Taiwan from 1983 to 1988.[11] About 60% (13/22) of the patients had a tumor thickness of more than 2.5 mm and 45% (10/22) had a tumor thickness over 4 mm. No patient had a thin melanoma (tumor thickness less than 0.76 mm) when first diagnosed. Forty-four percent of the cases, twice as many as those (22%) in a previous study done at the same hospital, were classified as having stage III disease. Eleven patients (50%) had ALM. The cumulative survival rate was 59% at 3 years and 39% at 5 years.

Chen et al. analyzed 65 patients diagnosed with melanoma at Veterans General Hospital, Taichung.[12] Fifty-one cutaneous melanomas were identified and analyzed by both clinical behavior and histology. ALM was the most common type (54.9%), followed by NM (29.4%), SSM, and LMM. Patients with an age at onset over 55 years, male gender, ulceration of the tumor, and a thicker tumor tended to have a poorer prognosis, but without statistically significant differences. Advanced stages (III and IV) and histological subtypes other than ALM were independent risk factors for poor prognosis.

Surgical management of malignant melanoma

Surgery is the most important treatment for malignant melanoma. Surgery includes surgical treatment of the primary site, surgical management of clinically normal and abnormal lymph nodes, and surgery for distant metastases.[13,14]

Chen et al. analyzed 89 cases of malignant melanoma at CGMH from 1983 to 1991.[15] A total of 46% of cases occurred in the soles. Regional lymph node or distant metastasis was found in 56.2% of cases. Nodal metastasis was an important prognostic factor. Surgical resection provided an increased survival rate for patients without nodal metastasis. In stage I patients, a prophylactic lymph node dissection decreased the incidence of nodal metastasis and prolonged overall survival (OS). The median survival in stage I disease was 52 months. Nonetheless, the median survival for metastatic melanoma was 5.2 months.

Surgical treatment of primary melanoma

Melanoma-in-situ and lentigo malignas are treated with narrower surgical margins, usually 0.2 to 0.5 cm.[16,17] Many surgeons consider 0.5 cm margins the standard of care for excision of melanoma-in-situ,[18] but 0.2 cm margins might be acceptable for margin-controlled surgery. For primaries ≤ 1 mm thick, 1 cm margins are adequate. For primaries between 1 mm and 2 mm thick, 1 to 2 cm margins are adequate while 2 cm margins are adequate for primaries up to 4 mm thick. Although patients with primaries > 4 mm thick have a relatively high risk of local recurrence, there are few data to support the use of margins wider than 2 cm.[19]

Surgical management of clinically normal lymph nodes

Regional node management remains controversial because 80% of patients undergoing routine elective complete lymph node dissection (CLND) do not have nodal metastases. Lymphatic mapping and sentinel lymph node (SLN) biopsy are used to detect occult nodal metastases and thereby identify patients who might benefit from CLND. The Multicenter Selective Lymphadenectomy Trial was designed to compare the survival of SLN-positive patients undergoing immediate lymphadenectomy (the biopsy arm) with that of patients treated by delayed lymphadenectomy when metastatic regional nodes became palpable (the observation arm).[20,21] Five-year disease free survival (DFS) was 78% versus 73% ($p = 0.01$) in favor of the biopsy arm. Five-year survival was significantly higher in the biopsy arm than the observation arm (71% versus 55%; $p = 0.0033$). SLN tumor status was the most important prognostic factor.

In Taiwan, lymphatic mapping has been utilized to detect SLN since 2001.[22] Liu et al. evaluated the usefulness of SLN detection by lymphoscintigraphy and excision with an intraoperative gamma probe in patients with malignant melanoma.[23] Thirty-six malignant melanoma patients with clinically normal lymph nodes were enrolled. A total of 44 SLNs were detected, with a mean of 1.22 SLNs per patient. The SLN detection rate by lymphoscintigraphy was 100%. During surgery, 39 (88.6%) of the 44 SLNs in 33 (91.7%) of 36 patients were identified. SLN metastasis was found in 8 (20.5%) of 39 dissected SLNs or in 8 (22.2%) of 36 patients. The SLN

metastatic rates in the patients with primary melanoma with a Breslow thickness ≤ 2.0 mm and > 2.0 mm were 10.0% (2/20) and 41.7% (5/12), respectively. SLN mapping changed the clinical stage in 22.2% of melanoma patients.

Surgical management of clinically abnormal lymph nodes

Clinically evident or biopsy-proven lymph node metastasis should be managed by complete dissection of the affected basin. Axillary lymph node dissection should include levels I, II, and III. Patients with cervical lymph node metastases should undergo dissection at all neck levels. Metastases to the inguinal lymph nodes should be treated by groin dissection.[13]

Adjuvant treatment

In melanoma prevalent countries, the majority of patients who present with melanoma have early stage disease, with 62.6% presenting with stage 0 or I disease, and an additional 23.1% with stage II disease.[24] Conversely, only 40% were in stage I or II in Taiwan.[10] High risk groups (stage IIb to IIIc) have a 5-year survival of approximately 50%.[25]

In the Eastern Cooperative Oncology group trial E1684,[26] both median DFS and median OS were significantly better for the adjuvant high-dose interferon (IFN) (HDI) group compared with the observation group (DFS 1.72 versus 0.98 years, $p = 0.0023$; OS 3.82 versus 2.78 years, $p = 0.0237$, respectively). Grade 3 toxicity occurred in 67% of patients, grade 4 toxicity in 9%, and two patients died secondary to hepatotoxicity. The E1690 trial compared HDI to low-dose IFN and a control. This study also showed an improvement in the 5-year relapse-free survival (44% versus 35%, $p = 0.05$);[27] however, it failed to show an OS benefit.[28] The E1694 trial compared HDI with the GM2-KLH/QS-21 vaccine,[29] and again showed improvement in the 5-year relapse-free survival (62% versus 49%, $p = 0.0007$) and also showed an OS benefit (78% versus 73%, $p = 0.015$).

To reduce toxicity, Eggermont *et al*. compared subcutaneous intermediate dose IFN to observation.[30] Unfortunately, no benefit in distant metastasis-free interval or OS was observed. Intermediate dose IFN for patients with stage IIb/III melanoma, therefore, is not recommended.

Four meta-analyses of randomized controlled trials (RCTs) reported the impact of adjuvant IFN on DFS and OS in patients with high-risk cutaneous melanoma.[31-34] Lens and Dawes demonstrated a statistically significant benefit in DFS but no clear benefit in OS.[33] The largest meta-analysis, with 8122 patients in 14 RCTs, was recently published.[34] Mocellin et al. demonstrated a benefit of IFN on both DFS and OS in the adjuvant setting. IFN treatment was associated with a statistically significant improvement in DFS in 10 of the 17 comparisons (HR for disease recurrence = 0.82, $p < 0.001$) and improved OS in 4 of the 14 comparisons (HR for death = 0.89, $p = 0.002$).[34] This encourages physicians to routinely use IFN in the treatment of high-risk melanoma patients, provided that toxicity can be well controlled. Further study is warranted to identify the subset of patients who would most benefit from IFN adjuvant treatment.

The PEGylation of IFN alters its pharmacokinetics, allowing for decreased frequency of administration with the potential for an improved toxicity-benefit profile.[35] The European Organisation for Research and Treatment of Cancer (EORTC) 18991 assessed the efficacy and toxicity of long-term PEGylated interferon alpha-2b (PEG-IFN) versus observation in the adjuvant setting.[36] Recurrence-free survival (RFS) was increased by 18% (HR = 0.82; $p = 0.01$) in the PEG-IFN arm compared with observation. There was no difference in OS between groups. Treatment with PEG-IFN was discontinued because of toxicity in 191 (31%) patients. EORTC 18991 demonstrated an improvement in a subset of patients with microscopic disease, but not in those with gross nodal involvement.[37] Hauschild et al. proposed practical guidelines for the management of IFN-associated toxicities.[38] Adverse events increase the risk of poor treatment outcome because of their frequent association with dose reduction or treatment discontinuation.

In our experience, patients usually can not tolerate the severe toxicity associated with HDI. Thus, adjuvant HDI is not routinely administered. There are currently no data regarding adjuvant therapy for high-risk melanoma following complete resection in the Taiwanese literature.

Management of metastatic melanoma

Metastatic melanoma is known to bear a very poor prognosis. No standard of care has yet been

established. Current systemic therapies include cytokine therapy, chemotherapy and biochemotherapy. Because of the resistance of melanoma to these therapies, other approaches such as cellular therapy, gene therapy and targeted therapy are undergoing investigation.

Systemic chemotherapy and cytokine therapy for the treatment of metastatic melanoma

Although not being considered a curative measure, chemotherapy continues to play a role in palliative treatment for patients with metastatic melanoma. Dacarbazine is the most active single agent.[39] The response rate ranges from 15% to 25% in melanoma. However, the response duration is generally short. A similar oral alkylating agent, temozolomide, has an objective response rate of 21%.[40]

In one study, a combination of dacarbazine, carmustine, cisplatinum and tamoxifen (Dartmouth regimen) yielded a higher response rate from 30% to 40% but had no progression-free survival (PFS) or OS benefit over dacarbazine alone.[41] A combination of dacarbazine, vinblastine and cisplatinum (CVD regimen) also yielded a higher response rate without survival improvement.[42] Other single agents, including vinorelbine, paclitaxel, and docetaxel were also shown to have modest activity in melanoma.[39] Despite the advances in chemotherapy, PFS has remained approximately 2-4 months and OS 6-9 months for patients with metastatic melanoma.[39,43]

Temozolomide is a well-tolerated, oral alkylating agent with activity in the central nervous system.[44,45] A multicenter, open-label, phase II study was conducted to assess the safety and efficacy of temozolomide in patients with brain metastases from metastatic melanoma.[46] Previously untreated patients received temozolomide 200 mg/m^2/d 5 days, and previously treated patients received 150 mg/m^2/d for 5 days every 28 days. Treatment continued for 1 year or until disease progression or unacceptable toxicity. Among previously untreated patients, 25% had more than four brain lesions, eight (7%) achieved an objective response (one complete and seven partial), and 34 (29%) had stable disease in brain metastasis. Median OS was 3.5 months. Among previously treated patients, 21% had more than four brain lesions, one had a partial response, and six (18%) had stable disease in brain metastasis. Median OS was 2.2 months. Temozolomide was well tolerated, with four (3%) patients discontinuing therapy because of adverse events. Further evaluation of temozolomide combination therapy is warranted.

Cytokine therapy, including IFN and interleukin-2 (IL-2), has been studied in the treatment of metastatic melanoma. IL-2 has an overall response rate of 12.5%.[47] More importantly, these responses have been durable, with a prolonged disease response. Patients with a partial response have a median response duration of 5.9 months. Up to a third of the responses observed with IFN were complete, with some durable responses. Responses have generally been in patients with small-volume cutaneous or soft tissue disease. IFN has primarily been used in combination with other agents, and a meta-analysis of multiple trials reported a higher overall response in IFN-containing regimens (24% versus 17%).[48]

In Taiwan, Yang et al. treated twelve consecutive metastatic melanoma patients with the Dartmouth regimen,[49] the most common palliative treatment modality. In 10 evaluable patients, there were 4 (40.0%) partial responders. Two of the responders maintained their remission for more than one year without maintenance chemotherapy. However, no one survived more than 5 years in the subsequent follow-up analysis in the same institution.[10] With the addition of IL-2 to the Dartmouth regimen, we evaluated the toxicity and efficacy of biochemotherapy for 40 patients with metastatic malignant melanoma. IL-2 18 MIU/day was given in divided doses by subcutaneous injection three times a week. A total of 5 patients achieved a survival longer than 5 years (unpublished results), suggesting the benefit of subcutaneous low-dose IL-2 in metastatic melanoma in Taiwan.

Cytoreductive surgery and curative metastectomy

Debulking or cytoreductive surgery is sometimes performed in metastatic malignancies of various types; the underlying rationale is to reduce the tumor burden to a level at which systemic therapies can become effective. This strategy has proven valuable in randomized trials of ovarian cancer and renal cell carcioma,[50,51] but only in non-randomized trials of melanoma.[14,52] Sondak *et al*. prospectively evaluated surgical resection for stage IV melanoma.[52] From 1996 to 2005, 77 patients who were considered to have resectable stage IV disease were enrolled.

Only 62 patients (81%) actually underwent surgical resection. After surgery, median PFS was 6 months, with 9 patients (15%) remaining progression-free. Median OS was 21 months. Nonetheless, a large randomized trial is still needed to confirm the benefit of cytoreductive surgery in metastatic melanoma.

Metastasectomy, which is the surgical resection of distant metastases with tumor-free surgical margins, can be successful in carefully selected patients with distant melanoma metastases in the soft tissue or at sites such as the lymph nodes, lung, liver, brain and other organs. With appropriate patient selection, surgery can provide effective palliation, regional disease control, and occasional long-term disease-free survival, even in patients with metastatic melanoma.[53]

Dendritic cells in cancer immunotherapy

Dendritic cells (DCs) pulsed by autologous tumor apoptotic bodies (monoclonal antibodies [MAB]) may induce a unique combination of the necessary antigen-presenting molecules and the appropriate tumor-associated peptides to generate a specific effector T-cell response.[54] We previously reported that MAB-pulsed DC vaccination was well tolerated in patients with metastatic melanoma; no significant side effects were observed. Of the nine patients receiving DC vaccination, one achieved a partial response with a reduction in a lung metastatic tumor mass. Two patients had stable disease for more than 24 months, one developed multiple metastases and survived for 33 months, and the other achieved long-term survival (> 70 months). No treatment-related grade 3-4 toxicity, neutropenia, skin ulceration, or tumor growth at the injection site was observed in any of the cases. Mild draining lymph node tenderness lasting less than 48 hours and enlargement of regional lymph nodes were common. No serious side effects were noted, indicating the safety of DC-based immunotherapy.[55]

Management of in-transit metastasis

Cutaneous melanoma is a malignancy that commonly spreads via the lymphatic vessels. A unique type of lymphatic-based metastasis is the so-called in-transit metastasis (Fig. 2), which results in multiple cutaneous or subcutaneous nodules. A large series of more than 400 patients with stage II melanoma reported an in-transit metastases rate of 6.6%, with an additional 3.3% of patients having local recurrences near the site of the initial excision. Both types of recurrences represent intralymphatic spread with an approximate 10% overall rate for cutaneous melanomas of the extremity.[56] When treating in-transit disease, surgery should be attempted first, if anatomically possible, with the goal of a complete resection.[53]

Isolated limb perfusion (ILP), if effective, is an ideal strategy for treating this pattern of disease and avoids amputation. Initial efforts with this technology used nitrogen mustard and then a related compound, melphalan (L-phenylalanine mustard). The initial report of a phase II regimen using melphalan and tumor necrosis factor (TNF) alpha for treatment of in-transit metastases reported 29 patients (90%) achieved a complete response and another 3% achieved significant (75%) partial responses.[57] TNF also has been used in the United States and in Europe, but has not shown significant benefits compared with melphalan alone in randomized trials.[58]

Isolated limb infusion (ILI), generally using melphalan plus dactinomycin, is a less invasive form of regional chemotherapy using a radiologically placed cannula and tourniquet occlusion to isolate the limb.[59-61] In a series of patients treated at the Sydney Melanoma Unit, the overall response rate in limbs treated by ILI was 85%, with a complete response rate of 41% and a partial response rate of 44%.[62] The median duration of overall response was 16 months. Most regional relapses (95%) occurred

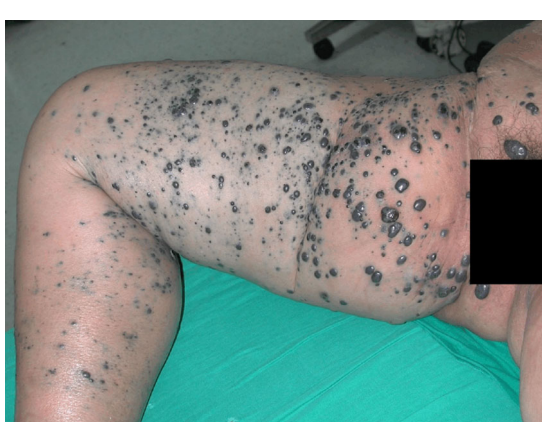

Fig. 2 Diffuse in-transit metastases in a patient with acral lentiginous melanoma. The lesions are confined to the right inguinal lymphatic draining region. There are no lesions on the skin of the other extremity or the abdominal wall.

within 2 years of ILI,[62] which is very similar to the figure reported within 3 years of ILP. The median duration of complete response after ILI (16 months) was comparable to that achieved after ILP (19 months). All these results indicate that the efficacy of ILI is similar to that of ILP.

Future treatment

We are entering a new era of molecular-targeted therapy. Preliminary results from trials of tyrosine kinase inhibitors in metastatic melanoma have been reported. In a phase 1 dose-escalating study, PLX 4032, a selective inhibitor of the V600E mutant of BRAF (found in approximately 50-60% of melanomas), was reported to achieve objective responses in patients with V600E-positive melanoma.[63] C-Kit mutation or amplification was found in approximately 30% of mucosal, acral, or chronically sun damaged melanoma.[64] Preliminary results from a phase 2 study of imatinib, a C-Kit inhibitor, showed objective responses in patients with melanoma tumors harboring mutation or amplification of C-Kit.[65] Since the majority of melanoma in Taiwan is of acral or mucosal histology, C-Kit inhibitors would play an important role in the future. Immunotherapy with an antibody against cytotoxic T-lymphocyte antigen 4, ipilimumab, was recently demonstrated to prolong median and long-term survival in patients with human leukocyte antigen-A2 positive metastatic melanoma.[66]

We conclude that increased understanding of the biology of primary tumors and metastasis will allow for dramatic improvement in the accuracy of staging metastatic disease and better techniques for surgical resection, providing the best chance for long-term palliation or cure of melanoma in Taiwan.

Article highlights box

1. Incidence rate of melanoma
* Melanoma is a rare disease in Taiwan. The age-adjusted rate for invasive melanoma in 2006 was 0.65/100,000, 0.71/100,000 for males and 0.58/100,000 for females.

2. Etiology of melanoma
* The etiology of acral lentiginous melanoma (ALM) is associated with penetrating injury and heavy exposure to agrichemicals, although ultraviolet irradiation is the most important etiology of melanoma in Western countries.

3. Characteristics and prognosis of melanoma in Taiwan
* The most common cutaneous melanoma was ALM (58%), followed by nodular melanoma (30.4%).
* The incidence of stages I, II, III and IV at presentation was 27.5%, 13.5%, 33.9% and 25.1%, respectively. The median survival was 3.71 years, and the 5-year survival rate was 45.63%.

4. Surgical management of malignant melanoma
* For primaries ≤ 1 mm thick, 1 cm margins are adequate. For primaries between 1 mm and 2 mm thick, 1 to 2 cm margins are adequate, while 2 cm margins are adequate for primaries up to 4 mm thick.
* Metastases to the inguinal lymph nodes should be treated by complete lymph node dissection (CLND). Lymphatic mapping and sentinel lymph node (SLN) biopsy are recommended to detect the status of nodal metastases. SLN biopsy followed by immediate CLND for patients with SLN metastasis provides better disease free survival (DFS) and overall survival (OS) than delayed CLND without SLN biopsy.

5. Adjuvant treatment
* Adjuvant high-dose interferon (IFN) treatment is associated with a DFS benefit while its impact on OS remains to be determined.
* The most recent meta-analysis demonstrated an OS benefit (HR = 0.89) using adjuvant IFN for high-risk melanoma.
* The toxicity of IFN limits its routine use in Taiwan.

6. Management of metastatic melanoma
* Dacarbazine-based chemotherapy remains the most common treatment for metastatic melanoma, although its goal is usually palliation.
* The addition of interleukin-2 provided a chance for long-term survival in a small group of patients.
* Surgical metastasectomy in selected patients may lead to long-term disease control.

7. Future treatment
* BRAF and C-Kit inhibitors may benefit a subgroup of patients whose melanoma bears mutations in these genes.

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皮膚黑色素癌：台灣經驗及文獻回顧

張文震

黑色素癌在台灣是一種罕見疾病，發生率每十萬人口 0.65 人。大部分台灣人黑色素癌與過度暴露於紫外線輻射是不相關的。肢端型黑色素癌佔皮膚黑色素癌 58%。手術切除是治療黑色素癌最重要的療法，包括切除原發黑色素腫瘤、前哨站淋巴結、臨床異常淋巴結以及少數遠端轉移腫瘤。輔助性高劑量干擾素療法可以延長無病存活期，但因副作用大，在台灣較少被使用。已發生轉移的疾病預後差，中位生存期爲 12 個月。在過去，單純化療是治療轉移性疾病最常用的療法。最近生物化療更普遍用於治療轉移性黑色素癌患者。(長庚醫誌 2010;33:602-12)

關鍵詞：皮膚黑色素癌，肢端型黑色素癌，台灣

長庚醫療財團法人林口長庚紀念醫院 血液腫瘤科；長庚大學 醫學院
受文日期：民國99年6月2日；接受刊載：民國99年8月25日
通訊作者：張文震醫師，長庚醫療財團法人林口長庚紀念醫院 血液腫瘤科。桃園縣333龜山鄉復興街5號。
Tel.: (03)3281200轉2524; Fax: (03)3286697; E-mail: wen1902@hotmail.com