Biochemotherapy with Carmustine, Cisplatin, Dacarbazine, Tamoxifen and Low-dose Interleukin-2 for Patients with Metastatic Malignant Melanoma

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Background: The toxicity and efficacy of biochemotherapy with low-dose interleukin-2 for patients with metastatic malignant melanoma (MM) were studied.

Method: Metastatic chemo-naïve MM patients were given biochemotherapy (BCDT regimen) with carmustine (BCNU), cisplatin (CDDP), dacarbazine (DTIC), and tamoxifen and interleukin-2 (IL-2) 18 Million International Units in divided doses by subcutaneous injection three times a week for four weeks. BCDT consisted of BCNU (150 mg/m^2, day 1 every 8 weeks), CDDP (25 mg/m^2, days l-3 every 4 weeks), DTIC (220 mg/m^2, days 1-3 every 4 weeks) and tamoxifen 10 mg twice a day. Treatment was repeated for a total of 6 cycles, or until disease progression or unbearable toxicity.

Results: From Nov 2001 to July 2005, 40 patients (20 men; 20 women) were enrolled. Their median age was 54 years (range 22-79 years). Subtypes of melanoma included 23 (57.5%) acral lentiginous, 11 (27.5%) nodular, 1 (2.5%) mucosal, and 5 (12.5%) others. Grade 3-4 toxicities included neutropenia (27.5%), anemia (45%), and thrombocytopenia (40%). Constitutional IL-2 toxicities included indurate injection site (57.5%), fever (60%), chills (55%), itchy skin (42.5%), bone pain (32.5%) and myalgia (45%). Grade 1-2 hypotension was noted in 12.5% of patients. Eosinophilia (range 5% to 71%) was evident in 72.5% of patients. The response rate was 32.5% including 5% with a complete response, 27.5% with a partial response, and 17.5% with stable disease. The median progression-free survival was 6.2 months (95% CI: 2.9~9.6 months). The median overall survival was 11.3 months (95% CI: 7.0~15.6 months). Five patients (12.5%) who presented with oligo-metastasis achieved five-year survivals.

Conclusions: Our data demonstrated that low-dose IL-2 plus BCDT is tolerable. A durable response and long-term survival can be achieved in a small subgroup of patients.

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Key words: malignant melanoma, carmustine, cisplatin, dacarbazine, tamoxifen, interleukin-2

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The Dartmouth regimen (dacarbazine, cisplatin, carmustine, and tamoxifen) is active against malignant melanoma.[1,2] Response rates of 26% to 38.2% have been reported in phase II studies and 18.5% to 30% in prospective randomized studies.[3-7] Interleukin-2 (IL-2) was shown to be active alone in renal cell carcinoma and melanoma,[8] and in combination with interferon (IFN), chemotherapy,[9,10] and tumor infiltrating lymphocytes.[11,12] Eton et al. demonstrated a favorable outcome using biochemotherapy with the addition of IL-2 and IFN.[13] High-dose IL-2 (HDIL-2) was shown to render long-term survival in a small proportion of selected patients.[14] However, the use of HDIL-2 was limited by its toxic profile.[15-19] Subcutaneous low-dose IL-2 (LDIL-2) for metastatic melanoma is tolerable and can be used in an outpatient setting.[20-22]

The Dartmouth regimen has been a standard regimen for metastatic melanoma at Chang Gung Memorial Hospital.[23] In our previous study of cutaneous melanoma in Taiwan, the median survival of the 43 patients with stage IV melanoma was 12.7 months and their 5-year survival rate was 0%.[24] We conducted this phase II trial for first-line treatment of metastatic melanoma using the Dartmouth regimen and LDIL-2. The primary objective was to determine the response rate, and the secondary objectives were evaluation of the toxicity, progression-free survival and overall survival.

METHODS

Patient eligibility

Before enrollment, all patients were required to have a physical examination, a chest radiograph, chest and upper abdominal computed tomography (CT), a bone scan, and a complete blood work-up. A brain CT or magnetic resonance imaging (MRI) was only performed when brain metastasis was suspected. Eligible patients for this study had histologically confirmed malignant melanoma. They were required to have measurable recurrent or metastatic lesions. Other inclusion criteria were age over 18 years, white blood cell count greater than 3,000/μL, platelet count greater than 100,000/μL, serum creatinine less than 2.0 mg/dL, serum total bilirubin less than 1.5 mg/dL, and Eastern Cooperative Oncology Group performance status ≤ 2. The exclusion criteria were as follows: previous systemic treatment, serious concomitant illness which may be aggravated by therapy, concomitant active malignancy, uncontrolled central nervous system metastasis, psychological instability, or severe impairment of cardiopulmonary function. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital and all patients provided informed consent.

Treatment

Eligible patients received tamoxifen 10 mg twice daily throughout the treatment. Carmustine 150 mg/m^2 was given on day 1 of every other cycle. Cisplatin 25 mg/m^2 and dacarbazine 220 mg/m^2 were given daily on days 1 to 3 of each cycle. Patients were treated every 4 weeks. On the day when carmustine was administered, the cisplatin and dacarbazine were given at least 1 hour after the carmustine. IL-2 18 Million International Units (MIU) was injected subcutaneously in two divided doses three times every week for four weeks.

Dose modification

The doses for cisplatin and dacarbazine were modified according to the neutrophil and platelet counts as well as the level of serum creatinine during chemotherapy. The applied doses of cisplatin and decarbazine were 100% for patients with serum creatinine levels less than 1.5 mg/dL and neutrophil and platelet counts over 2,000/μL and 100,000/μL, respectively. The dose of cisplatin was reduced to 75% when the patient's neutrophil count, platelet count, and serum creatinine were 1,500-2,000/μL, 75,000-100,000/μL, and 1.5-2.0 mg/dL respectively. However in these conditions, the dose of dacarbazine was stilled maintained at 100%. If the patient's neutrophil and platelet counts were between 1,000-1,500/μL and 50,000-75,000/μL respectively while the serum creatinine remained between 1.5-2.0 mg/dL, dacarbazine was reduced to 50%. However under these conditions, the dose for cisplatin remained at 75%. If the patient's neutrophil and platelet counts were less than 1,000/μL and 50,000/μL respectively, and the serum creatinine increased to more than 2.0 mg/dL, neither cisplatin nor dacarbazine was given. In the absence of disease progression or intolerable toxicity, patients were to remain on the treatment protocol for a total of six cycles of treatment. Treatment was discontinued if

there was evidence of disease progression.

Treatment evaluation

Responses were initially defined according to World Health Organization criteria for measurable disease, and later, according to Response Evaluation Criteria in Solid Tumors when these criteria became available. Response was evaluated every two cycles. Treatment was repeated for a total of 6 cycles, except in cases of disease progression or unbearable toxicity. Patients were reviewed every 3 months after protocol cessation.

The overall survival was calculated from the date of enrollment to the date of death. Otherwise, the patient was censored until the last day for which he or she was confirmed to be alive. Progression-free survival was assessed from the date of enrollment to the date of documented disease progression or death from any cause. Patients who received at least one dose of the study drug were considered assessable for adverse events based on laboratory tests and clinical signs and symptoms experienced during the treatment period. The National Cancer Institute Common Toxicity Criteria version 2.0 was used for assessment.

Statistical considerations

According to Simon's two-stage optimal design, we chose a lower activity (p0) of 0.15 and a target activity (p1) of 0.30. A total of 40 cases were required to test this hypothesis (type I error 0.05, type II error 0.20). At the end of the first stage, at least one response had to be found in 10 patients. Survival was calculated by the Kaplan-Meier method.

RESULTS

From Nov 2001 to July 2005, 40 patients (20 men; 20 women) were enrolled. Their median age was 54 years (range: 22-79 years). Subtypes melanoma included 23 (57.5%) acral lentiginous, 11 (27.5%) nodular, 1 (2.5%) mucosal, and 5 (12.5%) others. The general characteristics of patients in this study are shown in Table 1. The median follow-up time was 4.5 years, ranging from 3 to 6.5 years. The median number of cycles of treatment was 3.5 cycles, as 10 patients received 5~6 cycles (25%), 15 patients received 3~4 cycles (37.5%), and 15 patients received 1~2 cycles (37.5%).

Table 1. Patient Characteristics (N = 40)

Characteristics		%
Sex, %		
Male		50.0
Female		50.0
Age, years		
Median (range)	54 (22-79)	
Subtypes		
Acral lentiginous		57.5
Nodular		27.5
Mucosal		2.5
Others		12.5
Disease status		
M1a		25.0
M1b		20.0
M1c		55.0
Site of distant metastases, %		
Skin/Lymph node		85.0
Lung		47.5
Bone		25.0
Liver		20.0
Spleen		7.5
Brain		7.5
Breast		2.5
Number of metastatic sites, %		
1		37.5
2		40.0
> 2		22.5
Performance Status, %		
0		7.5
1		80.0
2		12.5

Grade 3-4 toxicities included neutropenia (27.5%), anemia (45%), and thrombocytopenia (40%). Constitutional IL-2 toxicities included indurate injection site (57.5%), fever (60%), chills (55%), itchy skin (42.5%), bone pain (32.5%) and myalgia (45%). Grade 1-2 hypotension was noted in 12.5% of patients. Eosinophilia (range: 5% to 71%) was evident in 72.5% of patients. Treatment toxicity is shown in Table 2. Twenty patients had IL-2 interruption during the study because of intolerable toxicity, including fever (6 patients, 15%), malaise (5 patients, 12.5%), thrombocytopenia (3 patients, 7.5%), neutropenia (2 patients, 5%), vomiting (2

Table 2. Toxicity of Carmustine, Cisplatin, Dacarbazine, Tamoxifen and Interleukin-2 for 40 Patients with Malignant Melanoma

	Grade 1/2	Grade 3/4
	%	%
Neutropenia	35	27.5
Thrombocytopenia	20	40
Anemia	42.5	45
Nephrotoxicity	15	0
Hepatotoxicity	5	0
Fever	57.5	2.5
Chills	55	0
Skin induration	47.5	10
Mylagia	45	0
Hypotension	12.5	0
Itchy skin	42.5	0
Bone pain	32.5	0
Eosinophilia	72.5	0
Nausea	62.5	0
Vomiting	57.5	0
Pain	40	2.5
Diarrhea	7.5	2.5
Peripheral neuropathy	2.5	0

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.

patients, 5%), infection (1 patient, 2.5%), and psychological problems (1 patient, 2.5%). Seven patients (17.5%) were admitted to the hospital for toxicities, including six patients with infection and one with prolonged neutropenia and diarrhea.

All patients had measurable lesions. Measurable bone lesions were defined as lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components which met the definition of measurability by CT or MRI. The response rate was 32.5% including 2 complete responses (5%) and 11 partial responses (27.5%). Seven (17.5%) patients had stable disease. Twenty (50%) patients experienced disease progression. The median progression-free survival was 6.2 months (95% CI: 1~11.4 months). The median overall survival was 11.3 months (95% CI: 6.3~16.2 months). The 1 year survival rate was 47.5% and the 5 year survival rate was 12.5%. The results are shown in Table 3, and the Fig. 1.

Three men and 2 women had long-term survival as detailed in Table 4. These 5 patients all presented with a single metastasis in the spinal cord, lung, bone, or lymph node. Two of these five patients, patients 4 and 5, developed lymph node recurrence and underwent complete resection.

DISCUSSION

The treatment of patients with metastatic melanoma remains challenging.[25,26] A variety of biochemotherapy regimens have been studied that appear to be associated with an increased response rate and in some cases increased overall survival.[27] HDIL-2 was indeed shown to prolong survival in 7.6% of patients with metastatic melanoma.[28] The efficacy of HDIL-2 is better than LDIL-2, and a high dose is usually recommended.[29] However, the toxicity of HDIL-2 and the requirement to treat in the Intensive Care Unit limit its wide application. The major toxicities of our treatment regimen with LDIL-2 were related to both chemotherapy and IL-2. Although more than 50% of the patients had side effects, these symptoms were not as severe or life-threatening as those with HDIL-2 treatment. Hypotension was encountered but no vasopressors were needed.

There were no long-term survivors in our retrospective study of patients treated between 1991 and 2000.[24] In this study the response rate and survival were comparable to other series in the literature.[1,30]

Table 3. Results of Treatment

	N = 40	%	Median months	95% CI
Complete response	2	5		0–12.0%
Partial response	11	27.5		13.0–42.0%
Stable disease	7	17.5		5.2–29.8%
Disease progression	20	50		33.8–66.2%
Progression free			6.2	2.9–9.6 months
Response duration			8.9	8.0–9.8 months
Follow up duration			54	36–78 months
Median survival			11.3	7.0–15.6 months
1-year survival	19	47.5		32.0–63.0%
5-year survival	5	12.5		2.3–22.7%

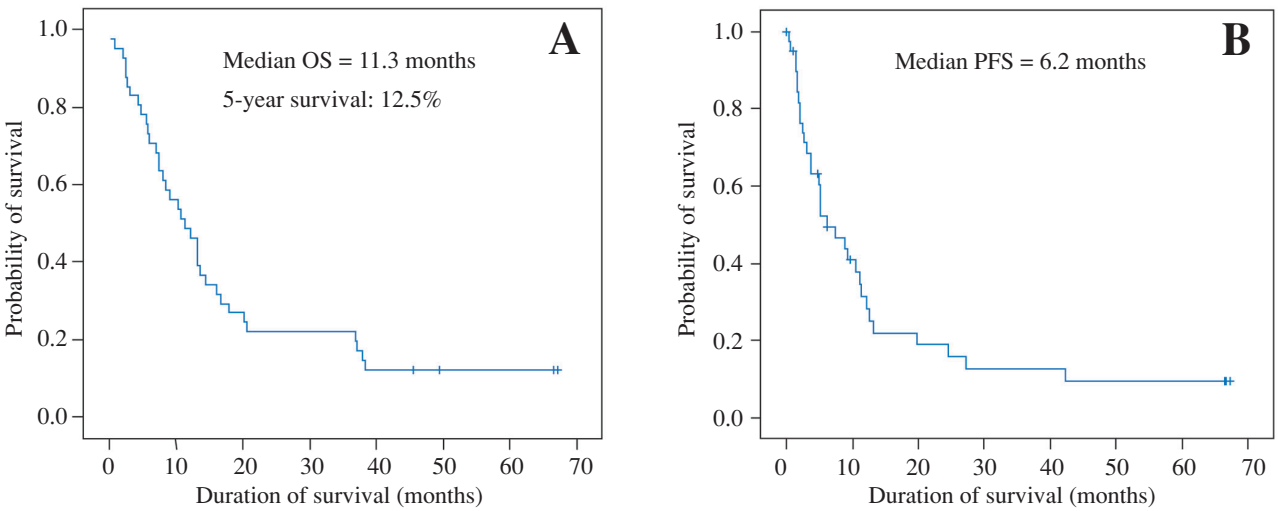

Fig. 1 Kaplan-Meier estimates of overall survival (A) and progression-free survival (B) for all 40 patients.

Table 4. Summary of 5 Long-term Survivors

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	Female	Male	Male	Female	Male
Age, years	51	42	32	32	62
Primary site	Unknown	Finger	Thigh	Sole	Sole
Pathologic type	Melanoma	ALM	NM	ALM	ALM
Initial diagnosis date, month/day/year	05/21/2002	04/01/2002	09/04/2002	02/09/2001	12/26/2000
Initial diagnosis stage	IV	III	IV	III	III
Date of recurrence or metastasis, month/day/year	05/21/2002	09/23/2002	09/04/2002	02/17/2004	07/05/2004
Site of metastasis	Spinal cord	Lung	Bone	Bone	LN
Metastasis diagnosed by	Pathology	Chest CT	PET-CT	Pathology	Pathology
Cycles of treatment	3	4	5	6	5
Response	SD	CR	SD	PR	PR
Status post treatment	SD	NED	SD	LN recurrence	Skin recurrence
Survival (months)	66+	67+	67+	42+	38+

Abbreviations: ALM: acral lentiginous melanoma; NM: nodular melanoma; LN: lymph node; CT: computed tomography; PET-CT: positron emission tomography-computed tomography; SD: stable disease; CR: complete remission; PR: partial response; NED: no evidence of disease.

Furthermore, the 5-year survival in this study was 12.5%. The addition of LDIL-2 to BCDT may play a major role in this improvement.

All 5 long-term survivors in this study had oligo-metastasis. The response to treatment included complete and partial responses and stable disease, indicating the ability of LDIL-2-containing biochemotherapy to induce tumor shrinkage and/or dormancy. One of these 5 patients who had stable disease after 3 cycles of biochemotherapy survived more than 66 months. This result might be due to the effects of biochemotherapy or the natural disease course. In addition, another two of these 5 survivors (patient 4 and 5) had recurrent tumors excised 24 and 36 months after the initial response to biochemotherapy. Aggressive metastasectomy is also important to

treat patients with a few metastases.[31]

At present, standard treatment for patients with metastatic melanoma remains undefined. The range of treatment options includes simple observation, therapy with single-agent decarbazine, combination chemotherapy, or participation in a clinical trial of biochemotherapy or other experimental approaches. Participation in clinical trials is strongly encouraged whenever possible. Additionally, the role of cytotoxic chemotherapeutic agents such as temozolomide and new cytotoxic combinations remain to be defined for metastatic melanoma.[32] In the future, a better understanding of the mechanisms of melanoma chemoresistance and the introduction of new molecularly based treatments such as antisense oligonucleotides can be expected to have major consequences for the treatment of patients with metastatic melanoma.[33]

We are entering a new era for the systemic therapy of melanoma in which the molecular events that drive tumor progression or the suppression of the host immune response to tumor are understood.[34] With this understanding, trials that target the events critical to tumor progression and immunosuppression are feasible. Sorafenib, a potent and selective multikinase inhibitor, exerts its anti-tumor and anti-angiogenic effects via inhibition of vascular endothelial growth factor receptor-1, -2 and -3, platelet-derived growth factor receptor-a and -β, and Raf. There have been promising results from a single-arm study of paclitaxel and carboplatin plus sorafenib in advanced melanoma, but there was no improvement in progression-free survival or the objective response rate in a randomized phase III study.[35] Although the list of potential therapeutic targets in melanoma is growing, few targeted therapeutic agents have been successful in phase III trials. Chemotherapy serves as a readily available and, at this time, the best-justified partner for signaling inhibition in the current generation of trials.[36] Before effective targeted therapy is available, chemotherapy and biotherapy remain the treatments of choice in the absence of appropriate clinical trials.

Therefore, for patients who are not candidates for HDIL-2, we propose treatment with a low-dose IL-2-containing regimen and aggressive metastasectomy for patients with limited metastases. In this study, we demonstrated a durable response and long-term survival in metastatic melanoma treated with LDIL-2 plus BCDT.

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以低劑量之介白素-2對晚期惡性黑色素瘤的生物化學治療

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背 景： 本計畫研究以低劑量介白素-2之生物化學療法治療晚期惡性黑色素瘤的毒性與效果。

方 法： 共四十位未接受過化學治療之轉移型惡性黑色素瘤患者參與研究。接受生物化學治療，化學治療 BCDT 處方的藥物包括卡氮芥 (carmustine, 150 mg/m^2, day 1 every 8 weeks)、順鉑 (cisplatin, 25 mg/m^2, day l-3 every 4 weeks)、氨烯咪胺 (dacarbazine, 220 mg/m^2, day 1-3 every 4 weeks) 與他莫昔芬 (tamoxifen 10 mg) 一天兩次，以及每週三天皮下注射介白素-2，一天中分兩次給予共 18 MIU。治療持續至最多六個療程，若患者之疾病惡化或是產生無法忍受之毒性，治療也會停止。

結 果： 研究期間從 2001 年 11 月至 2005 年 7 月，共有 40 位轉移型黑色素瘤患者納入研究。其中 20 位是男性，20 位是女性，平均年齡爲 54 歲，其惡性黑色素瘤的病理類型爲 23 個肢端型黑色素瘤，佔 57.5%；11 個結節型黑色素瘤，佔 27.5%；1 個黏膜型黑色素瘤，佔 2.5%；5 個其它類型，佔 12.5%。第三、四級毒性有嗜中性球低下 (27.5%)、貧血 (45%)、血小板低下 (40%)。介白素-2造成的毒性有注射部位硬化 (57.5%)、發燒 (60%)、寒顫 (55%)、皮膚癢 (42.5%)、骨頭疼痛 (32.5%)、肌肉痠痛 (45%)。有 12.5% 的患者產生第一、二級的低血壓，有 72.5% 的患者發生嗜伊紅性血球增多。對治療的反應率爲 32.5%，包括 5% 的完全反應率及 27.5% 的部分反應率，另外有 17.5% 的患者爲疾病穩定。無惡化存活期的中位數爲 6.2 個月 (95% 信賴區間爲 2.9~9.6 個月)，中位存活期爲 11.3 個月 (95% 信賴區間爲 7.0~15.6 個月)，有 5 位只有單一轉移的患者達到了五年以上的存活，五年存活率爲 12.5%。

結 論： 根據此研究的結果顯示低劑量介白素-2加上化學治療 BCDT 處方是可耐受的，並且在一些患者可以產生良好的反應與長期的存活。

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關鍵詞： 惡性黑色素瘤，卡氮芥，順鉑，氨烯咪胺，他莫昔芬，介白素-2

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