Journal of Neuro-Oncology (2006) 76: 59–64
DOI 10.1007/s11060-005-2914-0

Clinical Study

Temozolomide with or without radiotherapy in melanoma with unresectable brain metastases

Maja Hofmann[1], Felix Kiecker[1], Reinhard Wurm[2], Lorenz Schlenger[2], Volker Budach[2], Wolfram Sterry[1] and Uwe Trefzer[1]
[1]*Department of Dermatology and Allergy, Charité-University Medicine Berlin, Schumannstrasse 20–21, 10117, Berlin, Germany;* [2]*Department of Radiotherapy and Radiological Oncology, Charité- University Medicine Berlin, Berlin, Germany*

Key words: brain metastases, melanoma, radiotherapy, stereotactic temozolomide, toxicity, whole brain radiotherapy

Summary

Brain metastases are a common complication in patients suffering from metastatic malignant melanoma. We analyzed efficacy and toxicity of the alkylating agent temozolomide with excellent CNS penetration and known activity in brain metastasis in 35 patients with unresectable melanoma brain metastases. Patients received 200 mg/m^2 temozolomide on days 1 to 5 every 28 days as first or second-line therapy. This therapy regimen was combined with radiotherapy of the brain metastases in 22/35 patients. Grade III and IV toxicity was observed in 8/35 patients (leukopenia, granulocytopenia, thrombocytopenia, anemia, nausea and obstipation). Complete remission was observed in 1/34, partial remission in 2/34 and stable disease in 9/34 patients. In 5/34 a mixed response was assessed, 17/34 had disease progression and in one patient tumor response was not evaluable. The median progression free time was 5 (0–8) months for all patients, the median survival time for all patients from start of therapy was 8 (0–28) months, 9 (2–28) months in patients with concurrent stereotactic radiotherapy and 7 (3–17) months in patients with concurrent whole brain radiotherapy. Our results demonstrate that temozolomide can be combined with radiotherapy for the treatment of brain metastases in malignant melanoma, and that this combination may prolong survival in this patient group.

Introduction

Brain metastases occur in nearly half of the patients suffering from metastatic malignant melanoma [1]. In these patients only limited therapeutic options exist. Accordingly, there are no standardized treatment regimens. The chemotherapeutic regimens commonly used in metastatic malignant melanoma such as dacarbazine (DTIC), platinum analogs, vinca alkaloids, nitrosoureas and taxanes have not demonstrated any activity in the CNS [2]. Also immunotherapy or immunochemotherapy seem to have no benefit in patients with brain metastases [3]. Therefore, agents with activity against melanoma and the capacity to penetrate effectively the blood–brain barrier are needed. In the 90s fotemustine and whole brain irradiation in combination with dexamethason were the only therapeutic options for patients with malignant melanoma and brain metastases.

Temozolomide (TMZ) is a prodrug being metabolized to an alkylating agent with advantages in its pharmacokinetics as compared to the prodrug dacarbazine. Temozolomide is rapidly absorbed after oral administration. After spontaneous hydrolysis to its active metabolite 3-methyl-(triazen-1-yl) imidazole-4-carboxamide (MTIC) temozolomide can cross the blood–brain barrier because of its small molecular weight. The concentration of temozolomide measured in cerebrospinal fluid is about 30–40% of that measured in plasma [4].

Temozolomide is known to have efficacy in various solid brain tumors and highly resistant malignancies such as anaplastic astrocytoma or glioblastoma [5,6]. Furthermore in patients with recurrent brain metastases temozolomide achieved disease control [7]. Recently, temozolomide has been tested in clinical studies for patients with malignant melanoma. However, in these studies patients with brain metastases have not been included. When temozolomide was compared with DTIC in previously untreated stage IV melanoma without brain metastases the response rates and survival was found to be equivalent [8,9]. In the only published multicenter study in patients with brain metastases from melanoma 151 patients receiving temozolomide but no radiotherapy, median survival was 3.5 months in patients without prior chemotherapy and 2.2 months in patients with prior chemotherapy [10]. It has been suggested that temozolomide may reduce the risk of CNS relapse when compared to DTIC-based therapy [11].

In a selected population of patients with limited CNS involvement, surgical resection alone or in combination with whole brain radiotherapy has been demonstrated to prolong median survival [12,13]. If

surgical resection is not possible, chemotherapy and radiotherapy are the most common treatment options in brain metastases of malignant melanoma. When disease is limited to approximately one to three lesions stereotactic radiosurgery is the therapeutic alternative to neurosurgery. In patients with multiple brain metastases the only radiotherapeutic option is the whole brain irradiation (WBRT). Radiotherapy of brain metastases has been shown to produce a survival benefit for patients with local response [14,15]. Stereotactic radiation of solitary brain metastases alone showed favorable survival times [16,17].

We report our analysis of a consecutive series of patients with malignant melanoma and unresectable brain metastases treated with temozolomide with or without concurrent radiotherapy of the brain.

Patients and methods

From September 1998 until July 2003 patients with metastatic malignant melanoma with brain metastases were treated at Charité skin cancer unit with temozolomide. The selected patients had histologically or cytologically confirmed, bidimensionally measurable metastatic malignant melanoma in stage IV with obligatory brain metastases which were judged by the neurosurgeon to be unresectable. Patients with resectable brain metastases were resected and did not receive adjuvant treatment such as temozolomide chemotherapy. Therefore, these patients were not included in this study. In total we analyzed 35 patients with melanoma brain metastases ranging from 4 to 30 mm in diameter. Eligible patients also met the following criteria: age $\geq$ 18 years, WHO performance status 0 or 1, life expectancy $\geq$ 12 weeks, adequate hepatic function (serum bilirubin $<1.5\times$ the upper limit of normal, serum ALT and AST $<2.5\times$ the upper limit of normal), renal function (serum creatinine $<1.5\times$ upper limit of normal) and hematologic values (hemoglobin $\geq$ 10 mg/dl, leukocytes >2.0/nl, platelet count >100/nl). Previous therapy (chemotherapy and/or immunotherapy) was permitted.

Response assessment

Response was assessed 8–12 weeks after the beginning of the therapy and thereafter at 3-monthly intervals. Magnetic resonance imaging (MRI) of the brain and computed tomography (CT-scan) of the body was used. Standard response criteria (UICC) were used. CR (complete remission) was defined as the complete disappearance of all clinical and radiological evidence of metastatic malignant melanoma. PR (partial remission) was defined as a >50% decrease in the sum of the products of the perpendicular diameters of all bidimensionally measurable lesions. PD (progressive disease) was defined as a >25% increase in the sum of the areas of all lesions or the appearance of new lesion. Mixed response was defined as a CR, PR or SD in the brain, and PD or SD at other tumor localizations. Response durations were measured from the date of SD, PR or CR.

Pre-treatment evaluation

Before treatment a complete history and physical examination was performed with a recording of a measurable marker lesion. A laboratory evaluation including CBC, differential, chemistry profile including liver and renal function, serum electrolytes and coagulation parameters was performed before treatment was initiated. A complete staging examination including MRI of the brain and CT scan of the chest and abdomen was done prior to initiation of therapy. A bone scan was performed in patients with suspected bone metastases.

Treatment schedule

Oral temozolomide was administered at 200 mg/m^2/d $\times$ 5 days. The treatment was started on day 1 and restarted on day 28 on an outpatient basis. The maximum dose was limited to 350 mg totally per day, thus allowing the majority of patients (31/35 patients) to receive up to 350 mg temozolomide per day and possibly avoiding added toxicity in patients treated with an excess of 350 mg temozolomide per day in a combined setting with radiotherapy with only limited experience with respect to combined or possibly synergistic toxicity. Obligatory concomitant medication was oral ondansetron 8 mg given once daily. Therapy was administered at the Charité skin cancer unit and was continued until disease progression or unacceptable toxicity occurred.

Dose modification criteria

In patients with grade 3 or 4 toxicity treatment was discontinued and treatment was withheld until toxicity grade 1 or 2 occurred.

Radiotherapy

In patients with one to three brain metastases judged as unresectable stereotactic radiotherapy was evaluated. Patients with disseminated brain metastases judged as unresectable whole brain radiotherapy was combined with temozolomide if patients had a satisfactory performance status.

Whole brain radiotherapy

Patients who received whole brain radiotherapy were treated on a linear accelerator using 6 MV photons. The prescription point was to the mid-plane. Two lateral fields were used with 100 cm source-to-surface distance set-up. Both fields were treated once daily. Specified prescriptions included 20 Gy in five fractions and 30 Gy in ten fractions.

Stereotactic radiosurgery

Patients were fitted after local anesthesia in a stereotactic head ring (brainless, GmbH, Heimstetten, Germany). For treatment planning 1 mm no skip axial MRI slices obtained prior to stereotactic head ring fixation in a 1.5 Tesla scan were fused with a stereotactic

localization axial CT scan, with 2 mm no skip slices. The CT scan was obtained for dosimetry calculations and correction of possible MRI distortions. The fusion process increased precision of targeting. Once the target was defined the radiosurgery planning was developed using either 6–9 static beams or three to five dynamic arcs collimated by a micro-multileaf collimator. Radiosurgery was performed with a linear accelerator. For radiosurgery 20 Gy assigned to the 80% isodose covering the target were used, stipulating isodose prescriptions within ratios of prescription isodose/tumor volume (PITV) and maximum dose/prescribed dose (MDPD) previously set by the RTOG [18].

Statistical methods

The statistical analyses were performed with SPSS 11.5. Survival curves were plotted using the product limit method of Kaplan and Meier.

Results

Patient characteristics

Thirty-five patients with advanced metastatic malignant melanoma with brain metastases were treated at Charité skin cancer unit with temozolomide. The characteristics of the 35 patients are listed in Table 1. Nineteen patients were male and 16 were female, the median age was 53 years. The patients received a total of 169 cycles of the monochemotherapy. Twelve out of 35 patients had two metastatic sites while 19/35 patients had more than 2 sites of metastatic disease. Eighteen patients had received prior therapy before starting this therapy regimen, 10 patients received chemotherapy or chemoimmunotherapy, 4 patients immunotherapy and 4 patients surgery of distant metastases (Table 1). Radiotherapy was combined in 22 patients ($n = 12$ stereotactic radiotherapy and $n = 10$ WBRT). Thirteen patients did not receive radiotherapy because of patients refused radiotherapy ($n = 6$), patients had multiple brain and organ metastases ($n = 3$), toxicity occurred under chemotherapy ($n = 2$) and patients received prior radiotherapy ($n = 2$).

Table 1. Patient characteristics

Number of patients	35
Median age (years)	53
Sex m:w	19:16
Total cycles temozolomide administered	169
Number of metastatic sites	Number of patients
1	4
2	12
>2	19
Location of metastases	
Brain	35
Lymph nodes	17
Skin	12
Lung	16
Liver	13
Pancreas	2
Adrenal cortex	2
Retroperitoneum	2
Peritoneal	4
Soft tissue	1
Kidney	1
Bone	8
Prior therapy for stage IV melanoma	18
Chemotherapy	7
Immunotherapy	4
Chemoimmunotherapy	3
Surgery/radiosurgery	4

Toxicity

The toxicity evaluation is summarized in Table 2. Grade 1 and 2 toxicity were seen in most patients. Most common adverse events were nausea and vomiting. Grade 3 or 4 leukopenia occurred in 4 patients, grade 3 or 4 neutropenia in 3 patients. Other grade 4 adverse events were thrombocytopenia (2/35) and anemia (1/35). The main grade 3 adverse events were: thrombocytopenia (1/35), nausea (1/35), obstipation (1/35). One patient with a history of chronic gastritis developed a perforation of a previously undiagnosed duodenal ulcer. When toxicity in patients with or without radiotherapy was compared, the most severe hematological side effects were seen in patients with radiotherapy (leukopenia grade 3 or 4, $n = 4$ and granulocytopenia grade 3 or 4, $n = 3$), whereas other side effects were equally distributed.

Tumor response and survival

The tumor response to temozolomide in 1/35 patient was not evaluable because treatment had to be discontinued because of severe toxicities followed by immediate application of other treatment modalities. A complete remission was observed in 1/34 (3%), partial remission in 2/34 (6%) and stable disease in 9/34 (26.4%) patients. In 5/34 patients (14.7%) a mixed response was observed with partial remission or stable disease in the brain and disease progression at other locations. 17/34 (50%) patients had disease progression. The progression free time was estimated with Kaplan–Meier plots. The median duration of response was

Table 2. Adverse events of temozolomide therapy, graded according to NCI Common Toxicity Criteria (CTC, version 2). Number of patients and incidence rate

Adverse Event	Grade I	Grade II	Grade III	Grade IV
Leukocytopenia	1	2	2	2
Granulocytopenia			1	2
Thrombocytopenia	2	1	1	2
Anemia	2	2		1
Nausea	6	5	1	
Emesis	4	2		
Obstipation	1	1	1	
Apathy	2	2		
Infection	1	2		
Itching	1		1	
Abdominal cramps	1			
Headache	1	1		
Loss of appetite	2	1		

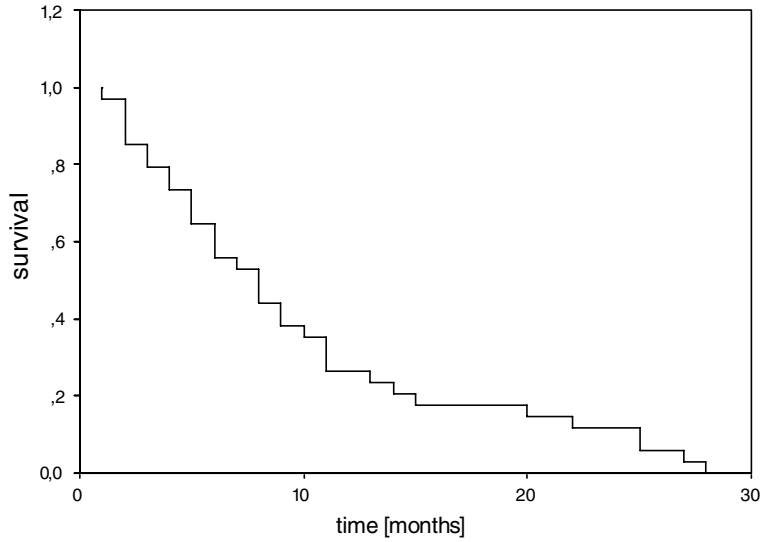

Figure 1. Kaplan–Meier plot of overall survival for 35 patients with stage IV melanoma with brain involvement. The median overall survival was 8 months (range 0–28).

5 month (range 0–16). The longest response duration was 16 months. Survival analysis showed the median survival time from start of therapy with 8 months (range 0–28) for all 35 patients (Figure 1). For patients who received monochemotherapy alone without radiotherapy ($n = 13$) the median survival time was 5 months (range 0–25), for patients with additional radiotherapy ($n = 22$) the median survival time was 9 months (range 2–28). Comparing these groups in the log rank test this difference was statistically significant ($P = 0.0440$). Splitting the radiotherapy group into a patient group with stereotactic radiotherapy ($n = 12$) and with WBRT ($n = 10$) the median survival times were 9 months (range 2–28) and 7 months (range 3–17), respectively, with no statistical difference ($P = 0.1067$).

Discussion

Patients with malignant melanoma and brain metastases have an unfavorable prognosis with only few available treatment options. To date an accepted standardized palliative therapy does not exist for the treatment of advanced metastatic melanoma with brain involvement. There is no general consensus with regard to the use of palliative chemotherapy in these patients [19]. Dacarbazine (DTIC) is the best known therapeutic option in patients with metastatic malignant melanoma with response rates of approximately 5–15%, but DTIC has no activity in patients with melanoma brain metastases. Often a CNS relapse occurs in treated patients, especially after immunotherapeutics [20]. In a multicenter phase-III-study comparing DTIC versus temozolomide in patients with metastatic malignant melanoma without brain metastasis, temozolomide showed efficacy equal to that of DTIC [8]. On the other side, temozolomide may be efficacious in preventing CNS relapses in patients responding to systemic therapy [11,21].

In melanoma patients with cerebral metastases, the overall survival time has been reported to be about 4 months [22]. Even treatment of patients with brain metastases with temozolomide did not improve this poor survival with a median overall survival of 3.5 months when temozolomide was given as first line therapy in patients with newly diagnosed brain metastases [10]. When temozolomide was given alone (6 patients) or in conjunction with docetaxol (10 patients) or with cisplatin (9 patients) in patients with brain metastases, the median survival time for the entire population of 25 patients was 4.7 months [23]. However, only one study in patients with metastatic malignant melanoma with obligatory brain metastases treated with temozolomide plus radiation therapy has been reported so far [24]. The overall median survival for 31 patients was 6 months when temozolomide was given 75 mg/m^2/day for 6 weeks in combination with WBRT.

Our results demonstrate that patients with malignant melanoma with unresectable brain metastases benefit from temozolomide with or without radiotherapy with a median survival of 8 months. The combination of temozolomide with radiotherapy of the brain, especially stereotactic radiosurgery showed a survival benefit for our patients with a median survival of 9 months compared to 5 months without radiotherapy. Surgical resection and WBRT have been the mainstays of the treatment of cerebral metastases. The overall median survival times in patients with melanoma brain metastases treated with WBRT have been reported between 12 and 20 weeks [25]. Stereotactic radiosurgery can achieve a similar median survival time as in patients with brain metastases of different solid tumors with a survival time reported to be about 10 months [16,17,26]. Mori et al. [27] reported a median survival of 7 months in patients with cerebral metastatic malignant melanoma after stereotactic radiosurgery. The number of metastatic sites is important in respect to the median survival time in patients treated with stereotactic radiotherapy: 22 months in patients with a solitary brain metastasis compared with 7.5 months with a single brain metastases and

other site metastases and 4 months in patients with multiple brain metastases [28]. Of course our results have to be seen cautious because of the small number of treated patients. It is difficult to decide whether the effect of responses of the brain metastases was caused by the radiotherapy or chemotherapy. It is of interest to note that the survival time of 5 months in patients treated with temozolomide alone fits well into the observations of other investigators [10,23]. However, combining temozolomide with WBRT (median survival time 7 months) or with stereotactic surgery (median survival time 9 months) on the other side seem to produce favorable results when compared to patients treated with WBRT (median survival less than 5 months) or stereotactic surgery alone (median survival 7 months) [25,27–29].

The frequency of objective responses in our patient group was very low with 1 complete and 2 partial responses among 35 melanoma patients. The patient with complete response received stereotactic radiotherapy, whereas one patient with a partial response was treated with temozolomide monotherapy alone. This patient had more than 5 brain metastases before treatment and after 3 courses of therapy a regression of all brain metastases was observed except for one. Two similar cases have been reported, in which multiple melanoma brain metastases disappeared after six cycles of temozolomide without radiotherapy [30,31] or in combination with radiotherapy [32]. The combination of daily temozolomide with thalidomide in 38 patients with melanoma brain metastases showed also one complete but 11 partial responses [33].

Although malignant melanoma is generally considered as a radioresistant tumor, we have evidence to suggest otherwise. The monotherapy with temozolomide seems to be more effective in patients treated in combination with radiotherapy of the brain metastases. These combined effects may be result of the two different antitumor activities: The antitumor effect of temozolomide has been reported to be due to its antiangiogenic properties [34], whereas the biologic effects of radiation are a result of damage to cellular DNA [19].

In a palliative setting simplicity and rapidity of treatment are also major issues. An advantage for the patient is that this palliative treatment can be performed in an outpatient setting. Furthermore, temozolomide has a favorable toxicity profile. However we emphasize that the limiting toxicity is the myelosuppression, which is known as dose limiting toxicity [35]. Lymphopenia is an important toxicity under treatment with temozolomide which can lead to occasional opportunistic infections [36].

In conclusion, we observed favorable results with temozolomide alone or combined with radiotherapy in patients with melanoma metastatic to the brain. In patients with a good general health status stereotactic irradiation or WBRT should be considered. Temozolomide was well tolerated by patients with melanoma brain metastases. Controlled randomized multi-center trials assessing palliative effect, quality of life and cost effectiveness are required.

References

1. Bullard DE, Cox EB, Seigler HF: Central nervous system metastases in malignant melanoma. Neurosurgery 8: 26–30, 1981
2. Franciosi V, Cocconi G, Michiara M, Di Costanzo F, Fosser V, Tonato M, Carlini P, Boni C, Di Sarra S: Front-line chemotherapy with cisplatin and etoposide for patients with brain metastases from breast carcinoma, nonsmall cell lung carcinoma, or malignant melanoma: a prospective study. Cancer 85: 1599–1605, 1999
3. Richards JM, Gale D, Mehta N, Lestingi T: Combination of chemotherapy with interleukin-2 and interferon alfa for the treatment of metastatic melanoma. J Clin Oncol 17: 651–657, 1999
4. Newlands ES, Stevens MF, Wedge SR, Wheelhouse RT, Brock C: Temozolomide: a review of its discovery, chemical properties, pre-clinical development and clinical trials. Cancer Treat Rev 23: 35–61, 1997
5. Yung WK, Prados MD, Yaya-Tur R, Rosenfeld SS, Brada M, Friedman HS, Albright R, Olson J, Chang SM, O'Neill AM, Friedman AH, Bruner J, Yue N, Dugan M, Zaknoen S, Levin VA: Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. Temodal Brain Tumor Group. J Clin Oncol 17: 2762–2771, 1999
6. Yung WK, Albright RE, Olson J, Fredericks R, Fink K, Prados MD, Brada M, Spence A, Hohl RJ, Shapiro W, Glantz M, Greenberg H, Selker RG, Vick NA, Rampling R, Friedman H, Phillips P, Bruner J, Yue N, Osoba D, Zaknoen S, Levin VA: A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. Br J Cancer 83: 588–593, 2000
7. Abrey LE, Olson JD, Raizer JJ, Mack M, Rodavitch A, Boutros DY, Malkin MG: A phase II trial of temozolomide for patients with recurrent or progressive brain metastases. J Neurooncol 53: 259–265, 2001
8. Middleton MR, Grob JJ, Aaronson N, Fierlbeck G, Tilgen W, Seiter S, Gore M, Aamdal S, Cebon J, Coates A, Dreno B, Henz M, Schadendorf D, Kapp A, Weiss J, Fraass U, Statkevich P, Muller M, Thatcher N: Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol 18: 158–166, 2000
9. Bleehen NM, Newlands ES, Lee SM, Thatcher N, Selby P, Calvert AH, Rustin GJ, Brampton M, Stevens MF: Cancer Research Campaign phase II trial of temozolomide in metastatic melanoma. J Clin Oncol 13: 910–913, 1995
10. Agarwala SS, Kirkwood JM, Gore M, Dreno B, Thatcher N, Czarnetski B, Atkins M, Buzaid A, Skarlos D, Rankin EM: Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. J Clin Oncol 22: 2101–2107, 2004
11. Paul MJ, Summers Y, Calvert AH, Rustin G, Brampton MH, Thatcher N, Middleton MR: Effect of temozolomide on central nervous system relapse in patients with advanced melanoma. Melanoma Res 12: 175–178, 2002
12. Brega K, Robinson WA, Winston K, Wittenberg W: Surgical treatment of brain metastases in malignant melanoma. Cancer 66: 2105–2110, 1990
13. Wronski M, Arbit E: Surgical treatment of brain metastases from melanoma: a retrospective study of 91 patients. J Neurosurg 93: 9–18, 2000
14. Buchsbaum JC, Suh JH, Lee SY, Chidel MA, Greskovich JF, Barnett GH: Survival by radiation therapy oncology group recursive partitioning analysis class and treatment modality in patients with brain metastases from malignant melanoma: a retrospective study. Cancer 94: 2265–2272, 2002
15. Overgaard J: The role of radiotherapy in recurrent and metastatic malignant melanoma: a clinical radiobiological study. Int J Radiat Oncol Biol Phys 12: 867–872, 1986
16. Seung SK, Sneed PK, McDermott MW, Shu HK, Leong SP, Chang S, Petti PL, Smith V, Verhey LJ, Wara WM, Phillips TL, Larson DA: Gamma knife radiosurgery for malignant melanoma brain metastases. Cancer J Sci Am 4: 103–109, 1998

17. Mingione V, Oliveira M, Prasad D, Steiner M, Steiner L: Gamma surgery for melanoma metastases in the brain. J Neurosurg 96: 544–551, 2002
18. Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, Farnan N: Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90–05. Int J Radiat Oncol Biol Phys 47: 291–298, 2000
19. Douglas JG, Margolin K: The treatment of brain metastases from malignant melanoma. Semin Oncol 29: 518–524, 2002
20. Atkins MB, Lotze MT, Dutcher JP, Fisher RI, Weiss G, Margolin K, Abrams J, Sznol M, Parkinson D, Hawkins M, Paradise C, Kunkel L, Rosenberg SA: High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 17: 2105–2116, 1999
21. Conill C, Gonzalez-Cao M, Jorcano S, Puig S, Malvehy J, Marti R, Castel T: Temozolomide as prophylaxis for melanoma brain metastases. Melanoma Res 14: 73–74, 2004
22. Sampson JH, Carter JH Jr., Friedman AH, Seigler HF: Demographics, prognosis, and therapy in 702 patients with brain metastases from malignant melanoma. J Neurosurg 88: 11–20, 1998
23. Bafaloukos D, Tsoutsos D, Fountzilas G, Linardou H, Christodoulou C, Kalofonos HP, Briassoulis E, Panagiotou P, Hatzichristou H, Gogas H: The effect of temozolomide-based chemotherapy in patients with cerebral metastases from melanoma. Melanoma Res 14: 289–294, 2004
24. Margolin K, Atkins B, Thompson A, Ernstoff S, Weber J, Flaherty L, Clark I, Weiss G, Sosman J, SW II, Dutcher P, Gollob J, Longmate J, Johnson D: Temozolomide and whole brain irradiation in melanoma metastatic to the brain: a phase II trial of the Cytokine Working Group. J Cancer Res Clin Oncol 128: 214–218, 2002
25. Stevens G, Firth I, Coates A: Cerebral metastases from malignant melanoma. Radiother Oncol 23: 185–191, 1992
26. Young RF: Radiosurgery for the treatment of brain metastases. Semin Surg Oncol 14: 70–78, 1998
27. Mori Y, Kondziolka D, Flickinger JC, Kirkwood JM, Agarwala S, Lunsford LD: Stereotactic radiosurgery for cerebral metastatic melanoma: factors affecting local disease control and survival. Int J Radiat Oncol Biol Phys 42: 581–589, 1998
28. Grob JJ, Regis J, Laurans R, Delaunay M, Wolkenstein P, Paul K, Souteyrand P, Koeppel MC, Murraciole X, Perragut JC, Bonerandi JJ: Radiosurgery without whole brain radiotherapy in melanoma brain metastases. Club de Cancerologie Cutanee. Eur J Cancer 34: 1187–1192, 1998
29. Conill C, Fernandez-Ibiza J, Malvehy J, Puig S, Sanchez M, Castel T: [Temozolomide in patients with melanoma brain metastases treated with whole brain irradiation]. Med Clin (Barc) 122: 413–415, 2004
30. Biasco G, Pantaleo MA, Casadei S: Treatment of brain metastases of malignant melanoma with temozolomide. N Engl J Med 345: 621–622, 2001
31. Dvorak J, Melichar B, Zizka J, Hadzi-Nikolov D, Petera J: Complete response of multiple melanoma brain metastases after treatment with temozolomide. Onkologie 27: 171–174, 2004
32. Conill C, Puig S, Toscas I, Castel T: Complete response of cerebral metastasic melanoma after a combined treatment of radiotherapy and temozolomide. Med Clin (Barc) 119: 758–759, 2002
33. Hwu WJ, Krown SE, Menell JH, Panageas KS, Merrell J, Lamb LA, Williams LJ, Quinn CJ, Foster T, Chapman PB, Livingston PO, Wolchok JD, Houghton AN: Phase II study of temozolomide plus thalidomide for the treatment of metastatic melanoma. J Clin Oncol 21: 3351–3356, 2003
34. Kurzen H, Schmitt S, Naher H, Mohler T: Inhibition of angiogenesis by non-toxic doses of temozolomide. Anticancer Drugs 14: 515–522, 2003
35. Newlands ES, Blackledge GR, Slack JA, Rustin GJ, Smith DB, Stuart NS, Quarterman CP, Hoffman R, Stevens MF: Phase I trial of temozolomide. Br J Cancer 65: 287–291, 1992
36. Su YB, Sohn S, Krown SE, Livingston PO, Wolchok JD, Quinn C, Williams L, Foster T, Sepkowitz KA, Chapman PB: Selective CD4+ lymphopenia in melanoma patients treated with temozolomide: a toxicity with therapeutic implications. J Clin Oncol 22: 610–616, 2004

Address for offprints: Maja Hofmann, Department of Dermatology and Allergy, Charité-University Medicine Berlin, Schumannstrasse 20–21, 10117, Berlin, Germany. Tel.: +49-30-450-618268; Fax: +49-30-450-518907; E-mail: maja.hofmann@charite.de.