

REVIEW

How I treat brain metastases of melanoma

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Brain metastases are common in advanced melanoma and cause death in >50% of patients. Until recently, median survival was only ~4 months. Improved systemic treatment including immune checkpoint inhibitors and combinations of BRAF/MEK inhibitors, however, has significantly improved intracranial tumor response and survival. In addition, advances in radiation therapy have also improved the intracranial outcomes for advanced melanoma patients with brain metastases (MBM). There has long been concern that systemic treatment of the central nervous system metastases would be ineffective due to inability of active agents to cross an intact blood–brain barrier. Recent studies have shown, however, that highly active systemic therapy can have significant benefit in these patients. When determining a patient's treatment, the important factors in predicting the likelihood of benefit including the presence of neurologic symptoms, the number and size of brain metastases, performance status/status of extracranial disease, and BRAF mutation status should all be considered. In this review, we will discuss the challenges and treatment options for patients with advanced melanoma and brain metastases.

Key words: melanoma, brain metastases, immunotherapy, targeted therapy

INTRODUCTION

Melanoma is the fifth most common cancer and metastasizes to the brain via hematological dissemination.¹ Male sex, high serum lactate dehydrogenase level, high Breslow thickness of primary melanomas, head or neck as the site of primary disease, visceral or nodal involvement are risk factors for melanoma brain metastasis (MBM) development.² MBM can cause serious neurologic morbidity, and 54% of patients with brain metastases die of central nervous system progression. Patients without treatment of brain metastases generally have progression and die within 3 months.³

Problem of treating brain metastases in melanoma

For a drug administered via blood to successfully treat brain metastases, it must first pass the blood–brain barrier (BBB), and then the barrier formed by the microenvironment around the tumor, and reach the tumor in sufficient quantity. While tumors can cause damage to the BBB, this does not always happen; therefore, which drug and how

much drug can pass the damaged barrier to reach the tumor is unknown. In addition, resistance to drug therapy is another significant cause of death from MBM. The expression of the drug transporter P-glycoprotein is known to cause resistance to a wide variety of cytotoxic chemotherapies; in addition, studies have shown that astrocytes increase progression of brain metastases due to their growth factor secretions, chemokines, and cytokines, including interleukin (IL)-6, tumor necrosis factor alpha, and IL-1.

Drug therapies for MBM

Immunotherapies. 'A 53-year-old man with a history of a stage II melanoma on his arm resected 5 years ago presented with cough and chest pain. Computed tomography scans revealed two lung and five small brain metastases, 0.5 and 0.7 cm in size, without edema. Lung biopsy confirmed recurrence of melanoma with a BRAFV600E-mutation detected. The patient had no symptoms from his MBM, and did not require steroids. His case was discussed in a multidisciplinary tumor board, and the decision was to start him on nivolumab plus ipilimumab systemic therapy, without any locoregional therapy such as radiation or surgery.'

The decision to treat asymptomatic MBM with immunotherapy was based on the results of the CheckMate-204 trial, a single-arm phase II trial that investigated safety and efficacy of nivolumab plus ipilimumab in MBM in both asymptomatic and symptomatic patients. Ipilimumab

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3 mg/kg was given in combination with nivolumab 1 mg/kg every 3 weeks for four cycles, followed by maintenance nivolumab until progression, toxicity, or 2 years of therapy. The intracranial response rate (ICRR) was 53.5% in patients with asymptomatic MBM.⁴ The median intracranial progression-free survival (PFS) and overall survival (OS) were not yet reached, with a 36-month PFS and OS rate of 54% and 72%, respectively, among asymptomatic patients.

For patients with symptomatic MBM with or without steroid therapy, however, the ICRR significantly decreased to only 22.2%. The median intracranial PFS and OS were 1.2 and 8.7 months, respectively, for symptomatic MBM.⁵ In the Australian anti-programmed cell death protein 1 (anti-PD-1) brain collaboration (ABC) study, patients with asymptomatic brain metastases were randomized to either nivolumab 1 mg/kg + ipilimumab 3 mg/kg, or nivolumab monotherapy 3 mg/kg every 2 weeks. The ICRRs were 51% for the combination and 20% for nivolumab. The 5-year intracranial PFS and OS rates were 46% and 51% for the combination, and 15% and 34% for nivolumab arm, respectively.⁶

As monotherapy, anti-cytotoxic T-lymphocyte antigen-4 (anti-CTLA-4) and anti-PD-1 inhibitors have lower ICRR, as in the 23 patient asymptomatic MBM cohort of a phase II trial of pembrolizumab, the ICRR was only 26%. The median PFS and OS were 2 and 17 months, respectively, and 48% of patients were alive at 2 years.⁷ It appears that ipilimumab provides similar control of MBM (16% ICRR)⁸ as it provides in extracranial disease, whereas PD-1 blockade may be less active in the brain than in extracranial metastases,⁷ although these results must be regarded with caution due to relatively small patient cohorts reported for PD-1 blockade alone, and the well-known impact of patient selection on treatment outcomes. Nevertheless, these apparent differences raise the mechanistic possibility that the activity of PD-1 blockade actually requires proximity to the T cells in the tumor microenvironment (whereas CTLA-4 blockade works peripherally), and the incomplete penetration of the BBB by PD-1 antibodies limits their activity in the brain.

Based on these data, patients with asymptomatic MBM are increasingly treated with upfront dual immunotherapy with delayed local therapy such as radiation, given the high ICRR and durable intracranial response now seen with CTLA-4 plus PD-1 blockade; this is especially true in the large majority of patients who also have extracranial disease that requires systemic therapy. (In addition, the ECOG EA6134 trial demonstrated that first-line ipilimumab/nivolumab was more effective than dabrafenib/trametinib in BRAF-mutant advanced melanoma, also supporting use of immunotherapy instead of BRAF/MEK inhibitors in treatment-naïve advanced melanoma.⁹) Whereas patients with MBM should be selected carefully for upfront immunotherapy without prior local therapy through a multidisciplinary discussion, brain metastases guidelines such as from ASCO—SNO—ASTRO are incorporating consideration to forgo radiation or surgery in select patients.¹⁰

Patients with symptomatic MBM, however, often do require upfront surgery and/or radiation therapy before systemic immunotherapy, either to relieve the effects of mass or hemorrhage, or to allow tapering off of steroids, which inhibit the response to immunotherapy. The effects of other modulations such as vascular endothelial growth factor blockade to supplant steroid therapy are under investigation (Table 1). Further, there are a number of other very promising immunotherapeutic agents with activity in melanoma that may prove to have an improved therapeutic index over the combination of CTLA-4 plus PD-1 blockade for patients with advanced melanoma and MBM.

Targeted therapies. The 53-year-old patient's brain and lung metastases shrunk with nivolumab and ipilimumab. At 18 months from start of therapy, however, he presented with new liver metastases. One brain metastasis had disappeared, while another remained stable in size, and without any symptoms. Therefore, given the patient's BRAF-mutant melanoma, he was switched to BRAF/MEK inhibitor therapy with dabrafenib and trametinib.⁷

The COMBI-MB study investigated combined BRAF/MEK inhibition with dabrafenib plus trametinib in 125 patients with BRAFV600-mutant MBM. The ICRR was 58%, while in patients with symptomatic MBM, a similar ICRR of 59% was observed.¹¹ A relatively short median PFS, however, was seen regardless of symptomatic status (5.6 months in asymptomatic and 5.5 months in symptomatic patients). Different microenvironmental factors in the brain, poor drug penetration into the brain, metabolic differences in tumor cells, and incomplete mitogen-activated protein kinase (MAPK) pathway inhibition are thought to be plausible causes of shortened response duration in the brain.^{12,13} In addition, MBM have been shown to be richer in oxidative phosphorylation (OXPHOS) and increased OXPHOS has been related with resistance to BRAF-MEK inhibitor therapy in melanoma.

It is interesting to reflect on the observation of identical results from BRAF/MEK inhibitors in both asymptomatic and symptomatic cohorts (with different steroid dependencies), which suggest that other elements of patient heterogeneity were without impact on targeted therapy, whereas the dramatic differences in outcome between asymptomatic and symptomatic patients on immunotherapy suggests a strong impact of the tumor microenvironment and/or use of steroids on the outcome for these patients. The phase II TRICOTEL trial that explored the combination of a BRAF/MEK inhibitor vemurafenib + cobimetinib with an anti-PD-L1 atezolizumab, with an intracranial PFS of 7.2 months in symptomatic MBM suggests there may be a role for a combination approach in symptomatic MBM.¹⁴ There are ongoing randomized trials such as SWOG S2000 exploring use of a combination of BRAF/MEK inhibitors with anti-PD-1 therapy including in symptomatic MBM versus immunotherapy (Table 1).

Radiation therapy. The 53-year-old patient's liver metastases shrunk while he was receiving dabrafenib and

Table 1. Ongoing clinical trials in melanoma brain metastases

Study	Regimen	Eligibility criteria	Primary outcomes
NCT02681549	Single-arm phase II trial: pembrolizumab with bevacizumab (melanoma or NSCLC) <i>N</i> = 53	Asymptomatic, prior radiation/surgery allowed if untreated target lesion, no prior immunotherapy, prior BRAF/MEKi allowed	Intracranial response rate using RECIST 1.1
NCT03175432	Single-arm phase II trial: atezolizumab with bevacizumab <i>N</i> = 60	Cohort A: asymptomatic, cohort B: mildly symptomatic Prior radiation/surgery allowed if untreated target lesion, BRAF/MEKi allowed	Intracranial response rate using iRANO
NCT04511013	Randomized phase II trial: encorafenib + binimetinib + nivolumab versus ipilimumab + nivolumab <i>N</i> = 112	Symptomatic permitted, BRAFV600 mutant prior systemic therapy in neoadjuvant or adjuvant setting allowed	Progression-free survival using RECIST 1.1
NCT03340129	Randomized phase II trial: ipilimumab + nivolumab with SRS versus ipilimumab + nivolumab <i>N</i> = 218	Asymptomatic. No prior systemic therapy allowed	Neurological specific cause of death
NCT03898908	Phase II trial: encorafenib + binimetinib before local treatment <i>N</i> = 38	BRAFV600-mutant, no prior local treatment: cohort 1 asymptomatic brain mets; cohort 2 symptomatic brain mets	Intracranial response rate by RECIST 1.1 before local radiotherapy
NCT03332589	Single-arm phase II trial: E6201 (MEK inhibitor) plus dabrafenib <i>N</i> = 24	Asymptomatic, BRAFV600-mutant. No prior systemic therapy allowed	Intracranial disease overall response rate using RANO-BM
NCT01904123	Phase I trial: WP1066 (STAT3 inhibitor) <i>N</i> = 33	Asymptomatic, prior systemic therapy allowed	Maximum tolerated dose

BRAF/MEKi, BRAF/MEK inhibitors; iRANO, immunotherapy response assessment in neuro-oncology; mets, metastasis; NSCLC, non-small-cell cancer; RANO-BM, response assessment in neuro-oncology brain metastases.

trametinib; however, 1 year later, he presented with new onset severe headache, and brain magnetic resonance imaging (MRI) showed a 1.5 cm new frontal lobe brain metastasis with vasogenic edema. His extracranial disease was well controlled. Therefore, this new MBM was treated with stereotactic radiation, while the patient continued with dabrafenib and trametinib therapy.⁷

Stereotactic radiosurgery (SRS) is a radiotherapy procedure capable of treating metastatic lesion(s) effectively and safely while sparing surrounding normal brain tissues by delivering a large, ablative radiation dose in one or few sessions. Melanoma is a relatively radioresistant malignancy, so the large ablative dose has a strong radiobiological rationale for improved cell killing. SRS is currently the standard local therapy for ≤ 4 brain metastases per ASTRO guidelines,¹⁵ with many centers having the ability to treat larger numbers of lesions, and ongoing prospective trials are evaluating the role of SRS for 5–15 brain metastases. SRS yields an excellent local control as high as 90% for multiple histologies including melanoma.¹⁶ Surveillance brain MRI every 2-3 months is recommended to detect distant brain recurrence, which often can be salvageable with repeat SRS.

For larger size lesions (>3 cm) or close to critical structures, fractionated stereotactic radiotherapy of three to five fractions is often used and has shown good local control of $>85\%$ in published studies. If patients are symptomatic due to mass effect of metastases, surgical resection followed by adjuvant SRS to the surgical cavity is a standard approach, with 1-year local control of 70%-90%.^{17,18} A randomized trial (NCT04114981) comparing post-operative single versus multi-fraction SRS is underway.

For numerous symptomatic MBMs not suitable for SRS, whole brain radiotherapy (WBRT) may be indicated. Given the long-term negative neurocognitive effects following WBRT, the role of WBRT is shrinking. Nevertheless, it continues to play a role for palliation in patients who have

numerous symptomatic MBM, and for those whose performance status is poor and systemic options are not available. In recent years, hippocampal avoidance WBRT has been shown to better preserve cognitive function.¹⁹ Addition of memantine has been shown to further improve preservation of cognitive function over time.²⁰

Given retrospective analyses exploring the combination of anti-PD-1 immunotherapy with concurrent radiation in patients with MBM,²¹ this approach is also under exploration in clinical trials, including the Australian ABC-X trial (Table 1). In this phase II trial, patients with asymptomatic MBM are randomized to ipilimumab and nivolumab with concurrent SRS versus ipilimumab and nivolumab alone.

SUMMARY

Management of MBM requires a multidisciplinary approach with medical oncologists, radiation oncologists, and neurosurgeons to assess all available treatment options. Targeted therapy with BRAF/MEK inhibitors and immunotherapy has shown promising results for patients with melanoma brain metastases. Local therapy such as SRS provides excellent local control for intracranial metastases, although its utility is evolving in the era of improving systemic therapy. Outcomes with systemic therapy remain poor for patients with symptomatic MBM, however, and locoregional treatments are often used for these patients. Ongoing and upcoming clinical trials along with preclinical research will hopefully lead to improvement in clinical outcomes for these patients.

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