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Melanoma brain metastases: current areas of investigation and future directions

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Abstract

Metastases to the central nervous system (CNS) are one of the most common and lethal complications of metastatic melanoma. Historically, melanoma patients with CNS metastases have had dismal outcomes and very limited treatment options. However, the development of more effective targeted, immune, and radiation therapies is now leading to promising new investigations and strategies. Optimizing the development and testing of such strategies will benefit from an improved understanding of the unique molecular features of these tumors and the influence of the brain microenvironment. Accounting for unique clinical features and challenges of CNS metastases will also be critical to making significant clinical impact in patients.

Keywords

Melanoma; brain metastasis; leptomeningeal disease; targeted therapy; immunotherapy; radiation therapy

Introduction

Metastasis to the central nervous system (CNS) is a common and challenging problem for patients with advanced melanoma. CNS involvement has been detected clinically in up to 43% of metastatic melanoma patients, and in up to 75% of patients in autopsy series.[1] Several previous series reported median overall survival (OS) of only 4-6 months from the diagnosis of melanoma brain metastasis (MBM).[1,2] The exclusion of patients with MBMs from most clinical trials further complicates clinical-decision making for them.[3]

Improved understanding of melanoma pathogenesis has led to many clinical breakthroughs in the last decade.[4] While little of this progress has focused specifically on the prevention and/or treatment of CNS metastasis, many of these advances have laid a strong foundation for tackling this challenge moving forward. This review will summarize current treatment

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options and research for melanoma CNS metastasis, and discuss key opportunities for progress and clinical impact in the future.

Targeted Therapy

Cytotoxic chemotherapy has demonstrated little activity in MBM patients.[1] While one possible reason for this limited activity is decreased bioavailability of agents in the CNS due to the blood-brain-barrier (BBB), temozolomide, a second-generation oral alkylating agent with significant CNS penetration, achieves intracranial responses in ≤10% of MBM patients [Table 1].[5] There is strong evidence that the BBB is significantly disrupted by brain metastases, particularly those that are large enough to be imaged by magnetic resonance imaging (MRI).[6] The lack of clinical activity with chemotherapy in MBMs also mirrors the disappointing results generally seen in extracranial metastases.

Much more promising results have been observed with targeted therapies in patients with activating *BRAF* mutations. Both vemurafenib (2011) and dabrafenib (2013) are approved by the FDA for the treatment of metastatic melanoma patients with $BRAF^{V600}$ mutations, which occur in ~50% of cutaneous melanomas. Both agents were approved based on phase III trials that excluded patients with active brain metastases.[7,8] However, both of these BRAF inhibitors (BRAFi) have demonstrated clinical activity in CNS metastases. The largest clinical trial experience has been with dabrafenib, which was evaluated in 172 MBM patients in the phase II BREAK-MB study.[9] All patients had either a $BRAF^{V600E}$or a $BRAF^{V600K}$ mutation, and results were analyzed separately for patients with treatment-naïve (Cohort A, n=89) and previously treated (i.e. surgery or radiation; Cohort B, n=83)brain metastases. Stable or tapering doses of corticosteroids were permitted. The intracranial response rates (ICRR) were 39.2% for Cohort A and 30.8% for Cohort B, the intracranial disease control rates (ICDCR) was greater than 80% in both groups, and the median OS was slightly greater than 8 months in both groups (cohort A: 33.1 weeks, cohort B: 31. 4 weeks). A smaller prospective clinical trial with vemurafenib in patients (n=19) with unresectable, previously treated, symptomatic brain metastasis reported an ICRR of 37%.[10] The median OS was also only 5.3 months, but several studies have shown that the presence of symptoms is an adverse prognostic factors in patients with MBMs.[1] Several clinical trials are now ongoing to evaluate the safety and efficacy of combined treatment with BRAF and MEK inhibitors (dabrafenib + trametinib; vemurafenib + cobimetinib), which have demonstrated superior anti-tumor activity and safety in metastatic melanoma patients without CNS metastases [Table 2].

While the BRAF inhibitors rapidly achieve disease control in most patients with MBMs, the majority of patients eventually develop resistance and disease progression. Molecular changes that cause resistance to BRAF inhibitors have been characterized extensively in extracranial melanoma metastases.[11] It is possible that similar mechanisms underlie resistance to BRAF inhibitors in MBMs. However, the clinical experience with targeted therapies in other cancers, particularly non-small cell lung cancer (NSCLC), support that distinct events may cause resistance in brain metastases.[3] Importantly, there is strong evidence that the tumor microenvironment of the CNS may induce unique effects on the molecular biology of tumor cells compared to other sites.[12,13] Additional experiments

support that both genetic and epigenetic molecular features of melanoma CNS metastases may differ from both primary tumors and other distant metastases in individual patients.[14-16] A number of these studies have specifically implicated a role for the PI3K-AKT pathway as a contributor to the pathogenesis of MBMs. This pathway has also been associated with resistance to BRAF inhibitors, and preclinical *in vitro* and *in vivo* studies support that PI3K pathway inhibitors may be an effective strategy for MBMs as single agents or in combination with BRAF inhibitors.[15,17,18] A phase II trial of the pan-PI3K inhibitor buperlisib (BKM120) in patients with MBMs is currently ongoing [Table 2]. Additional studies support that increased signaling by the JAK-STAT signaling pathway may be associated with MBM, and a phase II trial of the STAT3 inhibitor WP-1066 in MBM patients is underway.[19] Dysregulation of the p16-CDK4-CyclinD1 axis is also frequent in melanoma, and a clinical trial of the CDK4/6 inhibitor abemaciclib is currently ongoing in patients with brain metastases from solid tumors, including melanoma. While these single-agent studies are an important first step, it is likely that combinatorial approaches will be needed.

Immunotherapy

The status of the CNS as an immune privileged site suggested that the efficacy of immunotherapy for MBMs could be limited. However, there is growing evidence that immunotherapy can achieve durable clinical responses and benefit in MBMs, albeit with some unique challenges.

Similar to the experience with extracranial disease, the first immunotherapy to demonstrate efficacy in MBM patients was high dose interleukin-2 (HD IL-2). However, the response rate was significantly lower than in patients without CNS involvement, and the use of HD IL2 is challenging in these patients due to the need for aggressive fluid hydration, which can increase the risk of cerebral edema, and the neurological toxicities of this regimen.[20] Despite these factors, there is evidence that HD IL2 given in combination with adoptive cell transfer (ACT) of autologous tumor infiltrating lymphocytes (TIL) is feasible. In a phase II study of 26 MBM patients treated with ACT, 7 patients treated with unmodified TIL experienced complete remission (CRs) and achieved 6 partial responses (PR), and 2 of 9 patients treated with TCR-transduced lymphocytes had CRs in the brain (22%).[21]

Favorable outcomes have also been seen with immune checkpoint inhibitors. A prospective phase II trial of ipilimumab evaluated safety and efficacy in 51 patients with asymptomatic MBMs that did not require steroids and 21 MBM patients requiring steroids for control of neurologic symptoms [Table 1].[22] The patients not requiring steroids achieved an ICRR of 16%, ICDCR was 24%, global response rate of 10%, and 31% of patients were alive at 12 months, results which are similar to patients without CNS involvement. In contrast, only 1 (5%) patient requiring steroids achieved intracranial disease control, and the median OS was 3.7 months for those patients. Recently, initial results of a phase II study of pembrolizumab in MBM patients with asymptomatic metastases that did not require steroids have been reported.[23] The trial included 18 melanoma patients, but 4 patients were not assessable for response (3 with rapid extracerebral progression, 1 due to intracranial hemorrhage requiring radiation). The ICRR for assessable patients was 22%, the ICDCR was 43%, and all clinical

responses were ongoing at the time of publication (up to 12 months). The safety profile of both ipilimumab and pembrolizumab appears to be reasonable in MBM patients, although the pembrolizumab study did report controllable seizures (3 patients) and neurological symptoms due to increased cerebral edema (2 patients). Clinical trials with nivolumab, as a single-agent and in combination with ipilimumab, in MBM patients are currently ongoing [Table 2].

These results confirm that immunotherapy likely has an important role to play in treatment of MBM patients. However, there are clinical aspects that are distinct to immunotherapy compared to targeted therapies. As noted above, initial results suggest that MBM patients that require steroids to control intracerebral edema may not respond to immunotherapy. It is currently unknown if alternative strategies to control cerebral edema could overcome this limitation (i.e. cytoreductive therapy with targeted therapy, or angiogenesis inhibitors). Further, the fact that immunotherapies work by causing intratumoral inflammation can create a specific challenge to differentiate disease progression from inflammation, also known as pseudo-progression. A case report of one MBM patient enrolled on the pembrolizumab study described the development of multiple edematous lesions and new neurological symptoms, but pathological review of a resected lesion demonstrated no viable tumor cells.[24] Recent criteria proposed by the Response Assessment in Neuro-Oncology (RANO) group, including specific criteria for patients receiving immunotherapy, begin to address this challenge.[24] However, there remains a need for future studies to further characterize and validate the radiographic features that correspond with clinical benefit and with disease progression.

Radiation Therapy

For many years whole brain radiation therapy (WBRT) and corticosteroids were the standard of care for patients with multiple brain metastases.[25] Unfortunately, local control with WBRT is often suboptimal and there is a high incidence of associated neurocognitive decline. Furthermore, melanoma cells harbor efficient DNA damage repair mechanisms, leading to “radioresistance” that requires larger fractions for cell killing. Stereotactic radiosurgery (SRS) has largely replaced WBRT in a variety of settings, and can now be considered a cornerstone of the treatment for MBM.[26] SRS was historically performed on up to three MBMs, but a recent prospective study showed that outcomes with SRS treatment for 5-10 brain metastases are non-inferior to results in patients with 1-4 lesions. [27]

There is now growing interest and experience in combining radiation and systemic therapies for MBMs. In addition to the rationale to build upon the high rate of local control achieved by SRS, there is also evidence that cell killing by radiation therapy may improve systemic responses to immunotherapy.[28] A retrospective study reported a median OS of 18.3 months in MBM patients (n=33) who received ipilimumab either prior to or after SRS or WBRT, compared to 5.3 months for patients treated with radiation only. Similarly impressive outcomes were observed in patients (n=26) treated with nivolumab and SRS, with local MBM local control rates of 91% and 85% at 6 and 12 months, and a median OS of 11.8 months.[29] Multiple prospective trials are ongoing [Table 2].

While these results are promising, there is continued need for prospective evaluation.Radiation necrosis (RN), an inflammatory reaction to high-dose radiation to the brain, can develop after SRS (median onset 6-10 months) and is often associated with significant neurological morbidity.[30] Recent data suggests that RN rates may be increased in patients who receive concomitant immunotherapy with SRS.[31]

Leptomeningeal disease

Leptomeningeal disease (LMD) is defined by involvement of the membrane (meninges) surrounding the brain and spinal cord by cancer. The presence of LMD is associated with extremely poor prognosis among melanoma patients with CNS involvement, with median survival of ≤2 months from diagnosis.[1,2] Patients with LMD are generally managed palliatively with XRT, steroids, and supportive care. Recent case reports and retrospective series support that both BRAF inhibitors and checkpoint inhibitor immunotherapy administered systemically can achieve clinical responses in some patients with LMD.[32] Currently, a prospective trial is evaluating the safety and efficacy of systemic treatment with pembrolizumab in LMD patients [Table 2]. However, clinical experience with LMD in lymphoma and breast cancer patients also suggests that direct intrathecal (IT) administration of anti-cancer agents is a safe and effective strategy to achieve higher drug levels in the CSF and can result in clinical benefit.[33] Intrathecal IL-2 has been administered safely in melanoma patients with LMD, and in some patients has resulted in clinical responses and prolonged survival.[3,34,35] A clinical trial is currently open to evaluate intrathecal treatment with ACT, with a previous case report supporting the safety and feasibility of this approach.[36] There is a critical unmet need to develop new therapeutic strategies and clinical trials for patients with LMD.

Summary

Despite many challenges, there are now many promising insights and approaches for melanoma patients with CNS metastases. There is growing evidence from both trials and everyday clinical practice that agents that are effective in non-CNS disease can also be safe and effective in MBM patients, which hopefully will break down barriers to new trials for these patients moving forward. However, there is also evidence that there are unique clinical and molecular features of MBMs that require specific consideration. Overall, there remains a critical need for research efforts focused on the pathogenesis and treatment of MBMs, but also growing optimism about the likelihood that such efforts will have significant impact on patients.

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Table 1

Completed clinical trials in melanoma patients with CNS metastases.

Author, Journal, Year of publication	Treatment regimen	Number of patients with MBM	OIRR	Median OS
Khayat et al., *J Natl Cancer Inst.*, 1988	Fotemustine, 100-mg/m2 weekly induction schedule for 3-4 consecutive weeks, then maintenance q3 weeks	7	28%	NR ~
Jacquillat et al., *Cancer*, 1990	Fotemustine, 100-mg/m2 weekly induction schedule for 3-4 consecutive weeks, then maintenance q3 weeks	36	25%	164 Days
Agarwala et al., *J ClinOncol.*, 2004	Temozolomide200 mg/m(2) PO qd × 5 days every 28 days	No prior systemic therapy, n=117	7% (1% CR, 6% PR)	2.2 months
	Temozolomide 150 mg/m(2) PO qd × 5 days every 28 days	Prior systemic therapy, n=34	3% (3% PR)	
Schadendorf et al., *Ann Oncol.*, 2006	Temozolomide 150 mg/m(2) PO qd, days 1-7 and 15-21, every 28 days	No prior systemic chemo, n=21	2.2 % (all PR)	4.3 months
	Temozolomide 125 mg/m(2) PO qd, days 1-7 and 15-21, every 28 days	Prior systemic chemo, n=24	2.2 % (all PR)	3.5 months
Hwu et al., *Cancer.*, 2005	Temozolomide (75 mg/m2 PO qd for 6 weeks with a 2-week break between cycles) plus concomitant thalidomide (200 mg PO qd escalating to 400 mg PO qd for patients < 70 years or 100 mg/day escalating to 250 mg/day for patients > or = 70 years)	26	9% (3% CR, 6% PR)	5 months
Larkin et al., *Br J Cancer.*, 2007	Temozolomide 150 mg/m2 PO qddays 1-5 every 28 days and Lomustine 60 mg/m2 on day 5 every 56 days	26	0%	2 months
Vestermark et al., *Ecancermedicalscience*, 2008	Temozolomide, 150 mg/m2 PO qd for seven days, followed by seven days off therapy and Thalidomide 200 mg daily	40 (25 asymptomatic, 15 symptomatic)	17.5% (5% CR, 12.5% PR)	4.2 months *
Vestermark et al., *ActaOncol.*, 2008	Temozolomide dose escalated over 4 weeks from 100 mg PO qd to 400 mg PO qd	36	0%	3.1 months
Amaravadi et al., *Clin Cancer Res.*, 2009	Temozolomide 150 mg/m2 PO qdfor 5 of every 28 days, Sorafenib at 400 mg twice daily	53	NR	3.5 months
Di Giacomo et al., *Lancet Oncol.*, 2012	Ipilimumab 10 mg/kg every 3 weeks to a total of four doses, and 100 mg/m2 intravenous Fotemustine weekly for 3 weeks and then every 3 weeks from week 9 to week 24	20	NR	13.4 months
Long et al., *Lancet Oncol.*, 2012	Dabrafenib 150mg PO twice a day	No previous local treatment for MBM, BRAF V600E = 74; BRAF V600K = 15	BRAF V600E 39.2%, BRAF V600K 6.7%	BRAF V600E, 33.1 months; BRAF V600K, 16.3 months
		Previous local treatment for MBM, BRAF V600E = 65; BRAF V600K = 18	BRAF V600E 30.8%, BRAF V600K 22.2%	BRAF V600E, 31.4 months; BRAF V600K, 21.9 months

Author, Journal, Year of publication	Treatment regimen	Number of patients with MBM	OIRR	Median OS
Margolin et al., *Lancet Oncol.*, 2012	Ipilimumab 10 mg/kg × 4 doses, q3 weeks. Individuals who were clinically stable at week 24 were eligible to receive 10 mg/kg intravenous ipilimumab Q12 weeks	Asymptomatic patients, n=51	16%	7 months
		Symptomatic patients, n=21	5%	3.7 months
Kefford et al., *Pigment Cell Melanoma Res.*, 2013	Vemurafenib 960mg PO twice a day	Previously untreated MBM, n= 90	21%	7.1 months
		Previously treated MBM, n=56	NR	9.5 months
Goldberg et al., *Lancet Oncol.*, 2016	Pembrolizumab 10 mg/kg every 2 weeks until progression	18	22%	67% 6 months survival

MBM: melanoma brain metastasis, OIRR: overall intracranial response rate, OS: overall survival, NR: not reported, CR: complete response, PR: partial response, PO: by mouth

~ Duration of response and OS not separately reported for MBM patients

* No difference in survival comparing patients with symptomatic (n=15) and asymptomatic (n=25) brain metastases was found

Table 2

Current clinical trials in melanoma patients with CNS metastases.

NCT Number	Name of Study	Treatment	Phase	Estimated Accrual	Cancer type	Patients with LMD allowed?
		Immunotherapy				
NCT02681549	Pembrolizumab Plus Bevacizumab for Treatment of Brain Metastases in Metastatic Melanoma or Non-small Cell Lung Cancer	Pembrolizumab plus Bevacizumab	II	53	NSCLC, melanoma	no
NCT02886585	Pembrolizumab In Central Nervous System Metastases	Pembrolizumab	II	102	Solid tumors	yes
NCT02085070	MK-3475 in Melanoma and NSCLC Patients With Brain Metastases	Pembrolizumab	II	64	NSCLC, melanoma	no
NCT02621515	Nivolumab in Symptomatic Brain Metastases (CA209-322)	Nivolumab	II	70		yes
NCT02460068	A Study of Fotemustine(FTM) Vs FTM and Ipilimumab (IPI) or IPI and Nivolumab in Melanoma Brain Metastasis (NIBIT-M2)	Fotemustine; Fotemustine and Ipilimumab; Ipilimumab and Nivolumab	III	168	melanoma	not mentioned
NCT02374242	Anti-PD 1 Brain Collaboration for Patients With Melanoma Brain Metastases (ABC)	Nivolumab vs. Nivolumab with Iipilimumab	II	76	melanoma	concurrently with measurable brain metastases
NCT02320058	A Study to Evaluate Safety and Effectiveness in Patients With Melanoma That Has Spread to the Brain Treated With Nivolumab in Combination With Ipilimumab Followed by Nivolumab by Itself (CheckMate204)	Nivolumab plus Ipilimumab followed by Nivolumab monotherapy	II	110	melanoma	no
		Targeted Therapy				
NCT01978236	Dabrafenib/Trametinib, BRAF or BRAF AND MEK Pre-op With BRAF and MEK Post-op, Phase IIB, Melanoma With Brain Mets, Biomarkers and Metabolites	Dabrafenib plus Trametinib	II	30	melanoma	no
NCT02452294	Buparlisib in Melanoma Patients Suffering From Brain Metastases (BUMPER)	Buparlisib	II	22	melanoma	no
NCT02308020	A Phase 2 Study of Abemaciclib in Patients With Brain Metastases Secondary to Hormone Receptor Positive Breast Cancer, Non-small Cell Lung Cancer, or Melanoma	Abemaciclib	II	247	breast, NSCLC, melanoma	yes
NCT01904123	A Phase I Trial of WP1066 in Patients With Recurrent Malignant Glioma and Brain Metastasis From Melanoma	WP1066	I	33	melanoma, recurrent glioma	not mentioned
NCT02039947	Study to Evaluate Treatment of Dabrafenib Plus Trametinib in Subjects With BRAF Mutation-	Dabrafenib plus Trametinib	II	120	melanoma	no

NCT Number	Name of Study	Treatment	Phase	Estimated Accrual	Cancer type	Patients with LMD allowed?
	Positive Melanoma That Has Metastasized to the Brain					
NCT02537600	Vemurafenib and Cobimetinib Combination in BRAF Mutated Melanoma With Brain Metastasis (CONVERCE)	Vemurafenib plus Cobimetinib	II	137	melanoma	no
Radiation plus systemic therapy						
NCT02716948	Stereotactic Radiosurgery and Nivolumab in Treating Patients With Newly Diagnosed Melanoma Metastases in the Brain or Spine	Nivolumab plus SRS	Pilot	90	melanoma	not mentioned
NCT02097732	Ipilimumab Induction in Patients With Melanoma Brain Metastases Receiving Stereotactic Radiosurgery	Ipililumab plus SRS	II	40	melanoma	only if SRS is considered for LMD
NCT01703507	Phase I Study of Ipilimumab Combined With Whole Brain Radiation Therapy or Radiosurgery for Melanoma	Ipilimumab plus WBRT	II	24	melanoma	not mentioned
NCT02115139	GEM STUDY: Radiation And Yervoy in Patients With Melanoma and Brain Metastases (GRAY-B)	Ipilimumab plus WBRT	II	66	melanoma	not mentioned
NCT02858869	Pembrolizumab and Stereotactic Radiosurgery for Melanoma or Non-Small Cell Lung Cancer Brain Metastases	Pembrolizumab plus SRS	Pilot	43	NSCLC, melanoma	no
NCT01721603	A Phase 2 Prospective Trial of Dabrafenib With Stereotactic Radiosurgery in BRAFV600E Melanoma Brain Metastases	Dabrafenib plus SRS	II	39	melanoma	not mentioned

SRS: stereotactic radiosurgery, WBRT: whole brain radiation