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LETTER TO THE EDITORS

Clinical and radiological response of leptomeningeal melanoma after whole brain radiotherapy and ipilimumab

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Dear Editors,

Until recently, dacarbazine (DTIC) was the only registered chemotherapeutic drug for systemic treatment of metastatic melanoma. Patients with progressive disease during DTIC treatment can now also be treated with ipilimumab, a human monoclonal antibody directed against the cytotoxic T-lymphocyte antigen-4 (CTLA-4) receptor. Binding of ipilimumab to the CTLA-4 receptor enhances the immune response of T-lymphocytes, resulting in an offensive against the tumor and an increased median survival of patients with metastatic melanoma [1]. Few data are available on the effect of ipilimumab on central nervous system (CNS) metastases of melanoma [2, 3]. Here, we report a patient with stage IV melanoma, who showed a remarkable response of leptomeningeal metastases (LM) after whole brain radiotherapy (WBRT) and ipilimumab treatment.

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In January 2009, a 63-year-old woman was diagnosed with lung metastases of a melanoma. DTIC (800 mg/m^2, q3 weeks) was initiated. In May 2010, after 17 courses, treatment was discontinued due to progression of lung metastases. Concurrently, the patient complained of morning headache, nausea and vomiting. Neurological examination showed no abnormalities. MRI of the brain demonstrated a hyperintense signal in the cerebellar foliae on FLAIR images (Fig. 1a) and slight contrast enhancement of the leptomeninges on T1 images with gadolinium (Fig. 1b). No brain metastases were detected. According to the Dutch guidelines, LM was diagnosed [4–8]. The patient received WBRT (5 × 4 Gy) and low dose dexamethasone. However, her neurological symptoms did not diminish. In June 2010 ipilimumab (3 mg/kg, q3 weeks, four courses) was initiated. After the first course morning headache, nausea, and vomiting disappeared. After three courses the patient developed low grade dermatitis and diarrhea, which both recovered spontaneously. Repeated neurological examination after four courses of ipilimumab showed a slight dexamethasone-induced myopathy and some hearing loss due to the WBRT. The radiological signs of LM on MRI of the brain had disappeared and the CT-thorax showed regression of the lung metastases. On last follow-up, in October 2011, there were no signs of CNS recurrence on MRI (Fig. 1c, d) and lung metastases were stable. The patient had no complaints and she was near fully active in daily life (WHO 1).

This is the first case report describing a metastatic melanoma patient with LM demonstrating a complete clinical and radiological response of LM after WBRT and four courses of ipilimumab.

One should consider that, following the USA National Comprehensive Cancer Network (NCCN) CNS tumors section guidelines, CSF examination and MRI of the spine

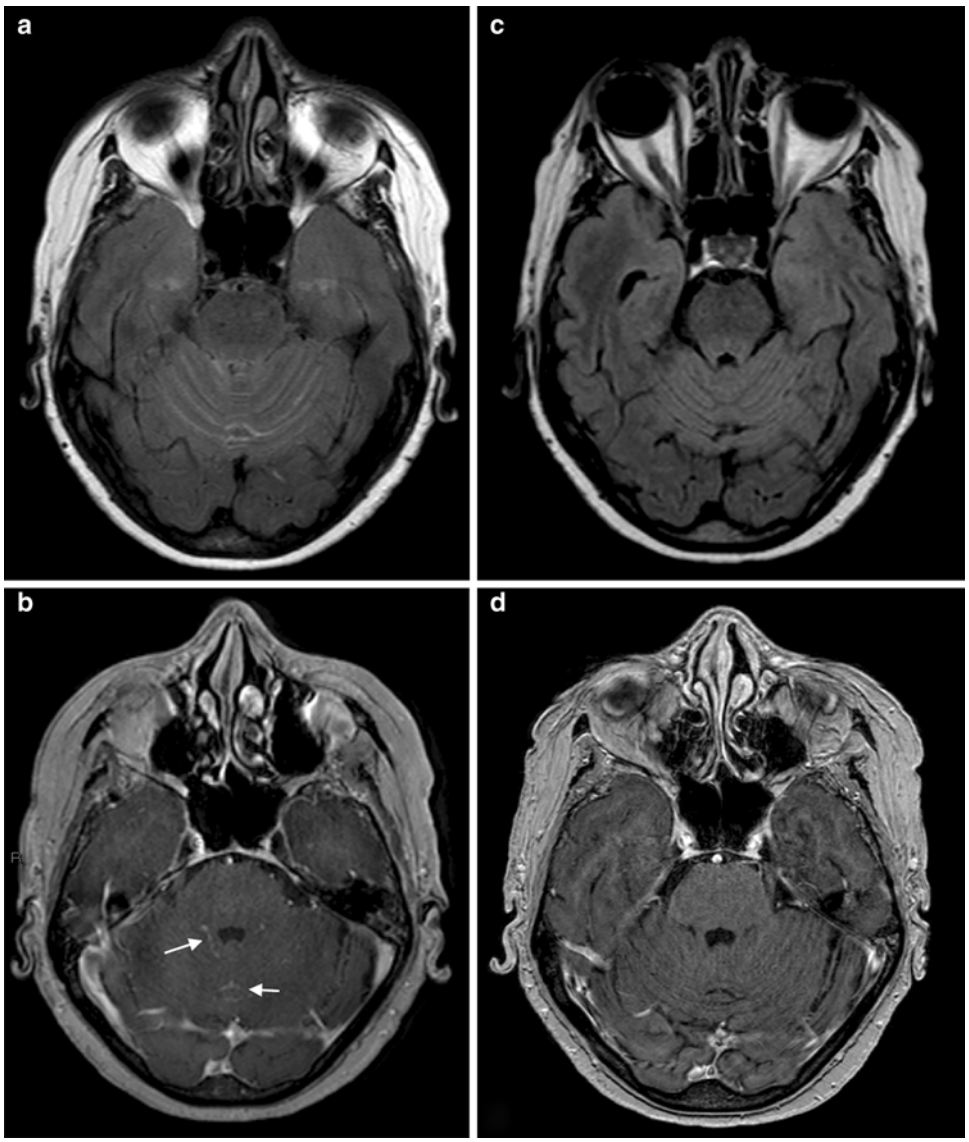

Fig. 1 **a** FLAIR MRI (May 2010): hyperintense signal of cerebellar foliae, **b** T1-weighted MRI with gadolinium (May 2010): slight contrast enhancement of cerebellar foliae (see *arrows*), **c** FLAIR MRI (October 2011): normal signal of cerebellar foliae, **d** T1-weighted MRI with gadolinium (October 2011): no contrast enhancement of cerebellar foliae

would have been required to diagnose LM [9]. However, according to the Dutch guidelines, LM can be diagnosed based on clinical and radiological signs in this patient with metastasized cancer and no signs of an infectious or autoimmune meningitis [4–8].

The complete clinical and radiological response of LM in our patient and survival of at least 1.5 years is a remarkable outcome, as the median survival of metastatic melanoma patients intensively treated for LM is 10 weeks [10]. Complete regression of LM in metastatic melanoma has never been reported. We cannot exclude that the response of LM is due to WBRT alone, as no MRI of the brain was performed after radiation. However, it is highly unlikely, as in a series of 110 patients with leptomeningeal melanomatosis treated with radiation, systemic or intrathecal therapy, the range of survival was 8–14 weeks and radiation was not a significant prognostic factor for survival [10]. The response in our patient could be the effect of the ipilimumab-initiated immune response alone or the combination of WBRT and ipilimumab. An ongoing response of more than 2 years has been described in a melanoma patient with brain metastases after treatment with ipilimumab only [3]. However, it is also possible that the WBRT preceding the ipilimumab courses had a synergistic effect with ipilimumab by enhancing the immune activation [11]. A suggested mechanism for this synergistic effect is that irradiation-induced tumor cell necrosis induces antigen presenting cell activation, followed by activation of antigen-specific T-lymphocytes initiating the cell-mediated immunity [12].

The favorable response of leptomeningeal melanoma after WBRT and ipilimumab in our patient justifies further clinical studies of ipilimumab and radiation for this devastating CNS complication of metastatic melanoma. Dr. C.U. Blank is consultant for Bristol Myers Squibb.

Conflicts of interest None.

References

1. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB et al (2010) Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363:711–723
2. Hodi FS, Oble DA, Drappatz J, Velazquez EF, Ramaiya N, Ramakrishna N et al (2008) CTLA-4 blockade with ipilimumab induces significant clinical benefit in a female with melanoma metastases to the CNS. Nat Clin Pract Oncol 5(9):557–561 (7)
3. Schartz NEC, Farges C, Madelaine I, Bruzzoni H, Calvo F, Hoos A et al (2010) Complete regression of a previously untreated melanoma brain metastasis with ipilimumab. Melanoma Res 20:247–250
4. Landelijke Werkgroep Neuro-oncologie (LWNO) (2006, revision 2010) Landelijke richtlijn Diagnostiek en behandeling van leptomeningeale metastasen van solide tumoren
5. Boogerd W, Du Bois WFJ, Teepenen JLJM, Rosenbrand CJGM (2007) Richlijn 'Leptomeningeale metastasen van solide tumoren'. Ned Tijdschr Geneesk 151:123–128
6. Freilich RJ, Krol G, DeAngelis LM (1995) Neuroimaging and cerebrospinal fluid cytology in the diagnosis of leptomeningeal metastasis. Ann Neurol 38(1):51–57
7. Straathof CS, de Bruin HG, Dippel DW, Vecht CJ (1999) The diagnostic accuracy of magnetic resonance imaging and cerebrospinal fluid cytology in leptomeningeal metastasis. J Neurol 246(9):810–814
8. Collie DA, Brush JP, Lammie GA, Grant R, Kunkler I, Leonard R et al (1999) Imaging features of leptomeningeal metastases. Clin Radiol 54(11):765–771
9. National Comprehensive Cancer Network (NCCN) (2012) NCCN Guidelines Version 1.2012 Leptomeningeal metastases
10. Harstad L, Hess KR, Groves MD (2008) Prognostic factors and outcomes in patients with leptomeningeal melanomatosis. Neuro Oncol 10(6):1010–1018
11. Dewan MZ, Galloway AE, Kawashima N, Dewyngaert JK, Babb JS, Formenti SC et al (2009) Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. Clin Cancer Res 15:5379–5388
12. Lugade AA, Moran JP, Gerber SA, Rose RC, Frelinger JG, Lord EM (2005) Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. J Immunol 174:7516–7523