Cerebral metastases of malignant melanoma: contemporary treatment modalities and survival outcome

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Received May 24, 2004

The aim of our study was to analyze prognostic factors, effect of treatment and survival outcome of a contemporary cohort of melanoma patients with cerebral metastases and eventually propose new recommendations regarding therapy.

Sixty four patients with melanoma brain metastases were treated in our department within a 15-year period. We performed a retrospective analysis of their survival with respect to the type of treatment instituted. Four groups were formed according to treatment: Group A patients treated with surgery followed by radiotherapy; group B temozolomide as first-line treatment and radiotherapy after cerebral disease progression; group C radiotherapy alone; group D supportive care only.

Patients' characteristics influenced the selection of treatment modality: Group A (7.8 %) patients with a single brain metastasis ($p=0.001$) and controlled extra-cranial disease ($p<0.0001$), while Group D (21.8 %) patients with ulcerated primary lesions ($p=0.010$) and uncontrolled extra-cranial disease ($p<0.0001$). Only group B (26.6 %) and C (43.7 %) patients with similar characteristics including more than one brain lesion. Median overall survival was 3 months. In univariate analysis, median survival for groups A, B, C and D was 12, 5, 3 and 2 months, respectively ($p<0.0001$). The survival difference between the surgery and non-surgery groups was statistically significant ($p=0.0011$). Patients treated with supportive care had the worse prognosis ($p<0.0001$). A survival benefit for patients receiving first-line treatment with temozolomide, as compared to those receiving radiotherapy alone was noted ($p=0.0267$). In multivariate survival analysis, the number of brain lesions ($p=0.0138$), the absence of uncontrolled extra-cranial disease ($p=0.00221$) and the type of treatment for the cerebral disease ($p=0.0053$) remained significant independent survival predictors.

Patients' characteristics remain a critical factor for treatment selection. The number of brain metastases, the extent of disease and the type of treatment represent independent survival predictors. Melanoma patients with a single brain metastasis and controlled extra-cranial disease gain a survival benefit, if surgically treated. Including temozolomide in the first-line treatment of melanoma patients with brain metastases who would have been treated with radiotherapy alone, might present a promising future direction affecting the length of survival.

Key words: melanoma, brain metastases, survival, treatment, temozolomide

Cutaneous malignant melanoma is the third most common cause of brain metastases [42]. The reported incidence of cerebral metastases in patients with disseminated disease is approximately 20 % [37]. Brain metastases remain the most common cause of death and still carry the worst prognosis of all visceral metastases in malignant melanoma patients [12, 18].

Overall, the effect of available therapeutic modalities on the mortality of such patients is disappointing; even when treatment is initiated median survival is extremely poor, ranging from 3 to 4 months [3, 13, 17, 23, 37, 42]. Whole brain irradiation is reported to be effective for local tumor symptom control [13] and still represents the standard care. Nevertheless, median survival of melanoma patients with cerebral dissemination treated with such a modality remains short [17]. Surgical resection can offer a significant palliative benefit with an eventual improved length of survival, in only selected cases of patients with a single metastatic brain lesion, having no pre-operative neurologic deficits and no lung or other visceral melanoma metastases [41]. Patients who undergo surgical resection of multiple melanoma brain metastases have good palliation, but a relatively short survival time after craniotomy [38, 41]. No survival benefit is reported when such patients receive postoperative radiother-

apy, compared to those treated with surgery only [38, 41]. Chemotherapeutic agents studied, alone or mainly in combination with radiotherapy, demonstrate only minor improvement of symptomatic palliation and no survival prolongation [10, 20, 34, 40]. Since effective treatment options remain limited, newly developed therapies are required.

Temozolomide is a novel oral alkylating agent, actively being investigated for the treatment of metastatic malignant melanoma [1, 2, 4, 5, 8, 27, 29, 33], with promising activity in the treatment of central nervous system disease [2, 16, 35]. The number of reports available in the literature evaluating temozolomide as a treatment modality of melanoma brain metastases is very small [7, 28, 30], and reliable evidence of its therapeutic value for such metastases is lacking.

In our institution, investigational treatment of metastatic malignant melanoma to the brain with temozolomide was initiated in January 1998, following approval of the institutional ethical committee. The purpose of this retrospective study was to review our experience with the treatment of melanoma patients with brain metastases and to analyze prognostic factors, effects of treatment and survival outcomes of the applied treatment modalities and to eventually propose new recommendations regarding therapy.

Patients and methods

The records of all patients with malignant melanoma treated in our institution from January 1986 until December 2001 (15-years) were retrospectively reviewed and 64 patients with cerebral metastases detected and confirmed by computerized tomography [CT] and/or magnetic resonance imaging [MRI] were selected. By surgical biopsy was diagnosis confirmed in 5 patients. All patients were dead at the time of the analysis.

Patients were divided into 4 groups, depending on the type of treatment given for the cerebral metastatic disease. Nevertheless, it should be stressed out that treatment decisions were based on the attending physician's discretion and on patients' and/or their relatives' wish; no specific randomization or algorithms were used.

Group A consisted of 5 patients (7.8 %) receiving surgery followed by radiotherapy. Surgery involved craniotomy and resection of the metastases. Radiotherapy was given at the total dose of 20 Gy in five equal fractions over 5 consecutive days. Group B consisted of 17 patients (26.6 %) treated with temozolomide. Our institution's ethical committee had approved the investigational use of this chemotherapeutic drug, according to a study protocol still under way. Patients with melanoma brain metastases were considered eligible for inclusion when they were unsuitable for surgery, and/or radiotherapy. All patients gave informed consent. Temozolomide was given orally at the total dose of 1000 mg/m^2, split over 5 consecutive days, once daily, on a 4-week cycle. Patients who had received previous chemotherapy or showed ≥grade 3 (according to the Common Toxicity Criteria) neutropenia or thrombocytopenia after one course, were treated with a total dose of 750 mg/m^2 per cycle. Patients receiving temozolomide were evaluated by brain CT and/or a MRI – every two cycles of treatment; whenever cerebral disease progression was suspected, temozolomide was no longer administered and patients were immediately submitted to whole brain irradiation. If patients responded well to chemotherapy, they received a total of six cycles of temozolomide. In such cases, whole brain irradiation was administered only after local tumor relapse. After documented cerebral disease progression or local tumor relapse, whole brain irradiation was given at a dose of 20 grays (Gy) in five equal fractions over 5 consecutive days. Group C consisted of 28 patients (43.7 %) who underwent whole brain irradiation therapy alone. Radiation fraction size varied from 180 to 550 cGy, but fractions were given one per day in all patients. The total dose varied from 22 Gy to 55 Gy. Group D consisted of 14 patients (21.8 %) with no specific treatment for the cerebral disease, receiving only supportive care.

Whenever a patient had received palliative chemotherapy other than temozolomide for the cerebral disease was not recorded because such treatment was thought unlikely to have influenced survival outcome.

Patient characteristics and prognostic factors were compared among the four treatment groups in order to analyze the influence of patient selection on treatment received. Data concerning each patient's age and gender, the primary tumor's location, Clark's level of invasion, Breslow's thickness, and histological type, the presence of ulceration and the development of local-regional disease prior to the diagnosis of brain metastases were obtained. Additionally the time interval (in months) between the diagnosis of the primary melanoma and the development of brain metastases, the number of metastatic brain lesions, the distribution of other metastatic sites and the presence of uncontrolled extra-cranial disease, as well as whether treatment for metastatic disease was given prior to the development of brain metastases were recorded.

The response of the cerebral metastatic disease to each treatment modality, the presence and duration of palliation offered to each individual patient were also recorded and compared. Tumor response after treatment was evaluated with brain CT and/or a MRI, and graded according to the World Health Organization Criteria. Patients were considered as not-evaluable-for-response, whenever imaging studies were not performed and/or were not available.

Overall survival was calculated as the time interval (in months) between the diagnosis of brain metastases and death. Similarly, survival rates of each treatment group were calculated and compared. Patient characteristics and known prognostic factors, available treatment modalities, and their responses were explored as possible factors affecting survival.

Statistical analysis. All patient characteristics and known prognostic factors were analyzed as categorical. Within treatment groups, characteristics and possible prognostic factors

affecting treatment selection were compared using the chi-square of Fischer's exact test. Estimated survival curves were calculated by the non-parametric Kaplan-Meier method. Statistical significance was evaluated using Log-Rank analysis for univariate (single) variable comparisons. Cox Regression proportional hazards model was used for multivariate comparisons. In all comparisons, statistical significance was defined as a probability value less than 0.05 (two tailed).

Results

Metastatic disease to organs other than the brain was present in the majority of patients; patient characteristics are listed in Table 1. Comparison of possible prognostic factors affecting treatment selection is also listed in Table 1.

Group A patients were different from patients of other treatment groups, in that they all had a single metastatic brain lesion ($p=0.001$). Furthermore, although metastatic extra-cranial disease was present in all patients, such disease was controlled ($p<0.0001$). Group B and C patients had similar clinical characteristics ($p>0.05$); all had more than one brain lesion (Tab. 1). The majority of group D patients had nodular ($p=0.077$) and/or ulcerated primary melanomas ($p=0.010$) and 92.9 % of them were having uncontrolled extra-cranial disease ($p<0.0001$).

Median survival for all patients was 3.0 months (95 % Confidence Intervals: 2.14–3.86 months, range: 1–21 months). Median survival according to treatment received for groups A, B, C, and D was: 12, 5, 3 and 2 months, respectively; univariate analysis showed a significant difference in median survival for each such group ($p<0.0001$) (Fig. 1).

Furthermore, when survival of patients treated with surgical resection of their single brain metastasis followed by radiotherapy was compared to the survival of all non-surgical patients statistical significance was found ($p=0.0011$); surgically treated patients had a definite survival benefit. Patients treated with supportive care only had a median survival significantly shorter than the survival of all other patient groups ($p<0.001$). Patients of group C had a median survival of 3.0 months, while those of group D of 2.0 months.

Furthermore, patients of group C had a median survival of 3.0 months, while those of group B 5.0 months ($p=0.0267$) (Fig. 1).

Significant factors affecting survival on univariate analysis are listed in Table 2. Multivariate analysis showed that the most important independent survival predictors were histological type and Breslow thickness, the number of metastatic brain lesions, the treatment offered prior to the development of brain metastases, as well as the available treatment for the cerebral disease and the absence of uncontrolled extra-cranial disease (Tab. 3).

Discussion

In our study, patients with malignant melanomas were not submitted to a specific screening for brain metastases. As a result, most of the patients were presented with clinically significant brain lesions andthat is why the yield of true-positive CT and/or MRI brain scans was high. Imaging findings were similar to those reported in the literature [32, 36].

Standard treatment for melanoma cerebral metastases includes whole brain irradiation and dexamethasone. Nevertheless, malignant melanoma is relatively radiation resistant and the effectiveness of radiotherapy is limited [6]. In our experience – as in others' [3, 6, 13, 17, 23, 24, 37, 38, 42] – median survival of patients treated with radiotherapy was 3.0 months. GUPTA et al [24] found that patients treated with radiotherapy showed no improvement in survival compared with patients who received dexamethasone alone. Our results are different: in univariate as well as in multivariate analysis, the type of treatment for the cerebral metastases was a significant prognostic factor affecting survival. Furthermore, patients treated with supportive care only had a median survival of 2.0 months, significantly shorter than the one of all other treatment modalities ($p<0.001$), suggesting that treatment modalities available for the cerebral disease (including whole brain irradiation) provide a survival benefit when compared to dexamethasone alone. Nevertheless, one could argue that this survival benefit reflects a selection bias, based on a number of additional factors used in the selection of patients treated with best supportive care. The problem of selection biases is inherent in any non-randomized study. GASPAR et al [21, 22] had already reported that patient selection plays a critical role in survival in brain metastases research series. In an effort to define factors affecting such patient selection in our patient population, we found that patients treated only with best supportive care had within all melanomas poorer prognosis (nodular, ulcerated), and – most importantly – had uncontrolled extra-cranial disease.

For patients with solitary and surgically resectable metastases craniotomy, metastasectomy and whole brain irradiation appears to be the treatment of choice, with a definite survival benefit [11, 25, 31, 38, 41]. Our study's conclusions were similar: a median survival of 12.0 months was calculated for patients with a surgically resected, single metastatic brain lesion. Despite the impression that surgical resection is almost invariably associated with an increase in median survival, one must always have in mind that selection biases – that undoubtedly exist [21, 22] – may be solely responsible for such differences. In our study patients treated with such a modality all had a single, metastatic brain lesion and controlled extra-cranial disease.

Recently, BUCHSBAUM et al [11] reported survival differences depending on the type of treatment, including stereotactic radiosurgery, similar to ours. These investigators found that median survival for patients with melanoma brain metastases receiving no treatment was only 1.1 months,

Table 1. Patient characteristics

Characteristics	All patient population (N=64)	Best supportive care (N=14)	Surgery and whole brain irradiation (N=5)	Whole brain irradiation only (N=28)	Temozolomide as first-line treatment (N=17)	p value
Gender (%)						0.248
Male	36 (56.3)	7 (50)	1 (20)	16 (57.1)	12 (70.6)	
Female	28 (43.7)	7 (50)	4 (80)	12 (42.9)	5 (29.4)	
Age (years) (%)						0.159
≤65	47 (73.4)	9 (64.3)	4 (80)	24 (85.7)	10 (58.8)	
>65	17 (26.6)	5 (35.7)	1 (20)	4 (14.3)	7 (41.2)	
Location of the primary lesion (%)						0.140
Lower extremities	14 (21.8)	4 (28.6)		5 (17.9)	5 (29.4)	
Upper extremities	5 (7.8)	1 (7.1)	1 (20)	2 (7.1)	1 (5.9)	
Trunk	16 (25)	4 (28.6)		9 (32.1)	3 (17.6)	
Head & Neck	17 (26.6)	4 (28.6)		8 (28.6)	5 (29.4)	
Other/Unknown	12 (18.7)	1 (7.1)	4 (80)	4 (14.3)	3 (17.6)	
Histological type (%)						0.077
Nodular	28 (43.7)	11 (78.6)	1 (20)	9 (32.1)	7 (41.2)	
Lentigo	8 (12.5)		1 (20)	6 (21.4)	1 (5.9)	
Acral lentiguous	5 (7.8)	1 (7.1)		1 (3.6)	3 (17.6)	
Superficial spreading	7 (10.9)			4 (14.3)	3 (17.6)	
Unknown/unclassified	16 (25)	2 (14.3)	3 (60)	8 (28.6)	3 (17.6)	
Clark level (%)						0.281
I–III	31 (48.4)	6 (42.9)	5 (100)	14 (50)	6 (35.3)	
IV	23 (35.9)	7 (50)		9 (32.1)	7 (41.2)	
≥V	10 (15.6)	1 (7.1)		5 (17.9)	4 (23.5)	
Breslow thickness (mm) (%)						0.270
0–4	25 (39)	4 (28.6)	2 (40)	13 (46.4)	6 (35.2)	
4.1–10	17 (26.6)	7 (50)		5 (17.8)	5 (29.5)	
≥10	2 (3.1)			1(3.6)	1 (5.8)	
Unknown	20 (31.3)	3 (21.4)	3 (60)	9 (32.2)	5 (29.5)	
Ulceration (%)						0.010
Yes	21 (32.8)	9 (64.3)		5 (17.9)	7 (41.2)	
No	26 (40.6)	2 (14.3)	2 (40)	17 (60.7)	5 (29.4)	
Unknown	17 (26.6)	3 (21.4)	3 (60)	6 (21.4)	5 (29.4)	
Local-regional disease prior to brain metastases (%)						0.392
Yes	40 (62.5)	7 (50)	3 (60)	21 (75)	9 (52.9)	
No	22 (34.3)	6 (42.9)	2 (40)	6 (21.4)	8 (47.1)	
Unknown	2 (3.2)	1 (7.1)		1 (3.6)		
Time interval prior to brain metastases (months) (%)						0.097
0–12	26 (40.6)	5 (35.7)	3 (60)	8 (28.6)	10 (58.8)	
12–24	10 (15.6)			7 (25)	3 (17.6)	
>24	28 (43.8)	9 (64.3)	2 (40)	13 (46.4)	4 (23.5)	
Symptoms (%)						0.585
Yes	56 (87.5)	14 (100)	5 (100)	23 (82.1)	14 (82.4)	
No	6 (9.4)			3 (10.7)	3 (17.6)	
Unknown	2 (3.1)			2 (7.1)		
Number of brain lesions (%)						0.001
Single	14 (21.8)	3 (21.4)	5 (100)	5 (17.9)	1 (5.9)	
Multiple	47 (73.4)	11 (78.6)		22 (78.6)	14 (82.4)	
Unknown	3 (4.8)			1 (3.6)	2 (11.8)	
Other organs involved (%)						0.054
Yes	56 (87.5)	13 (92.9)	5 (100)	26 (92.9)	12 (70.6)	
No	7 (10.9)	1 (7.1)		1 (3.6)	5 (29.4)	
Unknown	1 (1.6)			1 (3.6)		
Treatment prior to brain metastases (%)						0.246
Yes	23 (35.9)	5 (35.7)		13 (46.4)	5 (29.4)	
No	41 (64.1)	9 (64.3)	5 (100)	15 (53.6)	12 (70.6)	
Uncontrolled extra-cranial disease (%)						<0.0001
Yes	25 (39.1)	13 (92.9)		9 (32.1)	3 (17.6)	
No	39 (60.9)	1 (7.1)	5 (100)	19 (67.9)	14 (82.4)	
Response to treatment for the cerebral disease (%)						<0.0001
Complete response	4 (6.3)		3 (60)		1 (5.9)	
Partial response	8 (12.5)		1 (20)	3 (10.7)	4 (23.5)	
Stable disease	13 (20.3)	1 (7.1)	1 (20)	6 (21.4)	5 (29.4)	
Disease progression	39 (60.9)	13 (92.9)		19 (67.9)	7 (41.2)	
Palliation (%)						0.003
Yes	28 (43.7)	3 (21.4)	5 (100)	9 (32.1)	11 (64.7)	
No	36 (56.3)	11 (78.6)		19 (67.9)	6 (35.3)	

Table 2. Univariate analysis of prognostic factors

Variable	Median survival (months) (95 % Confidence Intervals)	Standard error	Log %rank p value
Gender (%)			0.9519
Male	4.0 (2.86–5.14)	0.58	
Female	3.0 (1.99–4.01)	0.52	
Age (years) (%)			0.7297
<65	3.0 (1.79–4.21)	0.62	
>65	3.0 (1.85–4.15)	0.59	
Location of the primary lesion (%)			0.5388
Lower extremities	3.0 (0.00–7.29)	2.19	
Upper extremities	4.0 (2.87–5.13)	0.58	
Trunk	3.0 (2.11–3.89)	0.46	
Head & Neck	3.0 (1.97–4.03)	0.52	
Other/Unknown	4.0 (1.06–6.94)	1.50	
Histological type (%)			0.0219
Nodular	2.0 (0.93–3.07)	0.55	
Lentigo	3.0 (1.19–4.81)	0.93	
Acral lentiguous	3.0 (2.07–3.93)	0.47	
Superficial spreading	5.0 (0.76–9.24)	2.17	
Unknown/unclassified	3.0 (2.03–3.97)	0.49	
Clark level (%)			0.6711
I–III	3.0 (2.08–3.92)	0.47	
IV	3.0 (2.08–3.92)	0.47	
>V	1.0	–	
Breslow thickness (mm) (%)			0.0437
0–4	4.0 (2.64–5.36)	0.70	
4.1–10	3.0 (1.98–4.02)	0.52	
>10	1.0	–	
Unknown	3.0 (2.05–3.95)	0.48	
Ulceration (%)			0.0554
Yes	3.0 (2.11–3.89)	0.45	
No	3.0 (1.78–4.22)	0.62	
Unknown	5.0 (2.35–7.65)	1.35	
Local–regional disease prior to brain metastases (%)			0.0856
Yes	3.0 (1.98–4.02)	0.52	
No	4.0 (2.53–5.47)	0.75	
Unknown	1.0	–	
Time interval prior to brain metastases (months)			0.3913
0–12	4.0 (2.78–5.22)	0.62	
12–24	4.0 (2.48–5.52)	0.77	
>24	3.0 (2.35–3.65)	0.33	
Symptoms (%)			0.7918
Yes	3.0 (1.95–4.05)	0.53	
No	3.0	–	
Unknown	2.0	–	
Number of brain lesions (%)			<0.00001
Single	7.0 (4.85–9.04)	2.95	
Multiple	2.0 (1.30–2.70)	0.35	
Unknown	1.0	–	
Other organs involved (%)			0.2147
Yes	3.0 (2.09–3.91)	0.46	
No	5.0 (2.74–7.26)	1.15	
Unknown	2.0	–	
Treatment prior to brain metastases (%)			0.1573
Yes	3.0 (1.69–4.31)	0.67	
No	3.0 (1.86–4.14)	0.58	
Uncontrolled extra–cranial disease (%)			<0.00001
Yes	2.0 (1.54–2.46)	0.23	
No	5.0 (4.17–5.83)	0.42	
Response to treatment for the cerebral disease (%)			<0.00001
Complete response	20.0 (5.60–34.40)	7.35	
Partial response	9.0 (6.92–11.08)	1.06	
Stable disease	5.0 (4.50–5.50)	0.25	
Disease progression	2.0 (1.57–2.43)	0.22	
Duration of response to treatment (months)			<0.00001
0–2	2.0 (1.56–2.44)	0.22	
2–6	5.0 (4.69–5.31)	0.16	
>6	11.0 (9.88–12.12)	0.57	
Palliation (%)			<0.00001
Yes	7.0 (4.96–9.04)	1.04	
No	2.0 (1.60–2.40)	0.21	

Table 3. Multivariate analysis of factors affecting survival

Variable	Hazard ratio	Standard error	p value
Gender* (%)			
Male			
Female	– 0.2763	0.8034	0.7310
Age* (years) (%)			
≤65			
>65	1.1151	1.2145	0.3585
Location of the primary lesion* (%)			
Lower extremities			
Upper extremities	1.7371	1.3229	0.2479
Trunk	1.9328	1.5671	0.1891
Head & Neck	1.9391	1.2337	0.2174
Other/Unknown	– 0.4908	1.1336	0.6907
Histological type* (%)			
Nodular			
Lentigo	1.6556	1.5317	0.2798
Acral lentiguous	2.5584	1.4222	0.0720
Superficial spreading	– 4.8106	2.4025	0.0452
Unknown/unclassified	4.5639	3.7244	0.2204
Clark level* (%)			
I–III			
IV	0.3936	0.9116	0.6659
≥V	1.1476	1.1564	0.3210
Breslow thickness (mm)* (%)			
0–4			
4.1–10	1.0963	1.0010	0.2734
≥10	7.6847	3.8716	0.0472
Unknown	1.236	1.0100	0.3216
Ulceration* (%)			
Yes			
No	–1.8617	1.2380	0.1326
Unknown	1.1344	1.2356	0.1290
Local–regional disease prior to brain metastases* (%)			
Yes			
No	0.0204	0.5980	0.9727
Unknown	0.0103	0.5730	0.8960
Time interval prior to brain metastases (months)* (%)			
0–12			
12–24	–1.8722	1.3542	0.1668
>24	–0.1411	1.0280	0.8908
Symptoms* (%)			
Yes			
No	–0.9438	1.2779	0.4602
Unknown	–0.8721	1.0121	0.3994
Number of brain lesions* (%)			
Single			
Multiple	6.3807	3.6335	0.0138
Unknown	3.8965	3.4305	0.1535
Other organs involved* (%)			
Yes			
No	–0.7053	1.8033	0.6957
Unknown	0.8904	2.9507	0.7628
Treatment prior to brain metastases* (%)			
Yes			
No	–2.0151	0.9846	0.0407
Uncontrolled extra–cranial disease* (%)			
Yes			
No	–1.8484	0.8079	0.0221
Type of treatment for the cerebral disease			
Best supportive care (group A)			
Surgery/radiotherapy (group B)	9.6831	7.0301	0.0053
Whole brain irradiation (group C)	0.4099	1.1010	0.7097
Temozolomide/radiotherapy (group D)	4.1874	2.2236	0.5497
Response to treatment for the cerebral disease* (%)			
Complete response			
Partial response	0.1372	2.9152	0.9625
Stable disease	2.9998	3.0081	0.3186
Disease progression	3.3455	3.9904	0.2460
Duration of response to treatment (months)* (%)			
0–2			
2–6	–8.0540	3.3714	0.669
≥6	–23.0494	160.3299	0.8857
Palliation* (%)			
Yes			
No	1.3229	1.8386	0.4718

* The model was run with the contrast simple (each variable was compared to the first of each category)

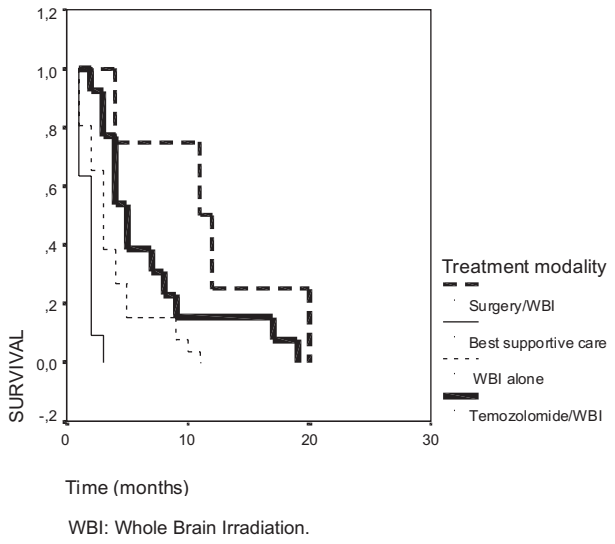

Figure 1. Kaplan-Meier univariate survival analysis depending on treatment type (p<0.0001)*. The differences between survival of the surgical group and all other treatment groups (p=0.0011), as well as patients receiving best supportive care and the remaining treatment groups are also statistically significant in univariate log-rank analysis (p<0.001). WBI – whole brain irradiation. *Pair-wise p value:
Survival of group A versus survival of group B: p=0.0005
Survival of group A versus survival of group C: p=0.0167
Survival of group A versus survival of group D: p=0.0001
Survival of group B versus survival of group C: p=0.008
Survival of group C versus survival of group D: p=0.0267
Survival of group B versus survival of group D: p=0.0250.

treated with whole brain irradiation alone was 2.3 months, treated with only local therapy (surgery or stereotactic radiosurgery) was 4.8 months, while for patients receiving combined therapy (whole brain irradiation and surgery or stereotactic radiosurgery) median survival was 8.8 months.

Although melanoma is a relatively chemoresistant tumor, the use of systemic chemotherapy for the treatment of cerebral metastases has been previously described with the nitrosourea fotemustine [10, 34, 40] and the combination of cisplatin and etoposide [20].

Temozolomide is the first new chemotherapy agent approved for the treatment of high-grade malignant gliomas [2], which has shown also some promising activity in the treatment of metastatic malignant melanoma [1, 4, 5, 8, 27, 29, 33]. Nevertheless, the number of reports available in the literature evaluating temozolomide as a treatment modality of melanoma brain metastases is very small [7, 28, 30]. Very recently, complete remission of metastatic melanoma brain lesions resulting in a significant resolution of symptoms, is reported in individual patients treated with temozolomide alone or in combination with thalidomide [7, 28].

In our study, we sought to investigate the role of temozolomide in the treatment of cerebral metastases from malignant melanoma, since such a treatment modality was available in our institution. MARGOLIN et al [30] are the only other investigators previously evaluating the role of temozolomide in combination with whole brain irradiation for the treatment of melanoma brain metastases. Our protocol study was based on the ability of temozolomide to cross the blood-brain barrier, enter the central nervous system and be spontaneously converted to its active metabolite [2]. Based on previous phase I studies [9], our patients were treated with the 5-day schedule every 28 days. Since the primary goal was to evaluate temozolomide's effect on the central nervous system disease, concomitant radiation therapy was not administered and all patients were radiotherapy-naive. Patients were treated with radiotherapy only when they did not respond to treatment or immediately after relapse.

Our results are more promising than those reported by MARGOLIN et al [30]. These investigators suggested that although the combination of whole brain irradiation and temozolomide was feasible, its anti-tumor activity was limited. Only one of 31 patients treated had a complete central nervous system response of 4.5 months, while only two patients had partial responses of 2 and 7 months' duration respectively.

In our patient population, survival of patients treated with whole brain irradiation alone was inferior when compared to that of patients treated with the combination of temozolomide and radiation therapy (3.0 versus 5.0 months, p=0.0267). Comparison of possible prognostic factors affecting treatment selection in such patients showed no difference; the two treatment groups had similar clinical characteristics, thus precluding selection biases.

Furthermore, multivariate analysis showed that the type of treatment offered for the cerebral disease was a significantly independent prognostic factor affecting survival (p=0.0053). Only one other recent study, the largest available in the literature, reports similar findings; median survival is analyzed as dependent on treatment, which in turn is dependent on patient selection [19].

One could argue that this survival benefit is partly due to the fact that treatment with temozolomide is a systemic one, capable of producing responses to other metastatic sites as well, or that patients treated initially with temozolomide had the opportunity to additionally receive whole brain irradiation. Nevertheless, our study suggests that further prospective, larger studies are required, in order to verify the possible survival benefit offered by the inclusion of temozolomide in the treatment of melanoma cerebral metastatic disease. To our best knowledge, we are the first to report a possible survival benefit of patients receiving first-line treatment with temozolomide, who otherwise would have been treated with radiotherapy alone. We believe that new, combination, including temozolomide treatment methods [14, 15, 26, 39] as well as protocol used in our study should be prospectively evaluated in patients with intra-cranial metastatic disease. Other investigators [11, 19] have also reported survival differences depending on the type of treatment, suggesting that

the type of treatment instituted is a significant factor-affecting outcome in melanoma patients with brain metastases.

As far as other prognostic factors affecting survival are concerned, our results are similar to those found in the literature [3, 11, 16, 17, 19, 21, 22, 38, 41]. It is obvious that the primary melanoma's histological type and Breslow thickness, the number of metastatic brain lesions and the presence of controlled extra-cranial disease are all potential independent predictors of survival.

In conclusion, we believe that properly selected patients may benefit from different types of treatment. We suggest that patients with a single metastatic brain lesion should be submitted to surgical removal followed by radiotherapy. Treatment with supportive care should be administered to selected patients only; eventually, to patients with end-stage disease, unable to receive any other form of specific treatment. We believe that temozolomide should be included in the first-line treatment of cerebral metastases, followed by radiotherapy. Further prospective, randomized, large studies are required to verify a potential survival benefit offered to such melanoma patients who otherwise would have been treated with radiotherapy alone.

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