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European Journal of Cancer 39 (2003) 1115–1120

European Journal of Cancer

www.ejconline.com

Bleomycin, vincristine, lomustine and dacarbazine (BOLD) in combination with recombinant interferon alpha-2b for metastatic uveal melanoma☆

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Received 30 September 2002; accepted 23 October 2002

Abstract

This EORTC multicentre study analysed the efficacy and tolerability in patients with metastatic uveal melanoma of BOLD chemotherapy in combination with recombinant interferon alpha-2b. The dose of bleomycin was 15 mg on days 2 and 5, of vincristine 1 mg/m^2 on days 1 and 4, of lomustine 80 mg on day 1, and of dacarbazine (DTIC) 200 mg/m^2 on days 1–5, given every 4 weeks for a minimum of two cycles. Subcutaneous (s.c.) interferon alpha-2b at a dose of 3×10^6 IU was initiated on day 8 of the first cycle, and continued at a dose of 6×10^6 IU three times per week after 6 weeks. A median of two cycles were administered to 24 patients (median age 60.5 years). None achieved an objective response (0%; 95% Confidence Interval (CI): 0–14), 2 (8.3%) remained stable, 20 showed progression, and 2 (8.3%) were inevaluable. The median progression-free survival was 1.9 months (95% CI: 1.8–3.4) and overall survival 10.6 months (95% CI: 6.9–16.4). Overall survival improved with increasingly favourable pretreatment characteristics (median, 14.7 versus 6.9 versus 6.0 months for Helsinki University Central Hospital (HUCH) Working Formulation stages IVBa, IVBb and IVBc, respectively; $P=0.018$). Grade 3 alopecia and neurotoxicity occurred in 13% of the patients. This multicentre study did not confirm earlier reports that BOLD with human leucocyte or recombinant interferon would induce at least 15% objective responses in metastatic uveal melanoma.

Keywords: Bleomycin; Dacarbazine; Interferon; Lomustine; Malignant melanoma; Phase II; Staging; Uvea; Vincristine

1. Introduction

Of patients with primary uveal melanoma, 18–43% develop haematogenous metastasis within 10 years depending on tumour size [1,2]. The initial site of meta-

☆ An EORTC Ocular Oncology Task Force Phase II Study, 88941 (see Appendix).

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0959-8049/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0959-8049(03)00132-1

stasis is the liver in 90% of patients [3]. This tumour is more resistant to chemotherapy than cutaneous melanoma [4–12]. Single-institution studies on hepatic chemoembolisation [10,13] and intra-arterial fotemustine- [12,14–16] and platinum-based [15,17] chemotherapy for hepatic metastases now report a response rate of 29–40% and a median overall survival of 6–18 months [12–17].

Many patients develop an extrahepatic relapse after chemoembolisation and intra-arterial chemotherapy [14,15], and likely had subclinical extrahepatic metastases. Systemic chemotherapy is consequently also needed. Only bleomycin, vincristine, lomustine and dacarbazine (BOLD) in combination with alpha interferon has been prospectively evaluated in single-centre studies [18–20]. To confirm the reported 15–20% response rate [18,19], the European Organization for Research and Treatment of Cancer (EORTC) Ophthalmic Oncology Task Force conducted a prospective phase II multicentre study.

2. Patients and methods

2.1. Study design

The purpose of this prospective, multicentre, non-randomised phase II feasibility study was to determine the objective response rate, progression-free and overall survival, and toxicity of BOLD chemotherapy in metastatic uveal melanoma given as first-line therapy in combination with recombinant interferon alpha-2b.

Patients were eligible if they had histologically- or cytologically-confirmed measurable metastases from uveal melanoma (Stage IVB (any T any N M1)) that were not amenable to surgical resection or intra-arterial chemoembolisation. Other eligibility criteria included age between 18 and 70 years, Karnofsky index $\geqslant 70$, no prior malignant tumour or major intercurrent medical illness, a white blood cell count $\geqslant 3.5\times10^9$/l, a platelet count $\geqslant 100\times10^9$/l, and serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (AP) levels $\leqslant 2.5\times$ the upper limit of normal values (UNL).

The study was approved by the EORTC Protocol Review Committee and by Institutional Review Board of each participating centre. It was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all of the patients.

2.2. Chemoimmunotherapy

The BOLD regimen was administered every 4 weeks: intravenous (i.v.) bleomycin 15 mg on days 2 and 5, i.v. vincristine 1 mg/m^2 (maximum 2 mg) on days 1 and 4, oral lomustine (CCNU) 80 mg on day 1, and i.v. dacarbazine (DTIC) 200 mg/m^2 on days 1–5.

Subcutaneous (s.c.) recombinant interferon alpha-2b (Intron® A, Schering-Plough Co., Kenilworth, NJ, USA) was initiated on day 8 of the first cycle at a dose of 3×10^6 IU per day for 6 weeks, followed by 6×10^6 IU three times per week. Antiemetics were given as indicated.

Lomustine and interferon were withheld during the next cycle if grade 3-4 haematological toxicity developed. Bleomycin dose was reduced by 50% if serum creatinine increased to $1.5\times$UNL, and it was omitted in case of grade 3-4 pulmonary toxicity. Vincristine dose was reduced by 50% if grade 2 constipation, neurotoxicity or hepatotoxicity were observed, and it was withheld during the next cycle in case of grade 3-4 toxicity.

Treatment was initially given for two cycles. In case of complete response (CR) or partial response (PR), one and up to four additional cycles were given, respectively, and in the case of stable disease (SD), two additional cycles were given. If progressive disease (PD) was observed, the patient was followed until death without any further protocol treatment.

2.3. Clinical evaluation and assessment of response

Baseline evaluation included physical examination, assessment of performance status (Karnofsky index), electrocardiogram, spirometry, haematology, blood chemistry (creatinine, AST, ALT and AP), chest radiogram, and ultrasonography (US) or computed tomography (CT). These examinations were repeated at the start of every cycle, except spirometry and imaging which were repeated every other cycle. Haematology was evaluated every 2 weeks.

Patients were staged retrospectively on the basis of three prospectively recorded baseline variables (Karnofsky index, serum AP level, and largest diameter of the largest metastasis) according to a recently drafted Helsinki University Central Hospital (HUCH) Working Formulation [3]. It provisionally divides Stage IVB uveal melanoma into three substages according to the predicted median duration of overall survival. These three variables were selected on the basis of Cox proportional hazards multiple regression using a data set of 91 patients with metastatic uveal melanoma [3]. Stage IVBa was formulated to correspond to a predicted median overall survival of 12 months or more, Stage IVBb to a survival of 6–11 months, and Stage IVBc to a survival of less than 6 months. In a data set of 53 patients, treated individually, who had a Karnofsky index of 60 or better, the observed median duration of survival for the three substages was 14.4, 8.9 and 2.0 months, respectively [3].

Patients were assessable for response if they had completed at least two cycles. Responses were assessed according to the World Health Organization (WHO) criteria [21]. Progression-free and overall survival were

calculated from the start of protocol therapy until documentation of progression and death, respectively. For 2 patients with inadequate follow-up measurements, progression-free survival was taken to equal overall survival. Toxicity was assessed according to the National Cancer Institute (NCI) Common Toxicity Criteria [22].

2.4. Statistics

The lowest response rate of medical importance was set at 20%. The study was designed to stop if no responses were found among the first 19 patients, otherwise 5 additional patients per response would be enrolled. Because one PR was initially reported (that was not subsequently verified as a response), the study recruited 24 patients.

Statistical package SAS 8.1 (SAS Institute Inc., Cary, NC, USA) was used for the analyses. Survival was estimated by Kaplan–Meier product-limit method and curves were compared with the log-rank test or the log-rank test for linear trend [23]. Cox proportional hazards regression model was used to determine baseline variables which were of prognostic importance for the duration of survival [23].

3. Results

Of 26 patients registered in this study between December 1995 and August 1998, 2 were ineligible (histopathology was consistent with metastasis from another cancer in 1 patient and the other patient had too extensive liver involvement to meet the eligibility criteria). A third patient had serum AP level 3.5 times the UNL, but was otherwise eligible and was therefore included in the analysis.

The median age of the 24 eligible patients was 60.5 years (Table 1). Karnofsky index was better than 80 in 18 (75%) of them. All had hepatic metastases and 7 (29%) had extrahepatic involvement, most often in the lungs, subcutaneous tissue and lymph nodes. The median metastatic burden was 46 cm^2 (Table 1) and the median largest diameter of the largest metastasis was 42.5 mm. Serum AP level was normal in 14 (58%) patients (Table 1), and 11 (46%) patients were staged to the most favourable HUCH Working Formulation substage (IVBa).

3.1. Treatment compliance

Of the 24 patients, 23 (96%) completed 2–5 cycles as planned and 1 died of progressive disease before the second cycle. A median of two cycles were administered: 15 patients (63%) completed 1–2 cycles, 8 patients (33%) completed 3–4 cycles, and 1 patient completed five cycles of protocol therapy.

3.2. Response

Of the 24 patients, 22 were evaluable for response (metastases were not adequately imaged in 2 patients, both of Stage IVBa, who survived for 31 and 32 months).

No objective responses were found (0%; 95% Confidence Interval (CI): 0–14). By the end of protocol treatment, 2 of the 24 patients (8.3%) had stable disease (both were Stage IVBa), and 2 (8.3%) were inevaluable. The other 20 patients (83.3%) progressed.

3.3. Toxicity

Grade 1-2 nausea, fever, flu-like syndrome, alopecia, hepatic toxicity (which could reflect progression of hepatic metastases) and neurotoxicity occurred in more than 30% of patients, and more than 10% of patients experienced grade 3 alopecia and neurotoxicity (Table 2). Grade 4 toxicity and toxic deaths were not observed.

Table 1
Characteristics of eligible patients

Male:Female	12:12
Median age, years (range)	60.5 (28–68)
Karnofsky index, no. of patients (%)	
100	7 (29)
90	11 (46)
80	6 (25)
Distribution of metastasis, no. of patients (%)	
Hepatic only	17 (71)
Hepatic and extrahepatic	7 (29)
Sites of metastasis, No. of patients (%)	
Liver	24 (100)
Lung	5 (21)
Subcutaneous	2 (8)
Lymph node	2 (8)
Perirenal	2 (8)
Other	1 (4)
Largest diameter of largest metastasis, mm (range)	42.5 (10–141)
Median metastatic burden, cm^2 (range)	46.0 (2.6–165.4)
Median serum AP level, ×UNL (range)	0.79 (0.4–3.5)[a]
Serum AP	
$\leqslant 1.0\times$UNL	14 (58)
$>1.0\times$UNL	10 (42)
HUCH Working Formulation [3], no. of patients (%)	
Stage IVBa	11 (46)
Stage IVBb	7 (29)
Stage IVBc	6 (25)

UNL, upper normal limit; AP, alkaline phosphatase; HUCH, Helsinki University Central Hospital.

[a] One patient had S-AP $>2.5\times$UNL.

3.4. Survival

All patients died of PD, except 1 who was lost to follow-up after the first cycle. The median progression-free (Fig. 1a) and overall survival (Fig. 1b) from the start of protocol treatment were 1.9 months (95% CI: 1.8–3.4) and 10.6 months (95% CI: 6.9–16.4), respectively.

The median overall survival from the start of protocol therapy for patients representing HUCH Working Formulation Stage IVBa, IVBb and IVBc (Fig. 1c) were 14.7, 6.9 and 6.0 months, respectively ($P = 0.018$, test for linear trend). Women survived longer than men (median, 14.7 versus 6.9 months; Fig. 1d; $P = 0.012$, log-rank test).

Table 2

WHO toxicity	Grade 1	Grade 2	Grade 3	Grade 4
	n (%)	*n* (%)	*n* (%)	*n* (%)
Haemorrhage	23 (96)	1 (4)	0 (0)	0 (0)
Infection	16 (67)	3 (13)	3 (13)	2 (8)
Alopecia	7 (29)	4 (17)	9 (38)	3 (13)
Nausea	10 (42)	5 (21)	8 (33)	1 (4)
Vomiting	17 (71)	4 (17)	3 (13)	0 (0)
Diarrhoea	17 (71)	5 (21)	1 (4)	1 (4)
Stomatitis	18 (75)	4 (17)	2 (8)	0 (0)
Hepatic	9 (38)	10 (42)	2 (8)	2 (8)
Renal	22 (92)	1 (4)	1 (4)	0 (0)
Pulmonary	19 (79)	2 (8)	2 (8)	1 (4)
Cardiac	23 (96)	1 (4)	0 (0)	0 (0)
Hypertension	23 (96)	1 (4)	0 (0)	0 (0)
Allergy	23 (96)	1 (4)	0 (0)	0 (0)
Fever	12 (50)	6 (25)	5 (21)	1 (4)
Flu-like syndrome	7 (29)	14 (58)	3 (13)	0 (0)
Neuro vision	23 (96)	1 (4)	0 (0)	0 (0)
Neuro hearing	23 (96)	1 (4)	0 (0)	0 (0)
Neuro other	5 (21)	7 (29)	9 (38)	3 (13)
Local toxicity	21 (88)	3 (12)	0 (0)	0 (0)
Other toxicity	5 (21)	5 (21)	6 (25)	8 (33)

WHO, World Health Organization.

By univariate Cox regression, gender, serum AP, and largest diameter of the largest metastasis were associated with overall survival (Table 3). By bivariate Cox regression, gender (HR 0.24) and Working Formulation substage (HR 2.27 per category) independently predicted survival (Table 3).

4. Discussion

The objective response rate (0%; 95% CI: 0–14) was lower than the 15% (95% CI: 0–38) and 20% (95% CI: 6–44) response rates in previous single-institution studies [18–20]. The overlapping confidence intervals of these small non-randomised studies, which all enrolled 22–24 patients, are compatible with a modest response rate between 6 and 14%. Disease stabilisation was less common than previously reported [20].

Apparently the better survival of women and low frequency of pulmonary toxicity in this non-randomised study may reflect selection bias. A gender difference in survival was not observed among patients managed with BOLD and leucocyte interferon [20]. Unpredicted pulmonary toxicity occurred in 3 of 23 patients in a study with BOLD and recombinant interferon-2b [18].

The interferon preparation and dosage differed in the three studies. In the two earlier ones, human leucocyte and recombinant interferon alpha-2b were used [18,20]. The latter was chosen for the present study because of availability and the fact that this preparation should induce less neutralising antibodies than recombinant interferon alpha-2a [24]. The dose in the former study [20] was identical to that of the present one (3×10^6 IU per day for 6 weeks, then 6×10^6 IU three times per week), whereas the dose in the latter was 4 times lower (3×10^6 on days 8, 10, 12, 15, 17 and 19 of each cycle) [18]. Neither the type nor the dosage of interferon in

Table 3
Cox proportional hazards regression of overall survival

Variable	Regression coefficient (SE)	Wald Chi-square	*P* value	Hazard ratio (95% CI)
Univariate regression				
Gender[a]	−1.115 (0.460)	5.87	0.015	0.33 (0.13–0.81)
Karnofsky index[b]	0.290 (0.281)	1.07	0.30	1.33 (0.78–2.27)
Serum alkaline phosphatase[c]	0.561 (0.299)	3.51	0.061	1.75 (0.97–3.15)
Median largest diameter of the largest metastasis[d]	0.122 (0.057)	4.58	0.032	1.13 (1.01–1.26)
HUCH Working Formulation[e]	0.618 (0.270)	5.22	0.022	1.85 (1.09–3.15)
Multivariate regression				
Gender[a]	−1.443 (0.509)	8.03	0.005	0.24 (0.09–0.64)
HUCH Working Formulation[e]	0.821 (0.298)	7.58	0.006	2.27 (1.27–4.08)

S.E., standard error; CI, Confidence Interval; HUCH, Helsinki University Central Hospital.
[a] Categories: Male = 0, Female = 1.
[b] Per 10-unit decrease in index.
[c] Relative to the upper normal limit (×UNL).
[d] Per 10 mm increase in size.
[e] Categories [3]: Stage IVBa = 0, IVBb = 1, IVBc = 2.

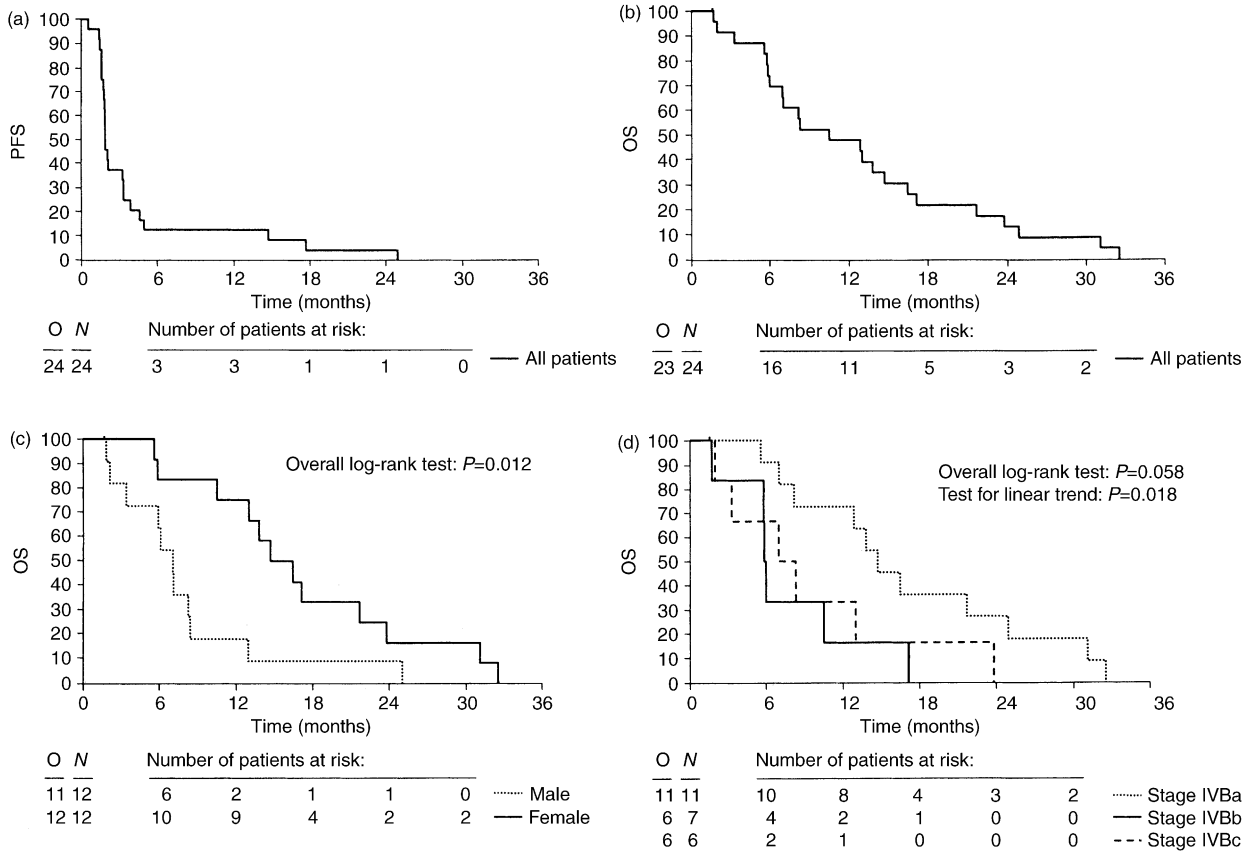

Fig. 1. Kaplan–Meier plot of progression-free survival (PFS) (a) and overall survival (OS) (b), and Kaplan–Meier plot of OS according to the Helsinki University Central Hospital (HUCH) Working Formulation substage (c), Stage IVBa corresponds to a predicted median overall survival of 12 months or more, Stage IVBb to a survival of 6–11 months, and Stage IVBc to a survival of less than 6 months [3], and according to gender (d). O, observed; *N*, number.

these studies can explain the differences noted in the frequency of pulmonary toxicity.

The median overall survival of 10.6 months in the present study is of the same order as the 6–18 months median overall survival with other current treatments such as cisplatin with chemoembolisation [10], intra-arterial fotemustine with or without surgical debulking [12,14–16], and intra-arterial dacarbazine and cisplatin [15,17].

Uveal melanoma is 15 times less common than cutaneous melanoma, which explains in part why no randomised trials have been initiated. In the absence of such trials, it would be beneficial to assess treatment outcome according to pretreatment characteristics such as the HUCH Working Formulation substages. The median overall survival of 14 months for the 11 patients staged to the most favourable HUCH Working Formulation substage IVBa with predicted median survival 12 months or more approached the median survival of 13–18 months reported for intra-arterial fotemustine and carboplatin [14,16,17]. Patients who received fotemustine were reviewed with 6- to 12-monthly liver imaging, they were asymptomatic, and often had normal liver function suggesting Stage IVBa [14,16]. The median overall survival after BOLD and human leucocyte interferon was 17 months when patients belonged to Stage IVBa [20]. These data do not suggest a major survival benefit from any of these treatments compared with the others [15].

BOLD with alpha-interferon may be useful until better regimens have been designed when patients have extrahepatic metastases, abnormal vascular anatomy or they can not sustain laparotomy to undergo targeted hepatic therapy [14–16]. *In vitro* chemosensitivity analyses suggest that more effective therapy might be based on drugs such as treosulfan and gemcitabine [25–27], but prospective trials on their efficacy in metastatic uveal melanoma are not yet available.

Acknowledgements

This publication was supported by grants 5U10-CA11488-25 through 2U10-CA11488-32 from the National Cancer Institute, Bethesda, USA. Its contents are solely the responsibility of the authors and do not represent the official views of the National Cancer Institute.

Appendix

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