Multidisciplinary Approach to Brain Metastasis from Melanoma: The Emerging Role of Systemic Therapies

Georgina V. Long, MD, PhD, and Kim A. Margolin, MD

OVERVIEW

Melanoma brain metastases are common, difficult to treat, and carry a poor prognosis. Until recently, systemic therapy was ineffective. Local therapy (including surgery, stereotactic radiotherapy, and whole brain radiotherapy) was considered the only option for a chance of disease control in the brain, and was highly dependent on the patient’s performance status and age, number and size of brain metastases, and the presence of extracranial metastases. Since 2010, three drugs have demonstrated activity in progressing or “active” brain metastases including the anti-CTLA4 antibody ipilimumab (phase II study of 72 patients), and the BRAF inhibitors dabrafenib (phase II study of 172 patients, both previously treated and untreated brain metastases) and vemurafenib (a pilot study of 24 patients with heavily pretreated brain metastases). The challenge and unanswered question for clinicians is how to sequence all the available therapies, both local and systemic, to optimize the patient’s quality of life and survival. This is an area of intense clinical research. The treatment of patients with melanoma brain metastases should be discussed by a multidisciplinary team of melanoma experts including a neurosurgeon, medical oncologist, and radiation oncologist. Important clinical features that help determine appropriate first line therapy include single compared with solitary brain metastasis, resectability, BRAF mutation status of melanoma, rate of progression/performance status, and the presence of extracranial disease.

Melanoma brain metastases are common, difficult to control, and have a poor prognosis, with a median overall survival (OS) of 16–22 weeks. Approximately 20% of patients have overt brain metastases at first diagnosis of metastatic melanoma, and nearly 50% of patients develop clinical evidence of brain metastases—a proportion that appears to be rising over time as the high frequency of brain metastases is recognized, and increasing percentages of patients are scanned for staging and prognostic purposes, even in the absence of symptoms. In autopsy series, 55% to 75% of patients with metastatic melanoma have brain metastases. Detection of the BRAF or NRAS mutation has been reported to increase the risk of brain metastases at first diagnosis of distant metastases.

SYSTEMIC THERAPY

Until recently, systemic therapy has had limited efficacy for patients with melanoma brain metastases as a result of the near-absolute resistance of melanoma to the available cytotoxic agents and the prevailing belief that immunotherapeutic agents would be ineffective and potentially more toxic for patients with brain metastases. Patients with brain metastases were routinely excluded from systemic therapy clinical trials in the past, because of their poor prognosis, the lack of drug activity, or the lack of evidence of drug penetration of the blood-brain barrier. The BRAF inhibitors dabrafenib and vemurafenib, and the anti-CTLA4 antibody ipilimumab have demonstrated varying degrees of activity in progressing melanoma brain metastases, as summarized below. The advent of these effective drug therapies for brain metastases has led to new trial designs that permit the inclusion of such patients and even focus on the further study of optimal selection of modalities (including radiotherapy and surgery) and drug selection strategies (including combinations and sequences) that provide the best survival outcome and highest quality of life to patients with melanoma brain metastases.

CHEMOTHERAPY

Cytotoxic chemotherapy has limited efficacy for patients with melanoma and thus for patients with brain metastases. Fotemustine and temozolomide are examples of drugs with modest activity for patients with melanoma, yet appeared to have a pharmacologic advantage as a result of their ability to penetrate the blood-brain barrier. Although a phase II trial of fotemustine showed a response rate (RR) of 25% of patients with brain metastases, the response was only 5.9% in the phase III trial of fotemustine compared with dacarbazine, and no responses in the brain were seen with
radiotherapy. The addition of cytotoxic agents to stereotactic radiosurgery has not been well studied but is likely to add toxicity without a high probability of enhancing local control or preventing intracranial recurrences distant from the site of radiation.

**IMMUNOTHERAPY FOR MELANOMA METASTATIC TO THE BRAIN**

**Interleukin-2**

Until the advent of immunotherapeutic agents that work through the blockade of immunologic checkpoints, such as ipilimumab and tremelimumab (human antibodies that block the engagement and function of the CTLA4 receptor on T lymphocytes) and the newer PD-1/PD-L1-blocking agents, the only effective and approved immunotherapy in the U.S. for advanced melanoma was interleukin-2. This drug appears to be active only in high doses associated with substantial multiorgan toxicities that, although reversible, limit the drug’s use to a small subgroup of patients. Although high-dose IL-2 has been extensively used for patients without brain metastases and reported to yield objective responses in 15% to 20% and durable complete responses in approximately 5% to 7%, the uncertainty of its safety and activity in those with untreated brain metastases has discouraged its rigorous evaluation in such patients. In a retrospective review from the U.S. National Cancer Institute, 27 patients with either previously irradiated brain metastases who were otherwise excellent candidates for high-dose IL-2 were reported to benefit, as expected, from IL-2 (18% objective response rate) and did not suffer increased toxicities but may have received fewer than the average number of doses, whereas those with untreated brain metastases responded less often (6% objective responses for both intracranial and extracranial sites).

Although the highly selected nature of patients in this retrospective report limits its value, further insight into the immunotherapeutic mechanisms and limitations of IL-2 will be necessary to find its role in the therapeutic armamentarium for metastatic melanoma. Until there is more insight into the replacement of high-dose IL-2 regimens by agents or strategies with a superior therapeutic index, its use in those with brain metastases should be avoided or considered only for those with very small, asymptomatic lesions that do not require steroid therapy.

**Ipilimumab**

Antibodies that inhibit immunologic checkpoints include the human CTLA4-Ab ipilimumab. The mechanism of action involves the blockade of negative signaling in cytotoxic T cells that occurs normally following cytotoxic T-cell activation. Ipilimumab was approved in 2011 for patients with metastatic melanoma based on a survival advantage over a melanoma vaccine, and subsequently showed superior activity and survival compared with single agent dacarbazine when given in combination with dacarbazine. It has a slow onset and, in some cases, progressive disease as defined by standard response criteria precedes an objective response or the achievement of long-term disease stabilization. Thus, a novel system for assessing drug benefit has been proposed for drugs of this class. Regardless of which system is used for reporting responses, up to 25% of patients have been shown to benefit and 10% to 20% to achieve long-term progression-free and overall survival (even from the overall benefit as defined above). Ipilimumab is currently undergoing testing as an adjuvant therapy after resection of high-risk melanoma, either compared with placebo or compared with α-interferon.

Ipilimumab underwent initial testing and subsequent registrational studies in patients with advanced melanoma who had no active brain metastases but may have had previously
treated brain metastases if not steroid-dependent. However, progressing brain, spinal, and leptomeningeal metastases regressed with ipilimumab in three separately reported patients, and histology from one brain lesion that was resected to control seizures showed major tumor regression with infiltration by large numbers of immune effector cells.23–25

On the basis of these encouraging single-patient observations, a phase II study was designed to specifically evaluate the activity of ipilimumab against brain metastases for two cohorts of patients with melanoma: The first cohort consisted of 51 patients with one or more untreated brain lesions and no neurologic symptoms or requirement for glucocorticosteroids, whereas a smaller cohort of 21 patients were screened for the activity and tolerance of ipilimumab in the presence of symptoms or radiographic findings requiring a stable low dose of steroid. Patients were treated with ipilimumab, 10 mg/kg intravenously every 3 weeks for 4 cycles followed by the same dose every 12 weeks if they were benefiting from therapy (objective response or stable disease). The novel “immune-related response criteria” (irRC) that allow overall measurements, even in the presence of new disease, to determine the best overall response rate,20 were applied to these patients as well as traditional bidimensional World Health Organization (WHO) response criteria. Most patients had concordant results for brain and extracranial disease (approximately 15% objective response/25% clinical benefit rate defined as overall response (OR) plus stable disease (SD) at 12 weeks following the initiation of therapy), most of the irRC outcomes were similar to the WHO responses, and the survival for patients in the steroid-free cohort (approximately 30% at 1 year and 25% at 2 years’ follow-up) was essentially the same as reported from other studies of ipilimumab in patients without active brain metastases. Patients in the steroid-treated cohort appeared only about half as likely to benefit, an outcome likely attributable to their less favorable prognostic characteristics and the inhibition by corticosteroids of the immunostimulatory effects of checkpoint blockade.3 Similar survival outcomes were observed among 165 patients with active brain metastases from the large database of patients with melanoma who were given access to ipilimumab just before its approval by the U.S. Food and Drug Administration (FDA) in 2011.26

In a related study, investigators from the Network Italiano per la Bioterapia dei Tumori (NIBIT) performed a phase II trial of ipilimumab plus fotemustine, a nitrosourea that crosses the intact blood-brain barrier and is approved for use in Europe. Among the 20 patients with brain metastases, seven of whom had progression after prior radiotherapy, half of the patients had irRC disease control, and the median survival was 1 year.27 Although the small sample size and the toxicities associated with this combination (predominantly chemotherapy-related nausea and myelosuppression) suggest that further work is required to find acceptable combinations for these patients, it is nonetheless encouraging “proof of principle” that the benefit of CTLA4 blockade extends to central nervous system (CNS) disease and is worthy of further study, including the dose-response relationship of the approved regimen (3 mg/kg every 3 weeks, given 4 times) versus higher doses and the role of maintenance therapy (all patients in these studies received ipilimumab doses of 10 mg/kg every 3 weeks times 4, followed by the same dose every 12 weeks until progression or toxicity). For the near-term, combinations with less toxic agents such as temozolomide as well as strategies that test the potential synergy between checkpoint-blocking antibodies and hypofractionated high-dose focused radiotherapy (e.g., SRS) need to be explored. As other immunostimulatory agents, particularly the promising antibodies that block negative signaling through the PD-1/PD-L1 axis, continue to be studied and optimized in melanoma, their potential for the management of CNS disease should also be explored.

**SMALL MOLECULE TARGETED THERAPIES IN MELANOMA BRAIN METASTASES**

**Small Molecule Targeted Therapies Are Active Against Specific Melanoma Mutations**

The decision regarding which systemic therapy to use for patients with metastatic melanoma depends on the patient’s performance status, the sites of metastases, and the mutation status of the melanoma. Patients should have the most recently biopsied tissue tested for the BRAF mutation, if available, and additional valuable information may come from testing selected tumors for CKIT and NRAS mutations, the latter of importance for enrolling patients in appropriate clinical trials.

When considering systemic therapy options for melanoma metastatic to the brain, patients can be categorized into two groups: (1) those with treated and stable (“inactive”) brain metastases, and (2) those with progressing or “active” brain metastases (new lesions and/or unequivocal regrowth at the site of irradiated or previously resected lesions). To measure the activity of drugs in brain metastases, it is important to study patients with “active” brain metastases. There are only four clinical trials of small molecule targeted therapies that have included such patients, all with BRAF inhibitors in V600 BRAF-mutant metastatic melanoma (discussed below).

**BRAF Mutations**

BRAF mutations occur in approximately 50% of melanomas,11,28,29 resulting in constitutive activation of the mitogen-activated protein kinase (MAPK) pathway. The most common mutation is V600E (amino acid alteration derived from a DNA mutation e.g., the most common is 1799T>G), occurring in 70% to 90% of BRAF-mutant melanomas and at a prevalence inversely proportional to age.32 Other less frequent mutations include V600K (10% to 30%), V600R (1% to 7%), and K601E (1% to 4%).11,28,29,32 V600K is independently associated with increased age and chronic cumulative UV exposure,31 and the prevalence varies by geographic region (<10% in northern Europe,33 12% in Tennessee,32 and 20% to 30% in Australia, Texas and Florida).11,31,34)
Most importantly, the method used for detection of a \textit{BRAF} mutation may not be sensitive and specific for these less common, but drug-responsive, mutations (see below). For example, the PCR-based Roche Cobas test only detects V600E at sufficient sensitivity and specificity for diagnosis; it variably detects V600K (sensitivity 40% to 70%)\(^{35,36}\) and does not detect any other \textit{BRAF} mutation. The impact on therapy selection and patient outcomes of more sensitive and specific DNA sequencing assays is under investigation.

\textbf{Only \textit{BRAF} Inhibitors Have Evidence of Activity in Active Brain Metastases}

Only four clinical trials of small molecule targeted therapies have included patients with active and progressing brain metastases; the phase I/II study of dabrafenib,\(^ {37}\) which included a cohort of 10 patients with asymptomatic untreated brain metastases, the phase II study of dabrafenib in 172 patients with asymptomatic active brain metastases (untreated or treated but progressed),\(^ {1}\) a pilot study of vemurafenib in 24 patients with heavily pretreated but progressed brain metastases\(^ {38}\) and the ongoing phase II study of vemurafenib in patients with active brain metastases (NCT01378975). Gadolinium enhanced magnetic resonance imaging (MRI) was used for assessment of response in the brain in all studies. There are several case reports of activity of \textit{BRAF} inhibitors in brain metastases,\(^ {39,40}\) including V600R \textit{BRAF}-mutant melanoma metastatic to the brain.\(^ {41}\) The combination of dabrafenib and the MEK inhibitor trametinib has a superior RR and PFS rate compared with single agent dabrafenib in metastatic melanoma,\(^ {42}\) but the combination has not been studied in active brain metastases.

The first report of activity of \textit{BRAF} inhibitors for patients with melanoma brain metastases was in 10 patients with V600E (\(n = 9\)) or V600K (\(n = 1\)) melanoma, and asymptomatic previously untreated brain metastases treated with dabrafenib (150 mg twice daily, the recommended phase II dose) as a separate expansion phase of the phase I/II study.\(^ {37}\) Thirty percent of patients had more than three brain metastases, and the minimum size requirement was greater than or equal to 3 mm (size ranged from 3 to 15 mm). Nine patients had a reduction in the size of the brain metastases and four had a complete response in the brain.

These results led to the largest trial ever conducted in active melanoma brain metastases (\(\geq 5 \text{ mm to} \leq 40 \text{ mm}\)) in 172 patients treated with 150 mg twice daily of dabrafenib (BREAK-MB) with V600E or V600K mutation-positive melanoma divided into two cohorts: patients in cohort A had not received any prior local therapy for brain metastases and cohort B had disease progression in the brain following local therapy with surgery, whole brain radiotherapy, or stereotactic radiosurgery.\(^ {1}\) Responses were seen in both cohorts, and in both V600E and V600K \textit{BRAF} mutation positive melanoma. However, the primary end point was the investigator-assessed overall intracranial response rate (OIRR) of patients with the V600E mutation, which were 39% and 31% in cohort A and B, respectively. The V600E intracranial disease control rate (DCR = complete response + partial response + stable disease) was 81% and 89% in cohorts A and B, respectively. For patients with the V600E \textit{BRAF} mutation, the median PFS was 16 weeks in both cohorts, and median OS was 33 and 31 weeks in cohorts A and B, respectively, which compares favorably with the only other large study of chemotherapy in a similar patient population with unknown \textit{BRAF} mutation status and active melanoma brain metastases\(^ {2}\) (median OS 9.5 weeks for those who had received prior chemotherapy and 15.6 weeks for those who had not). For patients in cohorts A and B with the V600K \textit{BRAF} mutation (\(n = 33\)), the OIRRs were 7% and 22%, respectively, the DCRs were 33% and 50%, the median PFS was 8 and 16 weeks, and the median OS was 16 and 22 weeks, respectively. It was expected that patients with V600K might not respond as well as those with V600E \textit{BRAF}-mutant melanoma, given the lower RR and PFS rate for these patients in the phase II study of dabrafenib in patients without brain metastases.\(^ {43}\) However the results for the untreated V600K cohort were particularly poor and should be interpreted with caution, given the small size of the cohort (15 patients) and the challenges of reliably measuring intracranial metastases.\(^ {44}\)

Interestingly, the brain is not necessarily the first site of progression. In a study of 23 patients with active brain metastases from the phase I/II and phase II studies of dabrafenib discussed above,\(^ {2,37}\) 20 were evaluable for progression.\(^ {45}\) Six (30%) progressed in the brain alone, six (30%) progressed at an extracranial site alone and eight (40%) progressed both in the brain and at extracranial sites. No patient progressed as a result of a new lesion alone, 9/20 progressed in existing lesions only, and 11/20 progressed as a result of existing and new lesions.

After the encouraging results of the phase I/II study of dabrafenib, vemurafenib (960 mg twice daily) was studied in 24 patients with V600E \textit{BRAF} mutation-positive melanoma (Roche Cobas test discussed above) and symptomatic and progressing yet previously treated brain metastases.\(^ {38}\) These patients had a very poor prognosis at enrolment into this study and there were no maximum or minimum size criteria for the brain metastasis. Of the 19 patients with measurable disease at baseline, only three (16%) had a confirmed partial response in the brain, whereas 13/21 patients (62%) had extra-cranial responses. The median PFS in the brain was 4 months and for other sites was 4.6 months. The median OS for all patients was 5 months. A phase II study of vemurafenib in patients with Roche Cobas V600 \textit{BRAF} mutation-positive melanoma and active brain metastases (NCT01378975) has nearly completed accrual and includes both symptomatic and asymptomatic patients, as well as untreated or previously treated patients.

There have been case reports of activity of dabrafenib and vemurafenib in V600R \textit{BRAF} mutation-positive metastatic melanoma, with dramatic symptomatic relief of neurological symptoms in patients with active brain metastases treated with dabrafenib.\(^ {41}\) There is a case report of neoadjuvant use of vemurafenib,\(^ {40}\) and indeed a subset of patients in cohort A of the BREAK-MB study were treated with surgical excision at progression in the brain.\(^ {45}\)
It is not clear whether there is a difference in activity between dabrafenib and vemurafenib in brain metastases although a recent preclinical study suggests there may be higher concentrations of dabrafenib versus vemurafenib in mouse brain over plasma after a single oral dose of drug. It is unlikely these drugs will be compared in a head-to-head study. Interestingly, the rates of various toxicities as measured in the phase I, II and III studies of these drugs differ—liver toxicity, arthralgia, and photosensitivity appear more common with vemurafenib, fever is more frequent with dabrafenib, and the latter has three active long-acting metabolites, one of which is lipophilic and may cross the intact blood–brain barrier. A study of neoadjuvant dabrafenib in resectable brain metastases is planned to clarify the mechanism of brain penetration.

Other combinations of small molecule targeted therapies that inhibit several levels of the activated pathway (e.g., BRAF and MEK) or linked pathways (e.g., MEK and PI3K/mTOR) are under investigation for BRAF-mutant and other molecular subtypes of melanoma. Patients with active brain metastases should be included in these trials as a subgroup to be separately analyzed. Triple therapies, for example, doublets of small molecule targeted therapies combined with immunotherapy or triplets of small molecule targeted therapies, should be considered for study in all melanoma subtypes, as there is evidence that delaying resistance with combinations is more effective than adding a therapy sequentially once resistance has occurred.

**CONCLUSION**

The treatment of patients with melanoma metastatic to the brain is an ideal example of the need for multidisciplinary team practice and research protocols to optimize and improve the outcome of patients with this life-limiting complication, especially in this disease that is rising in incidence in many parts of the world. From local therapies with surgery and radiotherapy to systemic agents with proven activity in brain metastases, the stage is set for finding the best and safest sequences and combinations. The advent of molecularly defined disease subsets and their targeted therapies as well as effective immunotherapies with potentially durable benefits has provided an opening to further investigations, raising the bar and the hope that with additional advances in the biology and therapy of melanoma, even patients with melanoma brain metastases will soon achieve the status of cancer survivors.

**Disclosures of Potential Conflicts of Interest**

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**References**


