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ORIGINAL ARTICLE

Bleomycin, vinorelbine and trofosfamide in relapsed stage IV cutaneous malignant melanoma patients

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Abstract
Purpose To evaluate the efficacy of bleomycin, vinorelbine, and trofosfamide (BVT) in 28 patients with pretreated relapsed AJCC stage IV cutaneous malignant melanoma.
Methods Patients in relapse after first- or second-line therapy received 8 mg/m^2 intravenous (i.v.) bleomycin, 25 mg/m^2 i.v. vinorelbine, on days 1 and 6, each, and oral (p.o.) trofosfamide 60 mg/m^2/day, days 1–7. BVT therapy was repeated every 5 weeks until progression of disease occurred. A maximum of six BVT cycles (mean, 2.2 cycles) was administered per patient.
Results Three patients (11%) reached a partial response; 5 (18%) patients showed stable disease, and 20 (71%) patients progressed upon BVT therapy. Median overall survival of all 28 patients was 6 months (6-month survival rate, 52%). Patients with partial remission or stable disease ($n = 8$) exhibited a median overall survival of 10 months (6-month survival rate, 75%), while patients with disease progression ($n = 20$) showed a median overall survival of 3 months (6-month survival rate, 43%). Most side effects were limited to WHO grade I/II mild anemia, leucocytopenia, fatigue, nausea/vomiting, pain, and anorexia. WHO grade III/IV side effects occurred in 7% (anorexia) and 4% (fatigue) of patients.
Conclusion Treatment with BVT was efficient in 29% of pretreated relapsed stage IV cutaneous melanoma patients, with overall good tolerability and safety.

Keywords Melanoma · Bleomycin, vinorelbine, and trofosfamide

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Introduction

The prognosis of patients with metastatic melanoma remains poor, with a median overall survival of about 6 months. The most widely used chemotherapeutic agent for the treatment of metastatic melanoma is dacarbazine (DTIC), alone or in combined chemotherapy regimens like the Dartmouth regimen (cisplatin, carmustine, tamoxifen, and DTIC), CVD (cisplatin, vinblastine, and DTIC) or BOLD (bleomycin, vincristine, lomustine, and DTIC) or in combination with interferon alpha and/or interleukin-2 [1–5]. While few long-term survivors have been reported with the Dartmouth regimen, the majority of metastatic melanoma patients did not exhibit a significant survival benefit from DTIC-based combination regimens when compared to DTIC alone [6]. Therefore, the development of new combined treatment strategies for stage IV melanoma patients was necessary.

Bleomycin is an antibiotic that causes double strand DNA breaks [7]. It has been used e.g., in the treatment of metastatic melanoma patients as part of the BOLD regimen plus interferon alpha, leading to a response rate between 24 and 27% [1, 5].

Vinorelbine, a semisynthetic vinca alkaloid drug, showed promising antiproliferative activity against human melanoma cell lines in vitro [8–11]. Several authors reported that a vinorelbine-based second-line regimen may

lead to objective remissions in stage IV melanoma patients [12–14].

Trofosfamide is an alkylating agent that is derived from the oxazaphosphorines [15–17]. In a preliminary single agent study in relapsed stage IV melanoma disease stabilization was demonstrated in 25 of 37 patients [18].

Since no standard systemic treatment is available for patients with metastatic melanoma who relapse after DTIC-based first-line chemotherapy, in the present manuscript we analyzed the efficacy and toxicity of a new treatment combination comprising bleomycin, vinorelbine, and trofosamide (BVT) as second- or third-line therapy in relapsed pretreated stage IV malignant melanoma patients.

Patients and methods

Patients

Between January 2007 and March 2008, 28 relapsed stage IV cutaneous melanoma patients at ages between 28 and 92 years received a combination treatment with BVT.

Criteria for entry into the study were: systemically pretreated relapsed AJCC stage IV cutaneous malignant melanoma; white blood cell count >3,500/μl; platelet count >100.000/μl; hematocrit >30%; serum creatinin and bilirubin <1.5 of the upper normal limit; age ≥18 years and a life expectancy of >3 months. Progressive CNS metastases were no exclusion criteria.

Written informed consent was obtained from all patients prior to therapy.

Treatment design

Patients in relapse after first- or second-line therapy received 8 mg/m^2 intravenous (i.v.) bleomycin, 25 mg/m^2 i.v. vinorelbine, on days 1 and 6, each, and oral (p.o.) trofosfamide 60 mg/m^2/day, days 1–7. BVT therapy was repeated every 5 weeks until progression of disease occurred. Patients received a mean of 2.2 cycles (range 1–6) of BVT until progression of disease occurred or until last known date to be alive.

Response, survival, and toxicity

Response to therapy was evaluated according to World Health Organization (WHO) criteria with regular reevaluation intervals every 2 months; complete response: disappearance of all signs of disease for a minimum of 2 months; partial response: 50% or more reduction in the sum of products of the greatest perpendicular diameters of measurable lesions, no increase in lesion size and no new lesions; stable disease: less than a partial response with no disease progression for at least 5 weeks; progressive disease: 25% or more increase in sum of products in the longest perpendicular diameters of measurable lesions or the development of new lesions.

In case of progression upon 1st re-evaluation after 8 weeks of treatment, progression-free survival was calculated at 0 months. Survival was measured from start of therapy to date of death or to the last known date to be alive.

Maximum toxicity was evaluated according to CTC criteria (version 3.0).

Statistical analysis

The probability of overall survival and progression-free survival was plotted over time according to the method of Kaplan and Meier; SPSS software (SPSS Inc., Chicago, IL, USA) was employed.

Results

Median follow-up of all patients was 3.5 months (range 0–15 months). The patient group consisted of 13 males and 15 females, at a median age of 58 years (range 28–92 years). All patients had failed previous first- ($n = 2$) or second- ($n = 26$) line therapy. Stage IV pretreatment consisted of chemotherapy, notably, DTIC, cisplatin, BCNU/fotemustine ($n = 20$), gemcitabine, treosulfan ± cisplatin ($n = 19$), DTIC, BCNU, hydroxyurea ($n = 10$), DTIC ± roferon ($n = 3$), and DTIC, cisplatin ± vinblastine ($n = 1$).

At start of BVT therapy, patients showed one metastatic site ($n = 4$), two metastatic sites ($n = 8$), three metastatic sites ($n = 11$), four metastatic sites ($n = 2$), five metastatic sites ($n = 2$), and six metastatic sites ($n = 1$), respectively. Metastases were localized in skin/soft tissue ($n = 18$), lung ($n = 17$), visceral ($n = 11$), lymph nodes ($n = 16$), bone ($n = 5$), CNS ($n = 6$), and other sites ($n = 1$).

Pretreatment serum lactate dehydrogenase levels and serum alkaline phophatase levels were elevated in 61 and 29% of patients, respectively. Overall, patients had a Karnofsky performance status of 90% ($n = 9$), 80% ($n = 14$), and 60–70% ($n = 5$), respectively (Table 1).

Objective response

Second- or third-line therapy of stage IV melanoma with BVT resulted in three patients (11%) with partial remission, five (18%) patients with stable disease, and 20 (71%) patients with continuous disease progression (Table 2).

At last follow-up, 7 (25%) of 28 patients are progression-free. Progression-free survival ranged from 0 to 12 months in all patients.

Table 1 Patient characteristics

	All patients
Entered	28
Age (years)	
Median	58
Range	28–92
Sex	
Male	13
Female	15
Bleomycin, vinorelbine, and trofosfamide therapy	
Second-line	2
Third-line	26
Stage IV previous systemic treatment[a]	
DTIC, cisplatin, BCNU/fotemustine	20
Gemcitabine, treosulfan ± cisplatin	19
DTIC, BCNU, hydroxyurea	10
DTIC ± roferon	3
DTIC, cisplatin ± vinblastine	1
Other	1
Pretreatment metastatic sites	
Number	
One	4
Two	8
Three	11
Four	2
Five	2
Six	1
Localization	
Skin/soft tissue	18
Lung	17
Visceral	11
Lymph nodes	16
Bone	5
CNS	6
Others	1
Pretreatment Karnofsky performance status	
90%	9
80%	14
60–70%	5
Pretreatment serum levels	
LDH elevated	17
AP elevated	8

DTIC dacarbazine, *BCNU* carmustine, *LDH* lactate dehydrogenase, *AP* alkaline phophatase

[a] Patients may have had more than one pretreatment

Out of eight patients achieving partial remissions or stable disease upon BVT, three patients had progressed upon first-line-dacarbazine-based treatment, while six out of eight patients had failed previous second-line gemcitabine/treosulfan-based therapy.

Table 2 Response to bleomycin, vinorelbine, and trofosfamide therapy of relapsed stage IV cutaneous malignant melanoma according to WHO

Patients	Response				Total
	CR	PR	SD	PD	
Bleomycin, vinorelbine, and trofosfamide					
n	0	3	5	20	28
%	0	11	18	71	

CR complete response, *PR* partial remission, *SD* stable disease, *PD* progression of disease

When compared to all patients, patients achieving partial remission or stable disease were not statistically different with regard to skin/soft tissue, lung, visceral, and lymph node disease; however, only one of eight patients achieving treatment related clinical benefit had CNS disease upon start of therapy.

Also, the proportion of patients with previous cisplatin-based therapy did not significantly differ when comparing all patients against patients with partial remission or stable disease.

Overall survival

Overall median survival of all 28 patients was 6 months (95% CI 2–10; 6-month survival rate, 52%; Fig. 1a). Patients achieving partial remission or stable disease ($n = 8$) exhibited a median overall survival of 10 months (95% CI 0–22; 6-month survival rate, 75%; Fig. 1b), while patients with disease progression ($n = 20$) reached a median overall survival of 3 months (95% CI 0–7; 6-month survival rate, 43%; Fig. 1c). At last follow-up, 12 (43%) patients continue to be alive with a median follow-up of 7 months (range 1–15 months).

Treatment related toxicity

Bleomycin, vinorelbine, and trofosfamide lead to overall tolerable side effects. No toxic deaths occurred (Table 3).

Patients experienced CTC grades I and II fatigue (57%), nausea/vomiting (18%), pain (14%), and anorexia (11%). Grade III/IV side effects were observed in 4% (fatigue) and 7% (anorexia) of patients. Hematologic toxicities were limited to CTC grade I/II anemia (59%) and leucocytopenia (26%).

Discussion

Patients with relapsed stage IV cutaneous melanoma failing standard dacarbazine-based chemotherapy have a

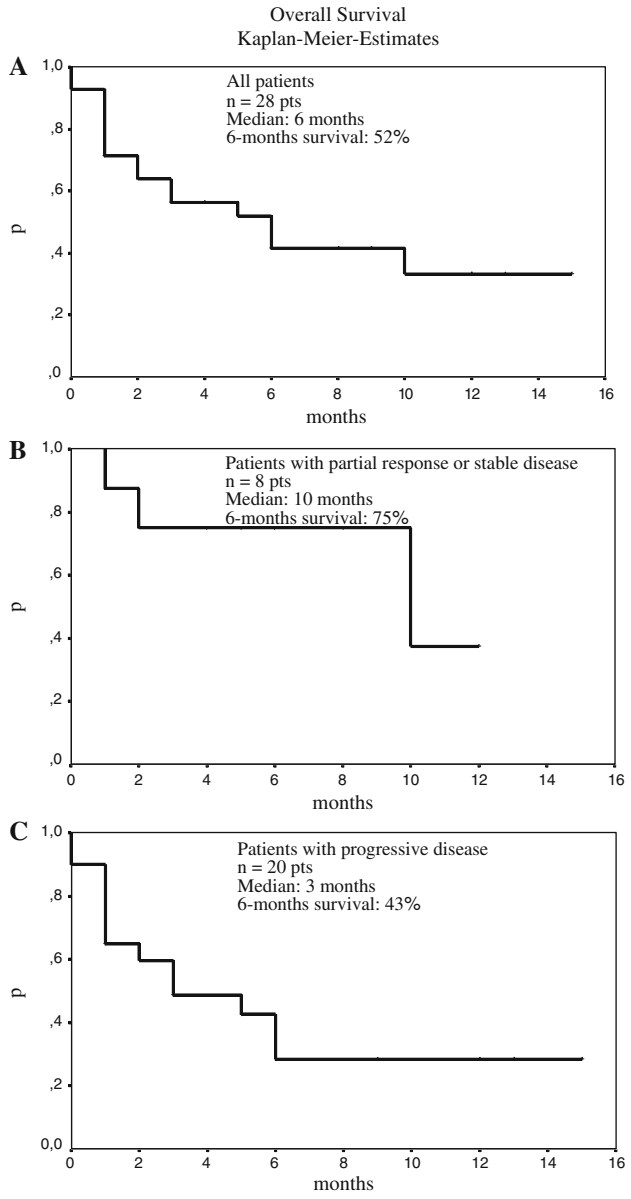

Fig. 1 Overall survival (Kaplan–Meier estimates) of **a** all 28 patients, **b** 8 patients with partial remission or stable disease, and **c** 20 patients with progressive disease. Patients were treated with bleomycin, vinorelbine, and trofosfamide. Survival was measured from start of therapy

poor prognosis. Here, we report on the efficacy and toxicity of a new chemotherapy combination comprising BVT in pretreated progressive stage IV cutaneous melanoma patients.

Treatment with BVT resulted in a median overall survival of 6 months from start of therapy; thus, median overall survival upon BVT second- ($n = 2$) or third- ($n = 26$) line treatment was similar to that reported in upfront dacarbazine-based regimens yielding a median overall survival between 5 and 7 months [5, 19].

Table 3 Systemic maximum toxicity of bleomycine, vinorelbine, and trofosfamide therapy

Side effects[a], CTC criteria (version 3.0)	Patients (%)	
	I/II	III/IV
Fatigue	54	4
Nausea/vomiting	21	–
Pain	14	–
Anorexia	4	7
Leucocytopenia	26	–
Thrombocytopenia	–	–
Anemia	59	–

[a] No life-threatening complications and no toxic deaths occurred

Notably, this novel multi-agent chemotherapy regimen led to 29% of patients achieving stable disease or partial remissions, with a prolonged median overall survival of 10 months. Previously, a second-line treatment of metastatic melanoma patients with a vinorelbine-containing therapy resulted in approximately 30% of patients with stable disease or partial remission [12, 13].

Although, in the present cohort, we could not observe a clear synergy of BVT when applied as combined therapy, the result was still remarkable given the proportion of high-risk patients exhibiting visceral (40%), CNS (21%), and bone (18%) metastases as well as elevated lactate dehydrogenase levels (61%) at start of BVT therapy.

In addition, BVT therapy showed clinical efficacy in eight patients, of which six patients had directly failed second-line gemcitabine/treosulfan-based therapy.

Thus, BVT therapy might represent a good option for progressive stage IV patients, even after an ineffective second- or first-line therapy.

Overall, BVT therapy was well tolerated in relapsed stage IV melanoma patients up to 90 years of age. Most systemic side effects were limited to CTC grades I and II, including mild anemia and leucocytopenia as well as mild fatigue, nausea/vomiting, pain, and anorexia, respectively.

In summary, the combination of BVT might be an alternative for patients with pretreated progressive stage IV melanoma, in whom drug tolerability and quality of life are most relevant.

Future studies should broaden this—so far—limited clinical experience using a multicentric approach.

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Conflict of interest All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work.

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