COMBINATION CHEMOTHERAPY (DACARBAZINE, CARMUSTINE, CISPLASTIN, AND TAMOXIFEN) IN ADVANCED MELANOMA

E H Tan, P T Ang

ABSTRACT

Melanoma is rare in Singapore with an age-standardised rate (ASR) of 0.4-0.8 per 100,000 per year. Thirteen patients with metastatic or locally advanced melanoma were referred to the Department of Medical Oncology, Singapore General Hospital between Feb 1991 and Nov 1993. Ten patients were given combination chemotherapy comprising carmustine (BCNU), cisplatin, dacarbazine (DTIC) and tamoxifen. The remaining 3 patients either rejected chemotherapy or were too ill to receive chemotherapy. Patient characteristics were as follows: there were 6 males and 4 females; age range 29-75 years; all were Chinese; sites of primary disease: extremities 8, retroorbital 1, vagina 1; sites of metastases: lymph nodes 6, skin 2, pulmonary 3, liver 1. All received the same combination chemotherapy comprising iv BCNU 150 mg/m² q8wk, iv DTIC 220 mg/m² x 3 days q4 wk, iv cisplatin 25 mg/m² x 3 days q4 wk and tab tamoxifen 40 mg daily. There were 6 partial responses and no complete responses, giving a response rate of 60% with a median survival of 11.5 months. Three patients with sites of disease in the vagina, retroorbital region and metastatic liver disease had progressive disease despite chemotherapy and one died of treatment related sepsis. The 6 responders include those with metastases to the skin, nodes and/or lung. Treatment was generally tolerable. Two patients experienced delays of their subsequent cycles of treatment by 1-2 weeks due either to neutropenia and/or thrombocytopenia. This regimen is a fairly active combination against metastatic melanoma, particularly those with metastases to the nodes, skin and the lung. Those with involvement of other sites tend to respond poorly.

Keywords: *advanced melanoma, Chinese, combination chemotherapy, response rates*

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INTRODUCTION

Melanoma is an uncommon disease in this part of the world. In Singapore, Chinese constitutes 77.7% of the population, with the Malays, Indians and Others constituting 14.1%, 7.1% and 1.1% respectively. The age-standardised rate of skin melanoma among Chinese is about 1 per 100,000 per year for males and 0.4 per 100,000 per year for females[1]. These rates are comparable with Chinese communities elsewhere. For the last 2 decades there has been no change in the incidence[1] unlike the rising incidence reported in Caucasian-dominated countries[2,3].

The Dartmouth regime comprising carmustine (BCNU), dacarbazine (DTIC), cisplatin and tamoxifen was first described by Del Prete et al who reported a response rate of 55% for metastatic melanoma[4]. A subsequent report by McClay et al reported similar response rate[5]. Since February 1991, we started using a modified form of this regimen for our patients with advanced melanoma to determine its efficacy in Asian patients.

PATIENTS AND METHODS

Patients were considered eligible for the combination regimen if they fulfilled the following criteria: histologically proven metastatic or locally advanced unresectable melanoma, no prior treatment (chemotherapy or radiation therapy), good performance status (ECOG 2 or less), normal cardiac and renal function, and measurable disease.

Department of Medical Oncology
Singapore General Hospital
Outram Road
Singapore 169608

E H Tan, MBBS, M Med, MRCP
Senior Registrar

P T Ang, MBBS, M Med, MRCP, FACP
Head and Senior Consultant

Correspondence to: Dr E H Tan

Thirteen patients with metastatic/locally advanced melanoma were referred to the Department of Medical Oncology, Singapore General Hospital between February 1991 and November 1993. Two patients rejected further treatment and one patient was deemed too ill to receive chemotherapy. The remaining 10 patients were given the combination regimen comprising iv BCNU 150 mg/m² once every 8 weeks, iv DTIC 220 mg/m² for 3 days every 4 weeks, iv cisplatin 25 mg/m² for 3 days every 4 weeks and tamoxifen 40 mg daily.

The hemogram, serum urea/electrolytes and creatinine clearance were checked before each cycle of treatment. Tumour response to treatment was assessed every 4 weeks before each course of treatment by physical examination, serial radiograph or other studies as indicated. Treatment was discontinued if the disease was progressive or when patients developed unacceptable toxicities.

Complete response (CR) was defined as disappearance of all documented lesions for at least 4 weeks. Partial response was defined as a reduction of 50% or greater in sum of the products of two perpendicular diameters of all the measurable lesions lasting for at least 4 weeks without appearance of new lesions. Progression was defined as appearance of new lesions or a greater than 25% increase in the sum of the products of the largest diameter and its perpendicular as compared with the lowest value recorded.

RESULTS

Clinical Characteristic (Table I)

There were 6 males and 4 females. Their age range was 29-75 years; all were Chinese. All had performance status of ECOG 2 or better. The sites of primary disease are as follows: extremities 8, retroorbital 1 and vagina 1. The sites of metastases: lymph nodes 6, skin 2, pulmonary 3 and liver 1. The patient with primary melanoma involving the vagina had locally advanced unresectable disease which extended into the pelvic cavity. She had no evidence of metastatic disease.

Table I – Patient Characteristics

Charateristics	(n = 10) No.	Percent
Sex		
Male	6	60
Female	4	40
Age (yr)		
Median	63	
Range	29-75	
Sites of primary		
extremities	8	80
retroorbit	1	10
vagina	1	10
Sites of metastases		
lymph nodes	6	60
skin	2	20
lung	3	30

Response to Chemotherapy (Table II)

There were 6 partial responses and no complete responses, giving a response rate of 60%. The responders included those with nodal, skin or pulmonary metastases. Four patients showed responses after the first cycle and 2 patients after the second cycle. The duration of response was less than 6 months in 3 patients and more than 6 months in 3 patients. One patient with pulmonary metastases responded very well to chemotherapy with good partial response noted after 2 cycles of treatment. The duration of response of the latter patient was more than 6 months (Fig 1). Two patients with vaginal, retroorbital advanced melanoma respectively and one patient with metastatic liver disease showed progressive disease during the course of chemotherapy. One patient died unexpectedly about 2 weeks upon completion of the first cycle of treatment. The median survival was 11.5 months.

Toxicities of Chemotherapy

Chemotherapy was generally well tolerated with the degree of nausea/vomiting not exceeding WHO grade 2. Two patients had thrombocytopenia, one of whom had grade 4 severity. One patient had grade 2 leucopenia. One patient died unexpectedly 2 weeks upon completion of the first cycle, probably treatment related though the cause was not ascertained. Deep venous thrombosis was not documented clinically in any patient. None of the patients developed nephrotoxicity as a result of the cisplatin administration. This is probably a result of aggressive pre- and post- hydration routinely given during cisplatin infusion.

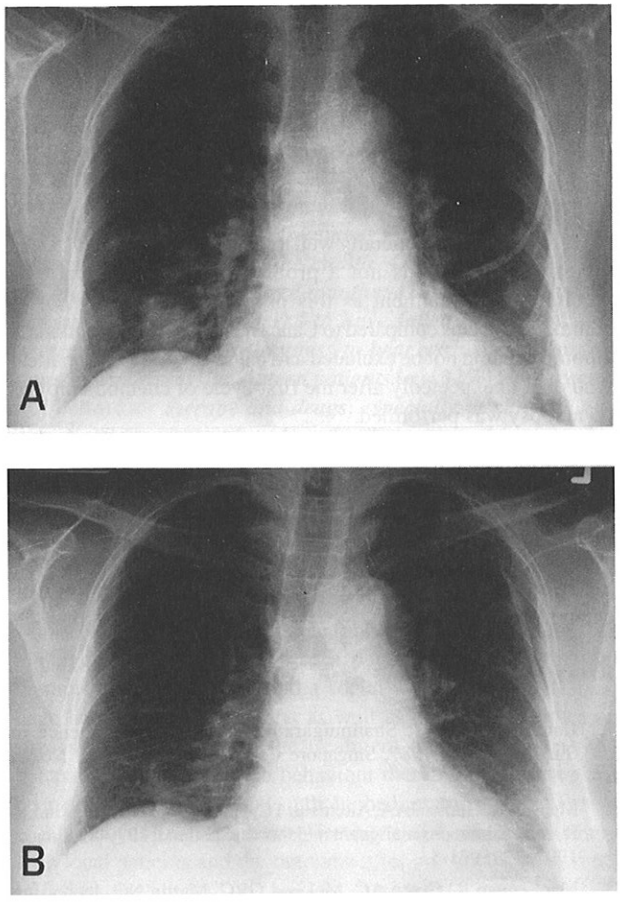
DISCUSSION

The best-studied single agents for treatment of melanoma are dacarbazine (DTIC) and nitrosoureas. Both have an objective response rate of between 10%-20% when used as single agents[6]. The platinum agents are also active against melanoma, though experience with this as a single agent is rather limited[7,8]. Since the reports by Fisher et al[9] and Sadoff et al[10], interest in the use of tamoxifen in advanced melanoma was started. A metanalysis

Table II – Response to chemotherapy

Response	No.	Percent
Complete	0	0
Partial	6	60
> 6 mths	3	
< 6 mths	3	

Fig 1 – Good partial response in a patient with pulmonary metastases. (A) Before chemotherapy, (B) after two cycles of combination chemotherapy



of 12 phase II studies of tamoxifen as single agent by the European Organisation for Research and Treatment of Cancer (EORTC), however, showed a low overall response rate of 7%[11]. Hence, tamoxifen as a single agent is of limited benefit in the treatment of patients with metastatic melanoma.

The Dartmouth regimen comprising dacarbazine, carmustine, cisplatin and tamoxifen was first described by Del Prete et al in 1984[4]. This combination was first reported as producing objective responses in 55% of the patients with metastatic melanoma which was confirmed by others[5]. Due to the high incidence of deep venous thrombosis (DVT) and pulmonary embolism (PE) encountered by McClay et al while using this regimen, tamoxifen was omitted in their second study[12]. Although no patient in the second study developed DVT or PE, the overall response rate was decreased to 10%. Tamoxifen was hence reincorporated in their third study which demonstrated an overall response rate of 52%[13]. The report by Lattanzi et al showed a similar effect of tamoxifen[14]. It is probable that tamoxifen has a synergistic interaction with one or more agents in the combination[15,16]. More recent studies using this combination or similar combination have been reported which have reproducibly demonstrated this regimen to be active in advanced melanoma[17-19].

Due to the rarity of melanoma in Singapore with Chinese comprising more than 70% of the population, only 13 patients with metastatic melanoma were referred to our department during this 3-year period. A response rate of 60% was obtained amongst the 10 patients who received combination chemotherapy which was similar to what was reported. Patients who responded tend to be those with skin, nodal or lung metastases which was similar

to what was observed by others. The majority of the responses were noted after the first cycle and the chemosensitivity of the tumour can generally be determined after 2 cycles of treatment. The relative low incidence rate of non-pulmonary visceral metastases in this group could account for the high response rate to chemotherapy and the reasonably good median survival of 11.5 months. The sole patient with liver metastases showed progressive disease during chemotherapy. The 2 patients with disease involvement of the retroorbit and vagina respectively also showed progressive disease despite chemotherapy, demonstrating the chemoresistance of these particular sites of disease.

This regimen is generally well tolerated by our patients. Deep venous thrombosis is not a problem amongst our patients receiving this treatment as this problem is generally not as common in Asians compared to Caucasians. However, pulmonary embolism could not be excluded as a cause of death in the patient who died unexpectedly after the first cycle of chemotherapy as no autopsy was performed.

This combination regimen, comprising DTIC, BCNU, cisplatin and tamoxifen is fairly active amongst our patients with metastatic melanoma especially in those with metastatic disease involving the skin, nodes or lung. We are still accruing patients into this regimen. With a bigger sample size, we hope to obtain a better assessment of the efficacy of this combination chemotherapy.

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