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Chemoimmunotherapy with bleomycin, vincristine, lomustine, dacarbazine (BOLD) plus interferon α for metastatic melanoma: a multicentre phase II study

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Summary High response rates in patients with metastatic melanoma have been achieved with combination chemoimmunotherapy. A response rate of 62% in 45 patients has been reported for treatment with dacarbazine, bleomycin, vincristine, lomustine (BOLD) plus interferon α (IFN- α). We conducted a multicentre phase II study to confirm these results. Melanoma patients with distant metastases were treated as outpatients with dacarbazine 200 mg m⁻² on days 1–5, vincristine 1 mg m⁻² on days 1 and 4, bleomycin 15 mg on days 2 and 5 i.v. and lomustine 80 mg orally on day 1, repeated every 4 weeks. IFN- α -2b was initiated s.c. on day 8 at 3 MU daily for 6 weeks, and 6 MU t.i.w. thereafter. Forty-three patients entered the study. The median number of metastatic sites was three (range 1–5), and 81% of patients had visceral metastases. Nine patients had brain metastases, and seven patients were systemically pretreated. Among the 41 patients that were evaluable for response, the response rate was 27% (95% CI 14–43%), with one complete and ten partial remissions. The response rate in 25 previously untreated patients without brain metastases was 40% (95% CI 21–61%). Median duration of response was 6 (range 2–14) months; median overall survival was 5 (1–26) months. The main toxicity was malaise/fatigue. We confirm that BOLD plus IFN- α has activity in metastatic melanoma. The lower response rate in our study compared with the previous report is probably related to patient selection, as in the previous study 46% of patients had stage III disease, whereas all our patients had stage IV disease, which is associated with a worse prognosis.

Keywords: metastatic melanoma; chemotherapy, interferon- α ; chemoimmunotherapy

Although long-term remissions have been achieved in patients with metastatic melanoma, the regimen of choice remains controversial in these patients. Single-agent therapy with dacarbazine (DTIC) or immunotherapeutic agents such as interleukin 2 (IL-2) and interferon- α (IFN- α) results in response rates of 15–20% (Houghton et al, 1992; Kirkwood, 1995; Marincola and Rosenberg, 1995). With combination chemotherapy regimens, such as cisplatin, vinblastine and DTIC (CVD) (Legha et al, 1989) or cisplatin, carmustine, DTIC and tamoxifen (Del Prete et al, 1984; McClay et al, 1992), response rates of 40–52% have been observed. The response rate of 40% initially reported for bleomycin, vincristine, lomustine and DTIC (BOLD) (Seigler et al, 1980) was not confirmed by others (York and Foltz, 1988; Prudente Foundation Melanoma Study Group, 1989). Combination immunotherapy with IL-2 and IFN- α has not unequivocally improved the results of either agent alone (Kirkwood, 1995) and was very toxic when administered at high doses (Kruit et al, 1994; Marincola et al, 1995; Kruit et al, 1996). Several chemoimmunotherapy schedules have been clinically tested. The results of DTIC plus IFN- α are conflicting, with most trials failing to show a benefit of the combination over DTIC alone (Falkson et al, 1991; Thompson et al, 1993; Bajetta et al, 1994; Mulder et al, 1994;

Falkson et al, 1996). Phase II results of DTIC plus IL-2 did not suggest a clear benefit for this combination (Stoter et al, 1991; Fiedler et al, 1992). High response rates of 42–73% have been achieved in (mostly single centre) phase II studies with combinations of IL-2, IFN- α and cisplatin (Khayat et al, 1993), IL-2, IFN- α and CVD (Buzaid and Legha, 1994), IL-2, cisplatin, DTIC and tamoxifen (Atkins et al, 1994), and IL-2, IFN- α , cisplatin, carmustine, DTIC and tamoxifen (Richards et al, 1992). The median duration of response and survival in these studies was reported to be up to 9 months and 14 months respectively.

Pyrhönen et al, (1992) reported a 62% response rate (95% confidence limit 48–77%) with 13% complete responses in 45 patients upon combination treatment consisting of BOLD plus IFN- α . Two patients with stable disease and two with progressive disease responded when the administration of IFN- α was changed from a weekly to an intermittent schedule. There was one toxic death, but overall toxicity was acceptable. Given these promising results, we performed a confirmatory study with the same schedule in patients with metastatic melanoma.

PATIENTS AND METHODS

Eligibility

Eligibility criteria included histologically proven metastatic melanoma, not amenable to surgery, bidimensionally measurable disease, WHO performance status 0–2, age 18–75 years, pretreatment with a maximum of one regimen containing ≤ 1 drug of the proposed regimen, serum values of creatinine ≤ 150 $\mu\text{mol l}^{-1}$,

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Table 1 Patients' characteristics

Characteristics	No. of patients
Total number of patients, men/women	43, 27/16
Primary melanoma of skin/uvea	42/1
Median age, years (range)	58 (22-74)
WHO performance status	
0	13
1	18
2	12
Median serum LDH, U l ⁻¹ (range)	369 (161-4768)
Prior therapy	
Systemic treatment	7
IL-2 + IFN- α + cisplatin	3
IL-2 + IFN- α	2
DTIC	2
Regional limb perfusion	1
Radiotherapy	8
Surgery for metastases	9
Disease sites	
Lungs	24
Lymph nodes	24
Skin/subcutaneous	22
Liver	17
Brain	9
Bone	5
Other	10
No. of disease sites	
1	8
2	13
3	11
4	5
5	6

bilirubin $\leq 25 \mu\text{mol l}^{-1}$, liver transaminases ≤ 1.5 times normal unless related to liver metastases, WBC $\geq 3.5 \times 10^9 \text{ l}^{-1}$ and platelets $\geq 100 \times 10^9 \text{ l}^{-1}$. Patients with a history of second malignancy, with the exception of adequately treated carcinoma in situ of the cervix or basal/squamous cell carcinoma of the skin, concomitant serious non-malignant illness, active infections, concurrent treatment with immunosuppressive agents and pregnant or lactating women were excluded. Patients with asymptomatic brain metastases were eligible provided they were not receiving treatment with steroids. Written informed consent was obtained from all patients. Before initiation of this trial, institutional review board approval was obtained at each of the participating centres.

Study design

Patients were treated as outpatients with chemotherapy (BOLD) consisting of lomustine 80 mg administered orally on day 1, DTIC 200 mg m⁻² i.v. on days 1-5, bleomycin 15 mg i.v. on days 2 + 5, and vincristine 1 mg m⁻² i.v. on days 1 + 4. Cycles were repeated every 4 weeks. IFN- α -2b (Intron A, Schering Plough, The Netherlands) was administered s.c. at 3 MU daily for 6 weeks starting at day 8 and 6 MU t.i.w. thereafter. Patients received prophylactic antiemesis with 5HT₃ antagonists during the 5 days of chemotherapy administration. The use of corticosteroids was prohibited. Before and after IFN- α administration, patients received acetaminophen 1000 mg orally. The addition of naproxen

Table 2 Grade 3/4 toxicity in 42 evaluable patients

Toxicity	Grade 3	Grade 4	Total no. of patients (%)
Malaise/fatigue	14		14 (33)
Alopecia	9		9 (21)
Anorexia	6		6 (14)
Nausea	5	0	5 (12)
Vomiting	1	0	1 (2)
Lung	1	0	1 (2)
Neuropsychiatric	1	0	1 (2)
Stomatitis	0	1	1 (2)
Diarrhoea	1	0	1 (2)
Myalgia	1		1 (2)
Leucocytopenia	8	0	8 (19)
Anaemia	2	0	2 (5)
Thrombocytopenia	1	0	1 (2)
Death		1 ^a	1 (2)

Toxicity according to WHO criteria: 1, mild; 2, moderate; 3, severe; 4, life-threatening. Numbers are patients. ^aSudden death on fifth day of first cycle - a causal relationship with treatment was unclear.

250 mg for constitutional symptoms caused by IFN- α was allowed. Patients were evaluated weekly for toxicity and every two cycles for response. WHO criteria for toxicity and response were used. Treatment was continued in the absence of tumour progression or severe toxicity. In the case of WHO grade 3 toxicities, treatment was withheld until complete resolution of the toxicity, and the dose of the responsible drug was reduced to 75% in subsequent cycles. Chemotherapy cycles were only restarted when WBC and platelet values were $\geq 3.5 \times 10^9 \text{ l}^{-1}$ and $100 \times 10^9 \text{ l}^{-1}$ respectively. In the case of WHO \geq grade 3 vincristine-induced neurotoxicity or bleomycin-induced pulmonary toxicity, these drugs were permanently discontinued. A 50% dose reduction of IFN- α was allowed for \geq grade 3 constitutional symptoms.

RESULTS

Forty-three patients were entered onto the study in seven different centres. Patients' characteristics are listed in Table 1. All patients had stage IV disease, i.e. with distant metastases. The median age of all patients was 58 years (range 22-74), median WHO performance status 1 (0-2), median serum lactate dehydrogenase (LDH) 369 U l⁻¹ (161-4768, normal values up to 330 U l⁻¹). The median number of metastatic sites was 3 (1-5). The sites of metastases were the lungs in 24 patients, lymph nodes in 24, skin/subcutaneous in 22, liver in 17, brain in nine, bone in five and other sites in ten patients. Visceral metastases were present in 81% of patients. Seven patients had received prior systemic treatment, eight had received prior radiotherapy and nine had had surgery for metastases. Patients received a median number of two (range 1-8) cycles.

Anti-tumour responses

Two patients were not evaluable for response. One patient died suddenly on the fifth day of treatment and one patient refused treatment after one cycle and was subsequently lost to follow-up. Thus, 41 patients were evaluable for response. The overall response rate was 27% (95% CI 14-43%) with one CR and ten PRs. No responses occurred in the seven patients who had been systemically pretreated. Of the nine patients with brain metastases,

one PR occurred in a patient who had received prior cranial irradiation, whereas all four patients with asymptomatic brain metastases who were not previously irradiated progressed at this site. The response rate in 25 previously systemically untreated patients without brain metastases was 40% (95% CI 21–61%). Responses occurred in the lungs, skin/subcutaneous, lymph nodes, liver, spleen, and adrenal metastases. Median response duration was 6 months (range 2–14+ months). Median overall survival was 5 months (1–26), and in the 25 patients without prior systemic treatment and brain metastases 6 months (1–26). In four patients with progressive disease the BOLD regimen was continued, but IFN- α was given intermittently in 2-week periods interrupted by a 2-week rest period. In contrast to the original report (Pyrhönen et al, 1992), no responses or disease stabilizations were seen in these patients.

Clinical toxicities

Forty-two patients were evaluable for toxicity. Grade 3/4 toxicity (WHO) occurred in 28 (67%) patients and consisted mainly of fatigue (33%), anorexia (14%), leucocytopenia (19%) and nausea (12%) (Table 2). A 72-year-old man with a partial response of lung metastases and a complete response of liver, subcutaneous and lymph node metastases developed pulmonary fibrosis with dyspnoea at rest after the third chemotherapy cycle. Treatment was discontinued and treatment with corticosteroids was instituted, after which his condition remained stable. He died 6 months later of brain metastases. A 59-year-old female patient with a partial response of lung metastases experienced a severe depression, which was quickly reversible after discontinuation of IFN- α . BOLD was continued for a total of six cycles. She died after 20 months of tumour progression. A 67-year-old man died suddenly at home on the fifth day of the first chemotherapy cycle before treatment with IFN- α was initiated. A tentative diagnosis of a myocardial infarction was made, and a definite causal relationship with treatment could not be established. Toxicity necessitated dose reductions or discontinuation of BOLD chemotherapy in 16 out of 134 cycles (12%) in eight patients (19%), and chemotherapy was delayed in 12 out of 134 cycles (9%) in ten patients (24%). The dose of IFN- α was reduced or discontinued in six patients (14%).

DISCUSSION

The mechanisms underlying the supposed synergistic interaction between chemotherapy and immunotherapy are still speculative. Arguments for the enhancement of the anti-tumour activity of immunotherapy by chemotherapy as well as vice versa have been postulated. Clinical support for an interaction between these treatment modalities comes from the observation that the sequence of administration of these treatment modalities appears to be an important factor (Buzaid and Legha, 1994). Furthermore, increasing CD4/CD8 ratios during chemoimmunotherapy with BOLD plus IFN- α have been correlated with response, implying the stimulation of host defence mechanisms (Hernberg et al, 1996). The response rate with BOLD plus IFN- α in patients with metastatic melanoma in our study of 27% (95% CI 14–43%) for all patients and 40% (95% CI 21–61%) for patients without prior systemic treatment and brain metastases are lower than reported by Pyrhönen et al, (1992), who used the same doses and schedule. This difference might be explained by two factors. First, the source

of IFN- α differed in the two studies. We used recombinant IFN- α -2b whereas Pyrhönen et al, used purified human leucocyte IFN- α from the Finnish Red Cross Blood Transfusion Service (Cantell et al, 1981). However, a clinical advantage for a specific type of IFN- α has never been demonstrated. Second, there are important differences between the patient populations of the two studies. In the study of Pyrhönen et al, (1992), 22 of the 48 patients (46%) had stage III disease, whereas all our patients had stage IV disease. For stage III melanoma patients with regional lymph node metastases, surgery with regional radical lymphadenectomy is the treatment of choice, and for patients with intransit metastases of an extremity isolated limb perfusion is preferred. For therapeutic groin dissections in stage III patients, 5-year survival rates of 30–47% have been reported, depending on the involvement of deep nodes (Karakousis et al, 1986). In the worst group of stage III patients, i.e. with both regional node and in-transit metastases, the 5-year survival may be 19% and the median survival time 17 months (Singletary and Balch, 1992). This is in contrast to stage IV patients with non-visceral and visceral metastases, who may have a 1-year-survival rate of 46% and 18% respectively and median survival times of 8 and 3 months respectively (Balch et al, 1992). Furthermore, 71% of our patients had a WHO performance status of ≤ 1 , whereas this was the case for 92% of patients in the study by Pyrhönen et al (1992). Another aspect associated with poor prognosis was the median number of three metastatic sites in patients from our study, and in a previous review no patients with this characteristic survived for more than 1 year (Balch et al, 1992). It can therefore be concluded that our patient population consisted of a group with a worse prognosis than those in the study by Pyrhönen et al (1992). In that study, 10% of patients had brain metastases and several patients had been systemically pretreated. The median duration of response was not different between the two studies, being 6 months in our study and 6.8 months in the study of Pyrhönen et al (1992). Although tested in only four patients, we could not observe any disease regression in non-responders upon changing the IFN- α administration to an intermittent schedule (Pyrhönen et al, 1992).

The most common severe toxicity in our study was IFN- α -related malaise and fatigue, which occurred in 33% of patients. This occurred in 20% of patients in the study by Pyrhönen et al, (1992). Surprisingly, patients in this last study experienced more grade 3/4 haematological toxicity than in our study (leucocytopenia and thrombocytopenia 17% and 2% vs 32% and 11% respectively). Whether this reflects the difference in the source of IFN- α is uncertain.

In conclusion, we confirm that BOLD plus IFN- α is an active regimen in patients with metastatic melanoma. The previous reported high response rate of 62% in 48 patients is probably related to a selection of patients with good prognosis. The median survival of 6 months in this group of patients is disappointing but may be related to poor prognostic parameters.

To date, the combination of immunotherapy (IFN- α and/or IL-2) with multidrug chemotherapy (mostly including DTIC and cisplatin) has yielded the highest response rates in metastatic melanoma, with response rates up to 70% (Pyrhönen et al, 1992; Richards et al, 1992; Khayat et al, 1993; Atkins et al, 1994; Buzaid and Legha, 1994). However, all these results were obtained in (mostly single centre) phase II studies. Recently, it has been demonstrated in the setting of a randomized phase III trial in metastatic melanoma that the addition of cisplatin to a regimen of

IL-2 and IFN- α significantly increases the response rate without prolonging survival (Keilholz et al, 1996). In order to provide patients with metastatic melanoma with the best possible care, further randomized phase III trials are warranted to establish the value of combination treatments vs less intensive and therefore less toxic regimens.

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