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Original Paper

Differential Responses to Chemoimmunotherapy in Patients with Metastatic Malignant Melanoma

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An open, multicentre non-randomised study was performed to evaluate the activity and toxicity of combination chemoimmunotherapy, consisting of cisplatin, interleukin-2 and interferon-α, in metastatic malignant melanoma. Between March 1992 and September 1993, 28 patients with pathologically proven metastatic malignant melanoma, bidimensionally measurable disease and an Eastern Co-operative Oncology Group score ≤1 were treated with the combination chemoimmunotherapy. The regimen consisted of cisplatin (100 mg/m^2 on day 0), interleukin-2 (Proleukin, Chiron, Middlesex, U.K.) 18 × 10^{6}IU/m^2/d continuous intravenous infusion on days 3–7 and 17–22, with interferon-α (Roferon-A, Roche, Hertfordshire, U.K.) 9 × 10^{6}U/d subcutaneously on days 3, 5, 7, 17, 19, 21 during the interleukin-2 infusions. The treatment cycle lasted 28 days. Among 27 assessable patients, 5 patients achieved partial responses, for an overall response rate of 18% (95% CI 6–37%). Median progression-free survival was 44 days (range 8–279) and median overall survival was 264 days (range 41–1432). Differential responses were noted in 41% of patients and responses were more frequent in non-visceral disease (skin, lymph node and soft tissue disease) ($P = 0.04$). These results indicate that differential responses to chemoimmunotherapy are common in patients with metastatic melanoma. This may account for the broad range of response rates reported in the literature. © **1997 Elsevier Science Ltd.**

Key words: melanoma, cisplatin, interleukin-2, interferon-α, chemoimmunotherapy, differential responses

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INTRODUCTION

SYSTEMIC TREATMENT of metastatic melanoma with conventional cytotoxic therapy remains disappointing. The most active cytotoxic agents include dacarbazine (DTIC), the nitrosoureas, cisplatin (CDDP) and vinca alkaloids. Only 10–25% of patients respond to single-agent chemotherapy and the response rates to combination chemotherapy are in the range of 20–50%. In general, only partial remissions are induced, complete responses are rare and responses are of short duration. In addition, no combination chemotherapy regimens have improved survival rates compared with single-agent dacarbazine in prospective randomised trials. At best chemotherapy is palliative but may induce significant toxicities [1, 2].

Melanoma is an immunogenic tumour and there is a long history of attempts to treat this tumour by altering the host immunological response. Over the last 15 years, the advent of recombinant technology has resulted in an increasing number of biological response modifiers (BRMs) becoming available for clinical trial. In particular, results of systemic immunotherapy with the recombinant cytokines interferon-α (IFN-α) and interleukin-2 (IL-2) have been encouraging, and responses have been reported in patients who have failed prior chemotherapy [3]. IL-2 is produced from T cells recognising antigen presented in the context of MHC class I or II molecules [4]. IL-2 upregulates the expression

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of the IL-2 receptor, activates natural killer (NK) cells and supports the growth and activation of large granular lymphocytes (LGL), lymphokine-activated cells (LAK), cytotoxic T lymphocytes (CTL), and tumour infiltrating lymphocytes (TIL) [5].

Clinical trials with IL-2 at various doses and in different schedules have reported response rates of 15–20% in metastatic melanoma, with some long-term survivors [6]. High-dose intravenous bolus IL-2 has been associated with significant toxicity and mortality [7], whereas continuous intravenous infusion schedules of IL-2 appear to be of equal efficacy and less toxic [8]. There is no marked dose–response effect with IL-2 in patients with melanoma [9]. IFN-α may act by upregulating the expression of MHC molecules that present tumour-associated antigens on the cell surface and it also enhances macrophage, cytotoxic T cell and NK cell activity [10]. Another major effect of IFN-α is thought to be its dose-dependent action as a direct antiproliferative agent [11]. Cumulative data on IFN-α as a single agent in the treatment of metastatic melanoma have shown a response rate of 16%, with 6% complete responses and occasional prolonged remissions seen [12].

In experimental models, the combination of IL-2 and IFN-α have shown an enhanced antitumour effect compared with either treatment alone [13]. In view of the different mechanisms of action of these two cytokines and their potential synergy, clinical trials of combination immunotherapy with IL-2 and IFN-α have been initiated and response rates of up to 33% have been reported [14, 15]. *In vitro* models have also reported promising results of combination therapy using immunomodulatory and cytotoxic agents [16]. Early clinical reports of combination therapy of cisplatin and IFN-α have reported response rates of up to 37% [17, 18] and preliminary reports of trials combining cisplatin, rIL-2 and IFN-α have reported response rates in excess of 50% [19]. In view of these results, we conducted an open, non-randomised, multicentre phase II study to evaluate the efficacy of a combination of cisplatin chemotherapy with recombinant IL-2 and IFN-α in patients with metastatic melanoma and to assess the toxicity of this regimen.

PATIENTS AND METHODS

Patients

Between March 1992 and September 1993, 28 patients with metastatic malignant melanoma were entered into the study if they fulfilled the following criteria: unresectable metastasis or locoregional measurable disease, ECOG performance status 0–1, age <75 years, life expectancy of >3 months, white cell count of $>4 \times 10^9$/l, platelets >120 000×10^9/l, haemoglobin >10 g/dl and normal coagulation parameters. In addition, serum bilirubin and creatinine had to be within an institution's normal range. All patients provided signed, informed consent and approval was granted from the respective institutional ethics committees.

Patients were excluded if they had a significant history of intercurrent disease, were likely to require corticosteroids for intercurrent disease, had evidence of serious active bacterial or viral infection, were pregnant or lactating, had contraindications to the use of vasopressor agents or had an organ allograft. Patients were also considered ineligible if they had a history of previous malignancy. Central nervous system (CNS) metastases, previous exposure to platinum chemotherapy, had received prior radiotherapy or locoregional chemotherapy in the 4 weeks prior to study entry or suffered from ocular melanoma.

Prior to the commencement of treatment, all patients underwent a full history and physical examination, measurement of vital signs, full blood count, serum urea and electrolytes, liver function tests, thyroid function tests, ECG and appropriate imaging (chest X-ray, computerised axial tomography scans and ultrasonography). Full blood counts, urea, electrolytes, creatinine and liver function tests were measured daily during each treatment cycle while IL-2 was administered, then repeated prior to each subsequent course.

Treatment

Patients received cisplatin 100 mg/m^2 i.v. on day 0 with standard intravenous hydration with normal saline. IL-2 (Proleukin, supplied by Chiron B.V., Middlesex, U.K.), 18×10^6 international units/m^2/day, diluted in 5% dextrose containing 0.1% human albumin to a final volume of 50 ml, was administered by continuous intravenous infusion on days 3–7 (96 h) and days 17–22 (120 h), and IFN-α (Roferon-A, Roche; supplied by Chiron B.V.) was administered by subcutaneous injection at 9×10^6 U/day × 3 on days 3, 5, 7, 17, 19 and 21 during the IL-2 infusions. The treatment cycle was 28 days. Patients were assessed for response after two cycles of therapy and, in the absence of severe toxicity and in the presence of complete remissions, partial remissions or stable disease, they could receive a further cycle to a maximum of three. Patients were followed up at monthly intervals in the first year after treatment stopped and bimonthly thereafter.

Hypotension grade 3 or 4, arrhythmia, suspected myocardial ischaemia, agitation or confusion, elevation of bilirubin to >85 μmol/l, elevation of serum creatinine to >500 μmol/l, sepsis and dyspnoea at rest resulted in a cessation of IL-2 until the toxicity resolved and the IL-2 was then recommenced at 50% of the starting dose. IL-2 was not restarted if there was myocardial ischaemia, grade 4 neurotoxicity or an elevated serum creatinine or bilirubin that failed to fall to ≤grade 1 toxicity.

Specific supportive measures such as antipyretics, intravenous albumin, intravenous dopamine, intravenous antibiotics, antiemetics and intravenous fluids were instituted as clinically indicated. Corticosteroids were not administered routinely and were only used for short periods (2–3 days) as second-line antiemetic therapy.

Assessment

Response assessment and toxicity were assessed according to standard WHO criteria [20]. Complete response (CR) was defined as the disappearance of all known disease on two separate measurements at least 4 weeks apart; partial response (PR) was defined as a reduction in the sum of the products of the largest perpendicular diameters of each lesion by at least 50%; stable disease (SD) was defined as a decrease of less than 50% or an increase of less than 25% with no new lesions; and progressive disease (PD) was defined as 25% or greater increase in measurable disease or the appearance of new lesions. Response and toxicity were assessed after each course of treatment just prior to when the next cycle would be due.

Statistics

Response duration was measured from the onset of the response to the date of disease progression for CRs, and for PRs from the first day of treatment until progression of the disease. Duration of survival was measured from the first day of treatment until the date of death. Response by site calculations were analysed with Fisher's exact test. The time to progression, response duration and survival were calculated using the Kaplan–Meier method. Exact values were used for proportions. The data on time to progression, duration of response and survival were updated on 1 December 1996. An interim analysis was peformed after 9 patients had been treated in order to assess continuation of the trial.

RESULTS

Patient characteristics

28 patients were entered into the study and their characteristics are shown in Table 1. Only 3 patients had received prior chemotherapy (2 patients DTIC alone, 1 patient DTIC plus vindesine) and 2 patients had received prior tamoxifen. No patients had received prior isolated limb perfusion, radiotherapy or immunotherapy. All patients had AJCC Stage IV disease.

Response

Response was analysed on an intention to treat basis. 27 out of the 28 patients were evaluable for response; 1 patient withdrew from therapy because of toxicity after only a few days of the first cycle and so response could not be objectively defined. 5 patients had a partial response (18%, 95% CI 6–37%), 8 patients had stable disease, and there were no complete responders. Progressive disease on treatment was noted in 14 of 27 patients (52%) after one cycle. 4 (14%) patients received two cycles of therapy and 7 (25%) patients received three cycles at which point treatment was ceased. Median progression-free survival was 44 days (range 8–279, Figure 1) and median overall survival 264 days

Table 1. *Patient characteristics*

Sex	
Male	13 patients
Female	15 patients
Age	
Range	26–65 years
Median	46 years
Performance status	
ECOG 0	15 patients
ECOG 1	13 patients
No. of metastatic sites	
1	5 (18%)
2–3	13 (46%)
≥4	10 (36%)
Sites of disease	
Skin/soft tissues	19 (68%)
Lymph nodes	16 (57%)
Lung	10 (36%)
Liver	9 (32%)
Bone	3 (11%)
Other	20 (71%)
No. of sites	
Skin/LN/soft tissue only	5 (18%)
Including 1 visceral site	7 (25%)
≥2 visceral sites	16 (57%)

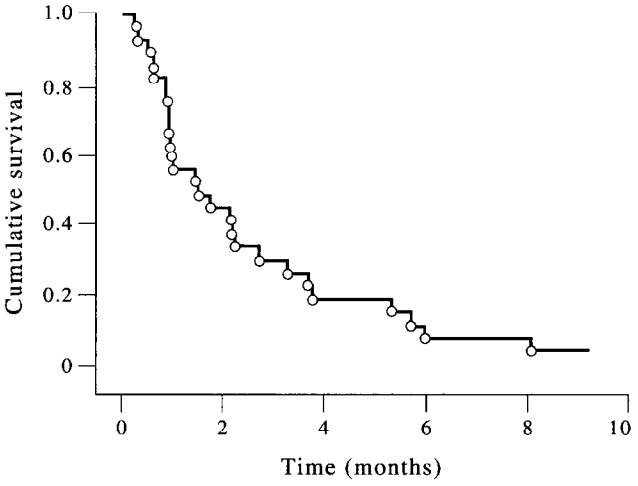

Figure 1. Kaplan–Meier cumulative survival plot for progression-free survival.

(range 41–1432, Figure 2). 2 patients are still alive, 1 patient had a complete response to DTIC having ceased chemoimmunotherapy because of toxicity, and is alive without evidence of disease. The other patient, who also withdrew from therapy after one cycle due to toxicity, has not required any further treatment.

Responses were noted in non-visceral and visceral sites. As expected, the response rate in non-visceral measurable sites was higher 78% (49/63) than the response in visceral sites 22% (14/63) ($P = 0.04$). However, within these two categories, there were some surprising differences; for example, the overall response rate for skin disease was 80% whilst that for lymph node disease was 16%; in visceral sites the response rate for liver disease was 70% and lung disease 13% (Table 2). Responses were noted in other visceral sites including spleen (PR), adrenal gland (PR), pelvis (PR assessed by magnetic resonance imaging), bone (PR) and peritoneum (CR). Overall the response rate by site was 45% (63/139). 11 patients (41%) exhibited the phenomenon of differential response which was defined as PR or CR occurring in some metastases whilst PD was noted in others; these progressive lesions were either at the same or at a

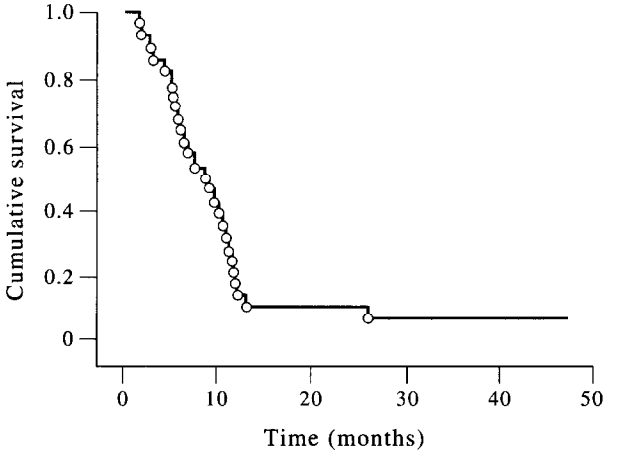

Figure 2. Kaplan–Meier cumulative survival plot for overall survival.

Table 2. Response by site

	CR (%)	PR (%)	OR (%)
Skin ($n = 51$)	31 (61)	10 (20)	80%
Soft tissue ($n = 7$)	1 (14)	1 (14)	29%
Lymph nodes ($n = 37$)	4 (11)	2 (5)	16%
Lung ($n = 16$)	1 (6)	1 (6)	13%
Liver ($n = 10$)	3 (30)	4 (40)	70%
Other ($n = 18$)	1 (6)	4 (22)	28%
Non-visceral ($n = 95$)	36 (38)	13 (14)	52%
Visceral ($n = 44$)	5 (11)	9 (20)	32%
Overall ($n = 139$)	41 (29)	22 (16)	45%

n = number of sites, CR, number of complete responses; PR, number of partial responses; ORR, overall responses.

different site as the responding metastasis. 8 patients responded differentially in the same site and 8 patients responded differentially at different sites (Table 3).

Toxicity

Three patients stopped treatment after one cycle because of toxicity: 1 patient due to myocardial ischaemia, and the other 2 due to malaise. These patients received no further therapy and in 2 of these patients, response was assessed at that time. The third patient only received a few days of treatment, and response, therefore, could not objectively be established. All 28 patients were evaluable for toxicity and the side-effects encountered in this study are shown in Table 4.

DISCUSSION

Combining cisplatin 100 mg/m^2 on day 0 followed by intermittent infusional IL-2 (18×10^6 IU/m^2/d) with concomitant three weekly subcutaneous IFN-α (9×10^6 U/d) in 28 patients with metastatic melanoma, we obtained five partial responses only. However, whilst we obtained more responses in non-visceral sites when compared to visceral sites ($P = 0.04$), we obtained a high rate of responses in liver

Table 3. Differential responses

Patient no.	Differential response at the same site	Differential response at different sites
1	Lymph node	
4	Lymph node	Skin (CR) versus lymph node (PD)
5		Skin (CR) versus lymph node (PD)
10		Skin (PR) versus lymph node (PD)
15	Lung	Skin (PR) versus lung (PD)
17		Liver (CR) versus lung (PD)
18	Lymph node	
19	Lymph node	Skin (PR) versus lymph node (PD)
22	Skin and lymph node*	Skin (CR) versus lymph node (PD)
23	Skin	
28	Skin and lymph node*	Skin (CR) versus lymph node (PD)

*Differential response occurred within both these sites.
PD, progressive disease; other abbreviations as in legend to Table 2.

Table 4. Toxicity

	WHO grade (%)		
	0	1–2	3–4
Alopecia	24 (86)	4 (14)	0 (0)
Anorexia	4 (14)	15 (54)	9 (32)
Diarrhoea	8 (29)	17 (61)	3 (11)
Dyspnoea	15 (54)	10 (36)	3 (11)
Fatigue/malaise	1 (4)	5 (18)	22 (79)
Fever	2 (7)	19 (68)	7 (25)
Flu-like symptoms	18 (64)	9 (32)	1 (4)
Haematuria	21 (75)	6 (21)	1 (4)
Hypotension	6 (21)	17 (61)	5 (18)
Nausea and vomiting	1 (4)	15 (54)	12 (43)
Oliguria	19 (68)	8 (29)	1 (4)
Proteinuria	9 (32)	19 (68)	0 (0)
Cutaneous	2 (7)	19 (68)	7 (25)
Taste changes	7 (25)	14 (50)	7 (25)
Anaemia	4 (14)	16 (57)	8 (29)
Leucopenia	149 (50)	11 (39)	3 (11)
Neutropenia	19 (68)	7 (25)	2 (7)
Thrombocytopenia	7 (25)	11 (39)	10 (36)
Creatinine	6 (21)	22 (79)	0 (0)
ALT	18 (64)	10 (36)	0 (0)
SAP	8 (29)	15 (54)	5 (18)
GGT	9 (32)	14 (50)	5 (18)
Bilirubin	9 (32)	16 (57)	3 (11)

( ) = %.

(70%) and notable responses in other visceral sites. Interestingly, a considerable number of differential responses were observed both within non-visceral sites and between visceral and non-visceral sites. The overall survival of patients in our study is similar to that reported using other systemic treatments [21–23].

Khayat and associates reported a response rate of 53.8% (5 CRs, 16 PRs) in 39 patients receiving cisplatin and IL-2 plus IFN-α with a median duration of response of 24 weeks (range 12–90+) and median duration of survival of 48 weeks [21]. Richards and colleagues reported a response rate of 57% (11 CRs, 30 PRs) in 74 patients treated with cisplatin, DTIC, BCNU, tamoxifen and IL-2 plus IFN-α with a median duration response of 9 months and median survival of 14 months [22]. Legha and colleagues investigated the sequencing of combination chemotherapy (cisplatin, vindesine, DTIC) and IL-2 plus IFN-α and reported a higher response rate (73% versus 47%; $P = 0.065$) and progression-free survival (8 versus 7 months, $P = 0.007$) in the group receiving chemotherapy prior to immunotherapy [23]. The authors concluded that their clinical investigations highlighted the impact of sequence on response rate and toxicity and have undertaken a randomised trial of CVD chemotherapy versus combination chemoimmunotherapy. The regimen we studied most resembles that of Khayat and colleagues. We failed to confirm the high response rates claimed by these and the other groups who reported similar chemoimmunotherapy schedules. Furthermore, in our experience, this combination of cisplatin, intravenous IL-2 together with subcutaneous IFN-α does not result in improved survival over chemotherapy alone and produces side-effects that do not warrant the poor response rates obtained.

Differential responses are well known to occur with chemotherapy, but we appear to be the first group to report a

high incidence of differential response to chemoimmunotherapy. It is possible that the phenomenon of differential response explains the wide range of response rates reported for chemoimmunotherapy regimens. We observed that, at some sites, notably skin and lymph nodes, the general rule was that in responding patients not all lesions at a particular site showed signs of regression. The failure of adjunctive immunotherapy to overcome the phenomenon of differential response suggests that there may be a high incidence of modulation of cell surface molecules, e.g. antigens, antigen-presenting complexes, co-signalling molecules, and this allows escape from immune-mediated cytotoxicity. This observation has great significance for the design of future immunologically based treatments because it implies that individual deposits of tumour differ from one another significantly enough to affect clinical responses.

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