Unexpected outcome (positive or negative) including adverse drug reactions

Survival over 6 years in a patient with brain metastases from melanoma treated with temozolomide

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Summary

Cerebral metastases from melanoma are generally associated with a dismal prognosis with survival ranging from 3 to 6 months after treatment. Systemic chemotherapy for these patients has limited effect and evidence for an overall survival benefit from randomised controlled trials is lacking. We report on a 59-year-old patient with a history of malignant melanoma who presented with multiple cerebral metastases after previous surgery and combined whole brain and stereotactic radiotherapy. She has been in sustained remission and in excellent clinical condition after treatment with continued cycles of oral temozolomide for more than 6 years. To our knowledge, similar prolonged survival has been described only once in patients with multiple cerebral metastases from melanoma. This case demonstrates that temozolomide for metastatic central nervous system (CNS) disease in melanoma patients may be highly effective without CNS toxicity.

BACKGROUND

Malignant melanoma is the third most common tumour developing metastases to the brain. Complications of central nervous system (CNS) metastatic involvement are a common cause of death in melanoma patients.¹ Brain metastases from melanoma generally show a poor prognosis with a median survival of 3–6 months.² Chemotherapy is historically thought to have limited impact on survival in patients with brain metastases, due to failure to reach therapeutic levels in the CNS. However, patients may surprisingly benefit from systemic therapy and show a long-term survival. We report here a patient with multiple brain metastases from melanoma, who has been successfully treated with temozolomide for more than 6 years.

CASE PRESENTATION

A 59-year-old woman presented with mild right-sided weakness, dizziness and difficulties in walking in May 2005. Her history was unremarkable except for a radically resected melanoma from the back (Breslow thickness of 1.4 mm) in 1999. On neurological examination she had some apraxia, agraphia without alexia, a dyscalculia and latent paresis of her right arm and leg. Cerebral MRI revealed a lesion in the left parieto-occipital lobe of 5×3.5 cm in diameter with some midline shifting and peritumoral oedema (figure 1). CT of the thorax showed two lesions, one with a diameter of 11 mm in the right lower lobe and one of 18 mm in the left lower lobe, that were asymptomatic but suspicious for pulmonary metastases. Bone scintigraphy and liver ultrasound showed no signs of any further metastases.

The left parietal lesion was surgically removed. Histopathological examination revealed a cell-rich proliferation with polymorph nuclei, some nucleoli and prominent

mitotic activity. Immunohistochemical markers were positive for S-100, Melan-A and HMB-45 and negative for cytokeratin and neurofilament, which confirmed that it was a metastasis from a malignant melanoma. Postoperative MRI showed a second lesion in the left parietal lobe with a diameter of 1 cm, which was initially missed on the first MRI. She was treated with postoperative whole brain radiotherapy (WBRT) of 10 times 3 Gy with a stereotactic boost of 21 Gy on the second lesion. At follow-up in January 2006 MRI of the brain revealed a third lesion of 5 mm in the right parietal lobe, which was treated with a stereotactic booster of 21 Gy. She remained without any symptoms. Follow-up MRI of the brain in May 2006 showed 10 small asymptomatic lesions compatible with multiple metastases (figure 1). It was decided to start with temozolomide chemotherapy 200 mg/m² orally for 5 days on a 28-day cycle. After three cycles, all cerebral lesions had become smaller on MRI, except for the lesion in the right parietal lobe that had been treated radiosurgically. She continued temozolomide without any side effects and MRI in March 2007 showed complete remission of the cerebral lesions, besides some contrast leakage at the right parietal lesion. In July 2008, she had wound leakage at the site of craniotomy. The bone flap appeared to be infected and was surgically removed, followed by cranioplasty. Afterwards she was treated with intravenous antibiotics and temozolomide was temporarily stopped. In October 2008, she restarted temozolomide at the previous dose of 200 mg/m². Since May 2011, she has been prescribed prophylactic cotrimoxazol because of a slowly developing lymphopenia (grade 2) and subsequent decrease of CD4 count (<0.2 10⁹/l=grade 3 toxicity). In June 2012, she received her 78th cycle of temozolomide, without any other side effects. Until now, she has remained free of any neurological symptoms, being able to perform all

Figure 1 Contrast-enhanced T1-weighted brain MRI of the brain with gadolinium: (A) MRI in May 2005 revealed a lesion in the left parieto-occipital lobe of 5×3.5 cm in diameter with some midline shifting and peritumoral oedema; (B) MRI in May 2006 showed multiple (a total of 10) small lesions compatible with brain metastases; and (C) MRI in August 2011 showed a remaining but stable contrast leakage at the right parietal lesion, but no signs of brain relapse.

her daily activities without any restrictions. The most recent MRI does not show signs of metastatic relapse in the brain (figure 1). Furthermore, the pulmonary lesions showed a complete remission on CT.

DISCUSSION

Brain metastases from malignant melanoma generally have a dismal prognosis ranging from 3 to 6 months after treatment. Survival is not substantially different from other solid tumours with brain metastases.² Long-term survival is very uncommon. In a cohort study of 702 patients only 2.4% survived for more than 3 years. However, the majority of these patients had a single brain metastasis without extracranial disease.² Survival of 6 years in patients with ≥ 3 brain metastases has only been reported once in a 76-year-old man with a melanoma of unknown origin.³ After treatment with temozolomide, anecdotal survival of 12–18 months has been reported in brain metastases from melanoma.

Treatment options for metastatic melanoma to the brain consist of surgery, stereotactic radiosurgery, WBRT and/or chemotherapy. The choice of therapy depends on known prognostic factors like age, performance status, number of cerebral metastases and systemic disease activity.⁴ In our patient age (<65 years) and excellent clinical condition may have contributed to a survival benefit, but her long-term survival is remarkable given the large number of brain metastases and the presence of extracranial metastases. Possibly, small asymptomatic brain metastases can be treated more successfully with systemic therapy, as has been suggested by Boogerd *et al.*⁵ Recently, this finding was supported by Margolin *et al.*,⁶ who showed that the antibody ipilimumab showed efficacy particularly in patients with small and asymptomatic brain metastases from melanoma.

Oral temozolomide is currently used as one of the systemic treatments for patients with metastatic melanoma to the brain, although there is much skepticism about its efficacy. Smaller studies suggest response rates about

10–20% and a survival benefit of 2–4 months.^{4–7} However, supporting evidence from randomised controlled trials is still lacking, as patients with brain metastases have often been excluded from clinical trials. In our patient the ongoing treatment with temozolomide might also have played a favourable role, as continuous administration may decrease resistance to alkylating chemotherapeutic drugs on a cellular level.

Although this case is exceptional, temozolomide should seriously be considered in melanoma patients with metastatic CNS disease, as it can be a highly effective especially in patients with small and asymptomatic metastases.

Learning points

- ▶ Long-term survival in patients with multiple brain metastases from malignant melanoma is very uncommon.
- ▶ Treatment consists of a combination of surgery, stereotactic radiosurgery, whole brain radiotherapy and/or chemotherapy.
- ▶ Temozolomide chemotherapy is generally associated with a modest increase in survival in a minority of patients with brain metastases from melanoma.
- ▶ Tailoring therapy to the individual patient is essential and could sometimes result in a surprisingly favourable outcome.

Competing interests None.

Patient consent Obtained.

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