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European Journal of Cancer 39 (2003) 476–480

European Journal of Cancer

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Brain metastases following interleukin-2 plus interferon-alpha-2a therapy: a follow-up study in 94 stage IV melanoma patients

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Received 2 April 2002; received in revised form 23 September 2002; accepted 5 November 2002

Abstract

This study analyses the frequency and therapy of brain metastases in 94 stage IV melanoma patients after treatment with high-dose interleukin-2 (IL-2) and interferon-α (IFN-α) within three subsequent trials between 1990 and 1995. Central nervous system (CNS) metastases occurred in 28 patients (30%) during the potential follow-up period of 6 years. Time to occurence of brain metastases varied between 1 and 53 months, with a median of 10 months. Of 28 patients, 19 had <5 metastases, which were treated with stereotactic radiosurgery (SR) in 9 patients. In 2 patients, SR was followed by resection. 9 patients had multiple metastases, of which 4 received whole brain irradiation (WBI). Median survival after the detection of CNS metastases was 6 months (95% Confidence Interval (CI) 1–11 months). SR plus resection was associated with a prolonged survival of 34 and 35 months in 2 patients, 1 patient survived for 41 months after WBI, demonstrating the efficacy of these therapeutic strategies.

Keywords: Brain metastases; Melanoma; Cytokine therapy

1. Introduction

The prognosis of advanced stage melanoma remains poor, with approximately 10% long-term survivors after cytokine therapy with high-dose interleukin-2 (IL-2) and interferon-α (IFN-α) and a response rate of 18–44% [1–3]. Immunological effector cells and most cytotoxic agents including dacarbazine (DTIC) and cisplatin struggle to cross the blood–brain barrier. Therefore, the effect of cytokine treatment, as well as biochemotherapy, on detectable or occult metastases in the central nervous system (CNS) is considered to be low, which has led to the exclusion of these patients from most trials employing systemic therapy.

It has been described in many studies that brain metastases frequently occur in the course of advanced melanoma. Cerebral metastases are found in 50–70% of autopsies in melanoma patients with advanced disease [4,5]. Little is known about the frequency of brain metastases in patients responding to cytokine therapy, although the occurrence of isolated CNS relapses have been described in numerous studies.

In this study, we report on 94 patients with a potential 6-year follow-up, who had received treatment with high-dose IL-2 + IFN-α for stage IV melanoma. We analyse the frequency of metastases to the CNS, the therapeutic interventions and survival.

2. Patients and methods

Patients with metastatic melanoma had been enrolled into three subsequent trials between 1990 and 1995 at the Department for Hematology and Oncology at the University of Heidelberg or the Department for Dermatology at the University of Ulm. The first two

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0959-8049/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
PII: S0959-8049(02)00731-1

trials used IFN-α and high-dose IL-2 and had been performed between 1990 and 1993 [6]. The third trial, conducted between 1993 and 1995, was a randomised trial of the EORTC-Melanoma Cooperative Group, in which patients received IFN-α and high-dose IL-2 + cisplatin [1]. From this study, only patients randomised for treatment without cisplatin are considered. Identical inclusion criteria for all three trials were histologically-confirmed metastatic melanoma, which could not be controlled by surgery, and a Karnofsky performance status of at least 60%. Exclusion criteria were the presence of brain metastases on brain computed tomography (CT) or magnetic resonance imaging (MRI); symptomatic cardiac, pulmonary, renal, liver or thyroid disease; autoimmune disease; corticosteroid treatment; and significant bone marrow dysfunction.

Tumour assessment was performed after the second and the fourth treatment cycle according to standard World Health Organization (WHO) criteria. Patients with stable disease or progressive disease after two treatment cycles were monitored without further protocol treatment. After completion of treatment in the study, patients were monitored clinically every 2 months during the first 6 months and every 3 months thereafter. Brain CT or MRI were performed only if CNS relapse was suspected clinically. The clinical trials had been approved by the institutional ethics committees.

2.1. Statistical evaluation

Survival curves were computed according to the Kaplan–Meier method, statistical significance was tested using the log-rank test.

3. Results

3.1. Response to high-dose IL-2 and INF-α and frequency of CNS relapse

A total of 94 patients had been treated between 1990 and 1995. Follow-up data of all patients are available. The overall response rate was 22%, 4 patients (4%) had a complete response (CR) and 17 (18%) had a partial response (PR). 26 (28%) had a disease stabilisation (SD) and 45 (48%) had progressive disease (PD). In 2 patients, response to treatment was not evaluated. A total of 28 patients (30%) developed symptomatic metastases to the CNS during the follow-up period (Table 1).

3.2. Relationship of response to cytokine treatment and development of symptomatic brain metastases

A total of 21 patients responded to cytokine therapy. A cerebral relapse was observed in 1 of 4 patients with a CR and 10 of 17 with a PR. In 8 of 26 patients with SD and 9 out of 45 patients with PD brain metastases were detected in the follow-up period (Table 1).

Table 1
Response to cytokine therapy and development of symptomatic CNS metastases

Response to cytokine treatment	All patients treated $N=94$	No. of patients with CNS metastases $n=28$
CR	4	1
PR	17	10
SD	26	8
PD	45	9
NE	2	0

CNS, central nervous system; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated.

3.3. Time to CNS relapse

The time to detection of symptomatic CNS metastases varied between 1 and 53 months with a median of 10 months (6–14 months, 95% confidence interval (CI)) after the initiation of cytokine therapy (Fig. 1).

3.4. Treatment of brain metastases

19 out of 28 patients with CNS relapse had <5 brain metastases (Table 2). These patients were evaluated for stereotactic radiosurgery (SR), if the largest diameter of the metastases was <40 mm.

Of the group of patients with <5 brain metastases, 5 patients had a relapse in CNS only without systemic disease progression. 4 patients were treated with stereotactic radiosurgery. In 2 patients, this was followed by complete resection of brain metastases. One patient had a ventriculoatrial shunt operation because of hydrocephalus and

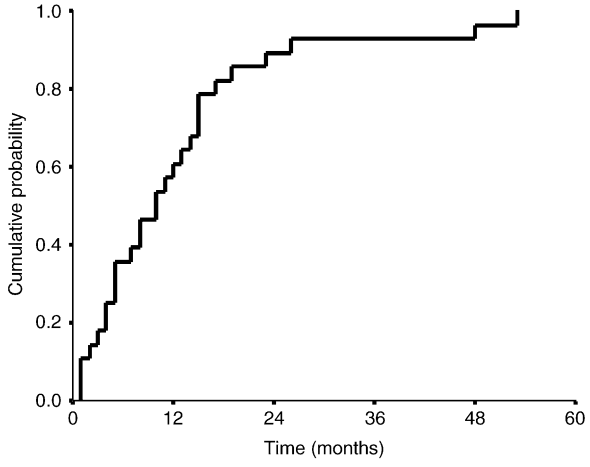

Fig. 1. Cumulative probability of central nervous system (CNS) relapse after cytokine therapy. Median time to CNS relapse was 10 months (95% confidence interval (CI) 6–14 months).

Table 2
Number of CNS metastases and therapy

Patients with CNS metastases, $n=28$ (30%)				
No. of CNS metastases (total no. of patients)	Site of progression	Treatment modality	No. of patients treated	Median survival (range)
<5 ($n=19$)	CNS only ($n=5$)	SR + resection	2	12 months (9–35)
		SR	2	
		Shunt-surgery	1	
	CNS + systemic ($n=14$)	SR + WBI	3	2.5 months (1–11)
		SR + D	2	
		WBI + D	4	
		D alone	1	
		no therapy	4	
$\geqslant 5$ ($n=9$)	CNS only ($n=1$)	WBI + D	1	20 months
	CNS + systemic ($n=8$)	WBI + D	3	4 months (1–41)
		no therapy	5	

CNS, central nervous system; SR, stereotactic radiosurgery; WBI, whole brain irradiation; D, DTIC-based chemotherapy; DTIC, dacarbazine.

did not receive any additional treatment (Table 2). Median survival in this group of patients was 12 months (9–35 months) (Table 2).

The other 14 patients with <5 brain metastases had concurrent systemic disease progression. Of these, 5 patients received SR, this was followed by whole brain irradiation (WBI) in 3 and by dacarbazine (DTIC) chemotherapy in 2 patients. 4 patients in this group were treated with WBI followed by DTIC chemotherapy. One patient received treatment with DTIC and 4 patients died from progressive disease shortly after detection of brain metastases and therefore did not receive any therapy. Median survival in this group was 2.5 months (1–11 months) (Table 2).

9 out of the 28 melanoma patients relapsed with $\geqslant 5$ brain metastases, of which 1 patient had disease progression in the brain in the absence of systemic progression. This patient received treatment with WBI followed by DTIC chemotherapy at the time when systemic disease progression occurred. She had a favourable survival of 20 months. The other 8 patients with >5 brain metastases had concurrent systemic disease progression. 3 of these patients were treated with WBI plus DTIC-based chemotherapy. The other 5 patients did not receive any therapy, due to rapid disease progression or patient's refusal in 1 case. The median survival in this group was 4 months (1–41 months) (Table 2).

3.5. Survival of patients with CNS metastases

The median survival of all patients with metastases to the CNS was 6 months from the detection of CNS metastases (95%, CI: 1–11 months) (Fig. 2a). Patients with an objective response to the initial cytokine therapy had a significantly longer survival, when compared with patients with progressive disease ($P<0.01$, log-rank test) (Fig. 2b). In addition, survival in patients with isolated disease progression in the CNS was longer than in patients with concurrent systemic disease progression (Fig. 2c). 5 patients had a favourable survival of more than 12 months. 2 of these patients were treated with stereotactic radiosurgery followed by resection of a single or two brain metastases, resulting in a survival of 34 and 35 months, respectively. These patients both had no systemic disease progression at the detection of CNS metastases. 2 patients had progression in the CNS 4 and 5 months after cytokine treatment. Although brain metastases occurred so early, their survival was 15 and 41 months (Table 3). 3 patients were

Table 3
Characteristics of patients with a survival >12 months

Patient	Time to CNS relapse (months)	Number of CNS metastases	Site of progression	Therapy of CNS metastases	Response to cytokine treatment	Survival[a] (months)
RS	10	1	CNS only	SR + resection	CR	34
KR	15	2	CNS only	SR + resection	PR	35
SC	4	5	CNS + systemic	WBI + D	CR	41
SR	53	Multiple	CNS only	WBI + D	NE	20
SU	5	Multiple	CNS + systemic	WBI + D	SD	15

CNS, central nervous system; SR, stereotactic radiosurgery; WBI, whole brain irradiation; D, DTIC-based chemotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated.

[a] From detection of CNS metastases.

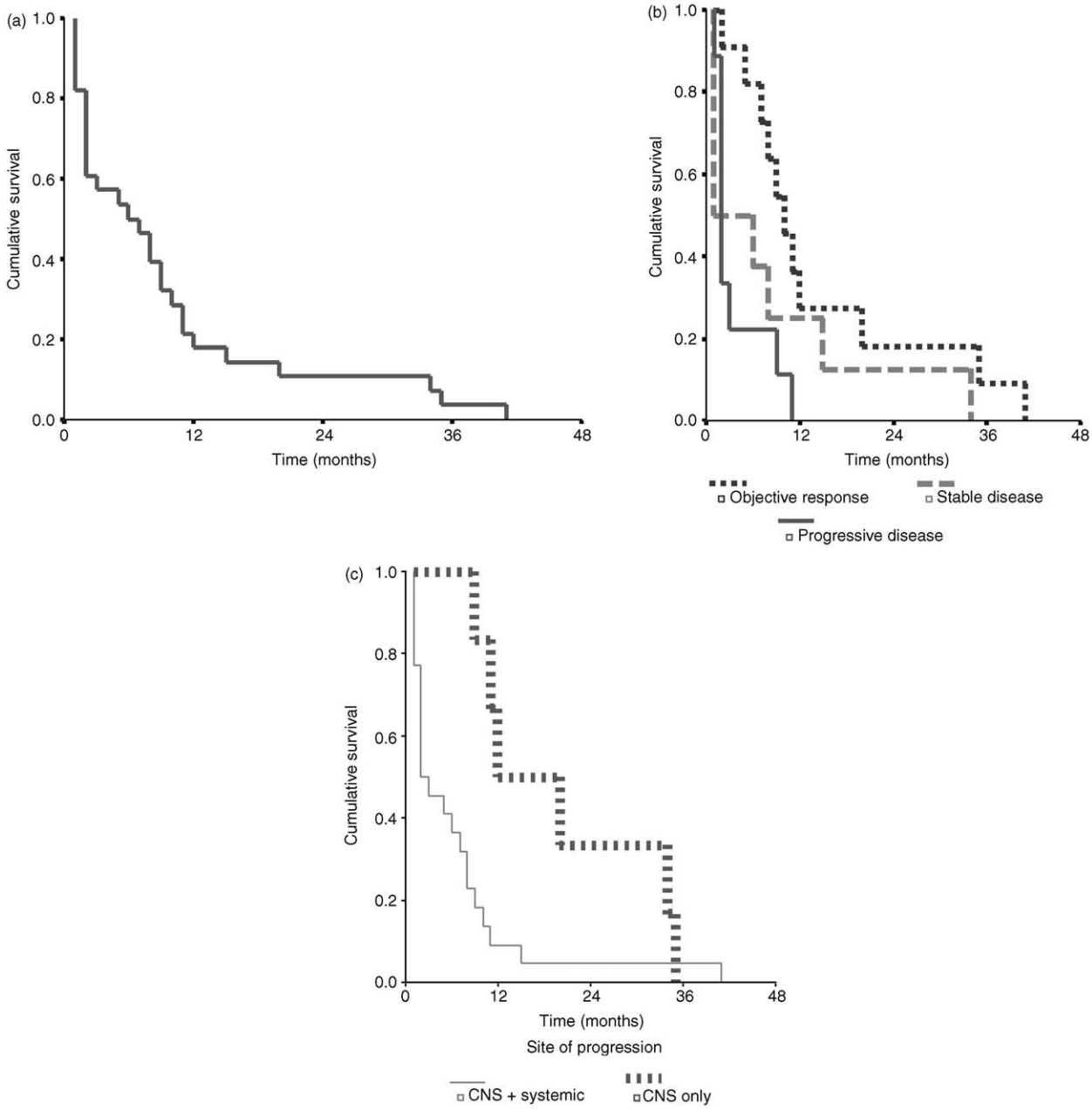

Fig. 2. (a) Survival analysis of patients after detection of CNS metastases (Kaplan–Meier plot). Median survival was 6 months (95% CI 1–11 months). (b) Survival analysis by response to initial high-dose interleukin-2 (IL-2) plus interferon-α (IFN-α) therapy (Kaplan–Meier plot). $P < 0.01$ objective response (OR) versus progressive disease (PD) and $P = 0.16$ OR versus stable disease (SD) (log-rank). (c) Survival analysis by site of disease progression. Isolated CNS progression (CNS only) versus CNS plus systemic progression.

treated with WBI plus DTIC-based chemotherapy for five or multiple brain metastases. Survival in these cases was 41, 20 and 15 months (Table 3).

4. Discussion

The initial mechanism of cytokine-mediated tumour regression is the unspecific activation of immunological effector cells like NK-cells, T lymphocytes and monocytes and macrophages, which may as a consequence lead to the induction of a specific T cell response [7]. The immune effector cells do not usually cross an intact blood–brain barrier and are therefore of limited efficacy on brain metastases, which has led to the exclusion of patients with brain metastases from most cytokine and chemotherapy trials in advanced melanoma. One could assume that progression with metastases to the CNS therefore frequently occurs after cytokine treatment. The follow-up data demonstrated here shows a frequency of 30% of symptomatic brain metastases. The incidence of asymptomatic brain metastases may be

higher, since brain CT or MRI scans were only performed in cases of clinically suspected CNS metastases and autopsies were performed in only a few patients who died with systemic disease progression. This might explain why the frequency of clinically-detected brain metastases is lower than the 50–70% described from autopsy series by two groups [4,5].

The median survival of patients with brain metastasis in our analysis was 6 months (95%, CI: 1–11 months). In a retrospective analysis of 87 patients with brain metastases, treated with various schedules of WBI, a median survival of 19 weeks was found [8]. This retrospective analysis also showed a significantly improved median survival of 45 weeks in a subset of 22 patients, who additionally underwent resection of metastases. Furthermore, median survival was 54 weeks in patients without extracranial evidence for disease [8]. Another retrospective study on a series of 136 patients reported a 1-year-survival rate of 28% after resection, which was significantly higher than radiotherapy or chemotherapy (1-year survival 6.7%) or no treatment (3.5%) [9]. Our analysis showed a similar trend: both patients in whom resection was possible had a favourable survival of 34 and 35 months. The prolonged survival is not only caused by the resection itself, control of systemic disease and a good performance status were also likely to be influencing factors.

SR has proven to be effective in achieving local disease control in solitary brain metastases in a variety of studies and histologies [10,11]. A local control rate of 90% and a median survival of 7 months for patients with solitary melanoma metastases was reported in a retrospective study on 60 patients [11]. In their analysis, the addition of WBI was not found to significantly influence survival. These data support the findings of our study: a total of 9 patients received SR, either alone ($N=2$) or in combination with DTIC-based chemotherapy ($N=2$) or in combination with WBI ($N=3$) or followed by resection ($N=2$). However, only resection resulted in an impressive survival exceeding 12 months. The majority of patients in our study received WBI ($N=11$). This treatment regimen was effective in at least three patients, who had a survival of 41, 20 and 15 months after detection of the brain metastases.

The patient population analysed in our study received cytokine therapy more than 6 years ago between 1990 and 1995. When in these patients brain metastases occurred fotemustine was the only cytotoxic agent available with the ability to cross the blood–brain barrier and had the disadvantage of a high myelotoxicity [12]. More recently, temozolomide, a novel oral DTIC analogue has been developed. It has significant activity in relapsed high grade gliomas [13,14]. In a phase III trial, it has been demonstrated to be equally effective as DTIC in Stage IV melanoma patients who had no CNS involvement [15]. Ongoing clinical trials are currently investigating whether the efficacy of temozolomide on asymptomatic brain metastases in malignant melanoma can be enhanced by WBI (EORTC 18981 trial), which might result in an improved outcome for these patients in the future.

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