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Original Research

Patterns of disease control and survival in patients with melanoma brain metastases undergoing immune-checkpoint blockade

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Abstract ***Objectives:*** Immune-checkpoint blockers (ICBs) significantly prolong overall survival (OS) in patients with advanced melanoma. Limited data are available on the efficacy and clinical benefit in patients with melanoma brain metastases (MBMs). The aim of this study was to determine whether ICB is active in an unselected cohort treated of patients with known brain metastases and if disease control correlates with the survival.
Methods: A total of 385 patients with metastatic malignant melanoma treated with ICB as monotherapy between 2005 and 2017 in two tertiary referral centres were included. Patient records were searched for the development of brain metastases. Demographic and clinical data of all patients were collected retrospectively.
Results: We identified 177 patients with MBM who received ICBs (ipilimumab, nivolumab, pembrolizumab). Patients with and without brain metastases received similar ICB regimens. Prognosis was inferior in patients with brain metastases; patients with >1 brain metastasis showed even poorer survival. For extracranial (ec) metastases, disease control was associated with improved survival. However, when comparing patients with intracranial (ic) disease control during immunotherapy to patients with ic disease progression, no difference in OS could be observed.

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Conclusions: In our study, ec disease control was the dominant predictive factor for OS in both patients with or without melanoma brain metastases. These data indicate that clinical trials in melanoma patients with brain metastases should address end-points such as symptom control, quality of life or OS in addition to ic response rates.

Introduction

The development of brain metastases is a frequent event in patients with melanoma and other solid malignant tumours [1]. Approximately 40% of patients with advanced melanoma will show intracranial (ic) metastatic spread at any time during the course of the disease [2,3]. The presence of brain metastases is associated with a poor prognosis and was incorporated into the American Joint Committee on Cancer (AJCC) staging system for melanoma as an independent prognostic factor, recently [4].

Melanoma brain metastases (MBMs) can be treated using lesion-directed interventions such as radiotherapy and surgery or by systemic antineoplastic therapeutics [3,5] or a combination of both. In patients with MBM harbouring mutated BRAF (V600), targeted therapy shows meaningful clinical efficacy in terms of objective response rates. Recently, a prospective study showed an intracranial response rate (icRR) of 44–59% for combined dabrafenib and trametinib. In the largest cohort within this trial, icRR was 58% with a median ic duration of response (DOR) of 6.5 months. Median ec DOR was 10.2 months in this cohort, indicating a more rapid development of resistance in MBMs than in other visceral metastases [6].

Ipilimumab (anti-CTLA-4), nivolumab and pembrolizumab (anti-PD-1 antibodies) as well as the combination of ipilimumab and nivolumab have shown increased progression-free survival (PFS) and overall survival (OS) in several clinical studies in patients with advanced melanoma [7–12]. For monotherapy with ipilimumab, an icRR of 16% with a median OS of 7.0 months was reported for asymptomatic MBM in a prospective phase II trial [13]. For pembrolizumab, a small prospective study showed an icRR of 22% (4/18) with duration of up to 10 months [14]. Data on the activity and outcome of patients with MBM receiving combined PD-1 and CTLA-4 blockade were reported recently [15]. In the ABC trial, patients with asymptomatic, previously untreated brain metastases achieved an overall icRR of 47% when receiving ipilimumab plus nivolumab (cohort A) while icRR was 20% for nivolumab monotherapy (cohort B). However, median OS was similar (~18 months) in both cohorts.

While extracranial disease control (ecDC) by Immune-checkpoint blockers (ICBs) translates into improved survival [16,17], no such data have been reported for the relationship of survival and ic response to ICB. To this end, we conducted a dual centre retrospective study to explore the outcome of patients with MBM receiving ICB. In particular, we investigated if intracranial disease control (icDC) translates into a better outcome than progression of MBM during ICB.

Methods

Patient cohort

The skin cancer database of the departments of dermatology of the University Hospitals of Essen and Würzburg was searched for melanoma patients (cutaneous or unknown primary) in whom either ipilimumab, nivolumab or pembrolizumab were commenced between 2005 and 2017. The AJCC 2009 classification was used to categorise patients [18]. Demographic and clinical data were collected. When MBMs were coincident with other distant metastases, patients are referred to as MBM at first diagnosis of stage IV. Those patients developing MBM at any time point after the first occurrence of other distant metastases are referred to as MBM during the course of the disease. In addition, the time point of the first occurrence of MBM was categorised as before (detection any time prior to start of the ICB), during (detection during ICB regime) or after ICB (detection any time after the last application). For therapy sequences, modalities starting prior to ICB were counted as 'prior' and those starting not earlier than the date of the first application of ICB were accounted 'concomitant'. The number of MBM refers to the number of MBM at first diagnosis of MBM. Brain metastases were identified by computed tomography (CT) scans or magnetic resonance imaging (MRI) in all patients. Patients with uveal and mucosal melanoma were excluded. Patients with distant metastases (stage IV) or unresectable stage III were combined and reported as patients with advanced melanoma [7,18].

Definition of end-points and data acquisition

OS was calculated from two different time points. Survival time was either calculated from the date of the first