Chapter

Advances in the Systemic Treatment of Melanoma Brain Metastases

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Abstract

It is estimated that up to 40% of patients with distantly metastatic melanoma develop clinically detectable brain metastases. The prognosis for these patients is very poor with an historical median overall survival of approximately 4 months. Targeted surgical and radiotherapy-based approaches can improve outcomes in certain patients. Over the past decade, the efficacy of systemic treatments for metastatic melanoma has improved with the development of anti-CTLA-4 and anti-PD-1-based immunotherapies (checkpoint inhibitors) that provide survival benefit. In patients whose melanoma expresses a V600 BRAF mutation which activates the MAPK signaling pathway, the targeted inhibition of BRAF and MEK also confers survival benefit. These immunomodulatory and molecular-targeted approaches have recently been studied in patients with melanoma brain metastases to determine efficacy of these approaches in treating the brain metastases. Advances in use of chemotherapy, immune checkpoint inhibitors, and BRAF plus MEK inhibitors to treat melanoma brain metastases are discussed.

Keywords: melanoma, brain, metastases, immunotherapy, PD-1, BRAF, targeted therapy

1. Introduction

Melanoma arises through the accumulation of genetic aberrations in melanocytes which lead to uncontrolled cellular proliferation, resistance to apoptosis, and escape from immune surveillance. Melanoma has the potential to metastasize distantly through hematologic and lymphatic channels. When distant spread is present, the melanoma is classified as stage IV. The American Joint Committee on Cancer (AJCC) eighth edition subcategorizes stage IV melanoma into four prognostic subgroups with the worst prognostic group (stage IV M1d) defined by the presence of brain metastases [1]. Melanoma is the third most common type of cancer to metastasize to the brain following breast and lung cancer. It is estimated that 10–40% of patients with stage IV melanoma eventually develop clinically detectable brain metastases [2]. In autopsy series, a high incidence of subclinical metastasis is noted as over 50% of patients have brain metastases [2].

2. Management of melanoma brain metastases

Brain metastases can lead to morbidity with the development of seizures, cerebral edema, and neurologic symptoms reflective of the part of the brain

involved. However, several retrospective analyses have shown that the majority of patients with brain metastases are asymptomatic [2]. While metastases can develop in any part of the brain, the incidence is not evenly distributed. A study evaluating the location of 115 brain metastases showed that 43.5% were located in the frontal lobe with only 8.6% in the cerebellum and less than 1% in the hippocampus [3]. Similarly, a retrospective single center analysis of 6064 brain metastases in 632 cancer patients revealed that fewer than 1% of the metastases develop in the hippocampus, while the distribution is highest in the frontal lobe (31.6%) [4].

The prognosis for patients with melanoma metastatic to the brain is very poor with an historical median overall survival of approximately 4 months [5]. However, prognosis is heterogeneous with a small subset of patients demonstrating greater than 3-year survival despite the development of brain metastases. A retrospective review of 702 patients with melanoma-related brain metastases identified a small subset of patients who survived greater than 3 years. These patients were largely categorized by the presence of an isolated brain metastasis that was treated surgically [5].

Several retrospective studies have attempted to associate clinical and pathological characteristics with the development of brain metastases and with the outcome following the development of brain metastasis. A review of clinical features and survival outcome in melanoma patients who enrolled in any of 12 clinical trials at a single cancer center identified factors prognostic for overall survival [6]. About 44% of 743 chemotherapy naive melanoma patients developed brain metastases with the median overall survival following diagnosis of brain metastases being only 4.3 months. Age at the time of diagnosis of brain metastases did not predict for survival outcome. However, the year of diagnosis was prognostic as patients diagnosed prior to 1996, the midpoint for inclusion of these patients, had worse survival than patients diagnosed after the start of 1996 (4.14 months vs. 5.92 months, $p = 0.01$). While prognosis has improved over time, survival outcomes remain very poor. Other prognostic factors included the number of brain metastases with a median survival for patients with one to three metastases of 5.92 months as opposed to 3.52 months for those with more than three brain metastases (HR 1.57, $p = 0.001$). The presence of leptomeningeal involvement conferred an even worse prognosis with a median overall survival of only 1.2 months. The development of brain metastases after receiving systemic therapy for extracranial metastases conferred worse overall survival compared to developing the brain metastases before or synchronous to extracranial metastases (HR 1.78, $p < 0.0001$). Therefore, in multivariate analysis, the year of diagnosis, number of parenchymal brain metastases, and timing of metastases relative to extracranial metastases were significantly associated with overall survival. Another retrospective analysis of 49 patients with melanoma metastatic to the brain identified as part of a melanoma database collected from 1998 to 2012 associated survival to the presence or absence of symptoms, number of parenchymal brain lesions (one vs. two or more), and response to chemotherapy [2]. A multivariate analysis of 89 melanoma patients from a single institution who developed brain metastases and who were part of a larger prospectively accrued cohort of 900 melanoma patients revealed that the presence of neurologic symptoms and extracranial metastases predicted for worsened survival [7].

The modality used to treat brain metastases may reflect prognosis. The median survival of 686 patients with melanoma and cerebral metastases treated at the Sydney Melanoma Unit between 1985 and 2000 was 8.9, 8.7, 3.4, and 2.1 months, respectively, in patients treated with surgery plus postoperative radiotherapy, surgery alone, radiotherapy alone, and supportive care alone [8]. While outcomes differed in patients receiving surgery and/or radiotherapy compared to best supportive care, the differences may reflect patient selection based on performance

status, extent of extracranial metastases, comorbidities, and number, size, and location of brain metastases. These features impact the decision to recommend surgery or radiation therapy. Furthermore, the size, location, and number of metastases impact the ability to perform stereotactic radiosurgery as opposed to whole brain radiation therapy.

Overall survival of stage IV melanoma patients also is determined by the effectiveness of systemic therapy. Systemic treatment options have improved over the past decade through the development of efficacious immunotherapies and molecularly targeted approaches translating into improvements in survival. Prior to 2011, the only two systemic therapies Food and Drug Administration (FDA) approved for the treatment of stage IV melanoma were the cytotoxic chemotherapy dacarbazine (DTIC) and the cytokine immunotherapy high-dose interleukin-2 (HD-IL2). DTIC is an intravenously administered alkylating agent that confers responses in 5–20% of stage IV melanoma patients but the responses are largely partial and not durable [9]. Treatment with HD-IL2 confers a 16% response rate with 5% of patients developing complete durable responses [10]. The potential for HD-IL2 to cause capillary leak syndrome and cerebral edema limits the ability to use this treatment in patients with brain metastases. Neither HD-IL2 nor DTIC have been shown in randomized studies to confer overall survival benefit.

Temozolomide is an oral alkylating agent that is metabolized to MTIC the same active agent that dacarbazine is metabolized to. Treatment of stage IV melanoma patients randomized to treatment with dacarbazine or temozolomide showed equivalency in terms of response rate and survival [11]. Temozolomide has better penetrance of the central nervous system. A retrospective analysis comparing CNS relapse rate in patients who responded to treatment with temozolomide versus dacarbazine showed that temozolomide-treated patients had significantly fewer CNS relapses [12]. This suggests that temozolomide may prevent development of brain metastases in melanoma patients. To assess efficacy of temozolomide in treating brain metastases in melanoma patients where the metastases did not require immediate radiation therapy, a phase II study was performed treating 151 patients with temozolomide at dose of 150 milligrams per meter squared (mg/m^2) per day for 5 days in row every 28 days. Among the 117 patients who did not receive prior systemic therapy, the response rate was 7%, while 29% had stabilization of the brain metastases. Of the 34 patients who received prior systemic therapy, only 1 patient responded and 6 patients developed stable disease in the brain [13]. Therefore, while temozolomide demonstrates efficacy in treating melanoma brain metastases, the benefit is limited and seen only in a small subset of patients.

An improved mechanistic understanding of the positive and negative regulation of the immune system through multiple immune-mediated checkpoints has led to the development of more efficacious treatment for stage IV melanoma patients. Since 2011, the FDA has approved for treatment of stage IV melanoma an inhibitor of the negative regular cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), ipilimumab, and two inhibitors of the negative regulator programmed death-1 (PD-1), nivolumab and pembrolizumab. Ipilimumab is administered intravenously at a dose of 3 milligrams per kilogram (mg/kg) every 3 weeks for a total of four doses. Nivolumab is administered intravenously at a flat dose of 240 mg intravenously every 2 weeks or 480 mg every 4 weeks. Pembrolizumab is administered at a dose of 200 mg every 3 weeks.

T-cell activation requires binding of the T-cell receptor to an antigen-derived amino acid sequence complexed to MHC molecules on antigen presenting cells. For T-cell activation, costimulatory interactions are necessary with binding of CD28 on the T-cell to B7 on the antigen presenting cell. CTLA-4 is expressed on T-cells and binds to B7 with higher affinity that CD28 leading to disruption of CD28-B7 interaction thereby

dampening the immune response. Ipilimumab is a fully human IgG1 monoclonal antibody that binds to CTLA-4 in an inhibitory fashion enhancing T-cell priming and decreasing suppressor T-cell activity [14]. A phase III study that randomized previously treated stage IV melanoma patients to treatment with ipilimumab alone at a dose of 3 mg/kg intravenously every 3 weeks for four treatments, a peptide vaccine GP-100 alone, or the combination of ipilimumab plus the vaccine demonstrated a statistically significant improvement in overall survival following ipilimumab treatment [14]. The median overall survival was 10.1 months in the ipilimumab group as opposed to 6.4 months in the gp100 vaccine group (hazard ratio for death of 0.68; p-value < 0.001). A pooled analysis of long-term data from 12 phase II and phase III studies encompassing 1861 melanoma patients treated with ipilimumab showed a mean overall survival of 11.4 months with a survival rate at 3 years of 22% [15].

Nivolumab and pembrolizumab are monoclonal antibodies which inhibit the activity of PD-1 leading to increased T-cell activity in the tumor microenvironment [16, 17]. PD-1 is expressed on the surface of tumor infiltrating T-cells and binds to PD-L1 which is aberrantly expressed on tumor cells leading to functional inhibition of the T-cells. Both of the PD-1 inhibitors confer 35–40% response rates and lead to significantly improved survival when compared to outcomes following ipilimumab treatment [18, 19]. The Keynote-006 phase III study randomized 834 melanoma patients to treatment with pembrolizumab or ipilimumab. Median overall survival with a median follow-up of 22.9 months was not reached in the pembrolizumab-treated patients as opposed to 16 months in the ipilimumab-treated patients ($p = 0.0009$). Twenty-four-month overall survival was 55 and 43% in the pembrolizumab and ipilimumab groups, respectively ($p = 0.0009$) [18].

CTLA-4 and PD-1 inhibitors modulate different parts of the immune system, and preclinical murine models demonstrate synergistic activity following concurrent CTLA-4 and PD-1 blockade [20]. The CheckMate 067 study randomized 945 advanced melanoma patients to placebo-controlled treatment with ipilimumab monotherapy, nivolumab monotherapy, or the combination of ipilimumab plus nivolumab [21]. Ipilimumab-treated patients received ipilimumab at dose of 3 mg/kg every 3 weeks for a total of four treatments. Nivolumab-treated patients were treated with 3 mg/kg nivolumab every 2 weeks. Patients receiving combination therapy were treated with ipilimumab at a dose of 3 mg/kg plus nivolumab 1 mg/kg every 3 weeks for a total of four doses and then nivolumab alone every 2 weeks at a dose of 3 mg/kg. Objective responses were noted in 58, 45, and 19% of combination therapy, nivolumab monotherapy- and ipilimumab monotherapy-treated patients, respectively. With a minimum 4 year follow-up, the median overall survival was not reached in the combination group, was 36.9 months in the nivolumab group, and was 19.9 months in the ipilimumab group.

Inhibition individually or in combination of the CTLA-4 and PD-1 checkpoints leads to survival benefit for stage IV melanoma patients. However, the initial clinical trials excluded patients with untreated brain metastases. To determine the antimelanoma efficacy of these immune modulatory approaches in patients with untreated brain metastases, clinical trials were developed specifically enrolling melanoma patients with untreated brain metastases.

A phase II study of patients with melanoma and untreated brain metastases treated with ipilimumab showed intracranial responses in 8 of 51 (16%) of asymptomatic patients who did not need steroids and 1/21 (5%) of patients requiring steroids because of perimetastasis edema or neurologic symptoms related to the metastases. Median overall survival remained poor being 7 months for patients not needing steroids and 3.7 months for patients requiring steroids [22]. The overall survival assessment also reflects the time period when the study was conducted prior to availability of anti-PD-1 immunotherapies.

A single center phase II study treated 18 stage IV melanoma patients with at least 1 untreated or progressive brain metastasis between 5 and 20 mm in diameter and without associated neurologic symptoms to treatment with pembolizumab at a dose of 10 mg/kg every 2 weeks. Four of the patients (22%) developed a partial response in the brain. The responses were durable lasting at least 4 months, and at the time of data, cutoff was ongoing in all responders [23].

To determine the intracranial efficacy of combined CTLA-4 and PD-1 blockade, a phase II multicenter study, CheckMate 204, treated melanoma patients who had at least one measurable nonirradiated brain metastasis with a diameter between 0.5 and 3 cm and with no associated neurologic symptoms to combined treatment with nivolumab and ipilimumab [24]. The primary endpoint was intracranial clinical benefit defined as complete or partial response or stable disease at 6 months. Brain metastases were felt to not need immediate resection or radiosurgery and patients did not receive steroid treatment for at least 10 days prior to treatment initiation. The nivolumab was administered at dose of 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks for four doses followed by single agent nivolumab at dose of 3 mg/kg every 2 weeks until disease progression or prohibitive toxicity. With a median of 14 month follow-up, the rate of intracranial benefit in the 94 patients who were followed for at least 6 months was 56% with a 26% complete response rate and 30% partial response rate. About 2% of patients had intracranial stable disease that lasted greater than 6 months. About 64% of patients did not experience intracranial progression of brain metastases 6 months after treatment initiation. The extracranial clinical benefit rate was 56% similar to the intracranial rate. As expected, the combination immunotherapy treatment led to a 55% rate of high-grade toxicity felt related to the immunotherapy. Treatment-related adverse events involving the central nervous system were seen in 36% of patients and high-grade CNS toxicity developed in 7% of the patients. The most common treatment-related nervous system toxicity of any severity was headache affecting 22% of patients with 3% having severe headaches.

Additional evidence that anti-PD-1 immunotherapy has efficacy in treating active brain metastases comes from the results of a phase II study conducted at four sites in Australia. Melanoma patients with asymptomatic brain metastases that did not receive prior localized treatment were randomized to systemic therapy with nivolumab or combined nivolumab plus ipilimumab blockade. Efficacy was appreciated in both cohorts with intracranial response rates of 20 and 46% seen in nivolumab alone versus combination therapy-treated patients, respectively [25].

Treatment of stage IV melanoma has improved not only through the use of immunotherapy but also through the use of molecular-targeted therapies. Approximately, 40% of melanomas select for an activating mutation in the protein BRAF which is a component of the mitogen-activated protein kinase (MAPK) signaling pathway. The MAPK signaling pathway is a cascade initiated by extracellular signals binding to cell membrane receptors activating RAS which then activated CRAF and BRAF leading to downstream activation of MEK and ERK. Greater than 90% of BRAF mutations in melanoma are activating hotspot mutations present at position 600 with the most common being a V600E mutation. Activation of BRAF leads to melanoma proliferation and survival due to enhanced signaling through the MAPK pathway. Three different combinations of BRAF plus MEK inhibitors (the BRAF inhibitors dabrafenib, vemurafenib, and encorafenib combined with the MEK inhibitors trametinib, cobimetinib, and binimetinib, respectively) are FDA approved for the treatment of unresectable melanoma expressing a V600E BRAF mutation [26–28]. Randomizing 947 previously untreated patients with unresectable melanoma to treatment with dabrafenib plus placebo or dabrafenib plus trametinib as part of an international phase III study demonstrated overall survival

benefit favoring the dual inhibitor approach [29]. Treatment with dabrafenib monotherapy conferred a 53% response rate, while dabrafenib plus trametinib treatment led to a 69% response rate. Efficacy is limited by the development of resistance with median progression free survival being 8.8 and 11 months for patients treated with dabrafenib monotherapy or combination therapy, respectively. Two-year overall survival was 42% for patients treated with BRAF inhibition alone and improved to 51% for patients treated with concurrent BRAF and MEK inhibition [29]. Eligibility requirements for the trial required definitive treatment of any preexisting brain metastases with confirmed stability of at least 12 weeks. Patients with untreated or unstable brain metastases were excluded from enrollment.

To determine the ability of combined BRAF and MEK inhibition to treat progressive brain metastases in patients with melanoma expressing a V600 BRAF mutation, a multicenter international phase II (COMBI-MB) study was performed which treated four cohorts with dabrafenib plus trametinib [30]. The four cohorts were: A. Patients with melanoma expressing a V600E BRAF mutation and with asymptomatic brain metastases, no prior localized therapy to the brain metastases, and an ECOG performance status 0 or 1. B. Patients with melanoma expressing a V600E BRAF mutation and asymptomatic brain metastases and an ECOG performance status 0 or 1 but who received prior localized therapy to the brain metastases. C. Patients with melanoma expressing a V600 D/K/R mutation and asymptomatic brain metastases and ECOG performance status of 0–1 with or without prior localized treatment of the brain metastases. D. Patients with melanoma expressing a V600 D.E/K/R BRAF mutation and with symptomatic brain metastasis and an ECOG performance status of 0, 1, or 2. The primary endpoint was investigator-assessed intracranial response in the first patient cohort. Intracranial response in the other three cohorts was a secondary endpoint. With a median follow-up of 8.5 months, the intracranial response rate in the 76 patients enrolled in cohort A was 58%. The intracranial response rates in the 16 patients enrolled in cohort B, 16 patients enrolled in cohort C, and 17 patients enrolled in cohort D were 56, 44, and 59%, respectively. Therefore, clinical benefit intracranially was appreciated in all four cohorts even in patients with worsened performance status (ECOG 2) and symptomatic brain metastases. Longer follow-up is needed to determine effects on survival and long-term intracranial metastases control rates.

While systemic therapies can lead to intracranial efficacy in a subset of metastatic melanoma patients, multimodality approaches may lead to further improvement in clinical outcome. A meta-analysis performed in April 2017 identified six retrospective studies which compared treatment with stereotactic radiotherapy alone to radiotherapy plus ipilimumab [31]. Of the 411 patients identified, 128 were treated with a combined radiotherapy and immunotherapy approach, while 283 received radiotherapy alone. Combination therapy significantly improved survival (HR 0.74, $p = 0.04$) without significantly increasing the incidence of adverse events. The authors conclude that combining stereotactic radiosurgery (SRS) is safe and effective treatment option.

Given the survival benefits of initial immunotherapy treatment with a PD-1 inhibitor as opposed to ipilimumab in patients with melanoma who have brain metastases, one may expect that SRS plus a PD-1 inhibitor may incrementally improve intracranial response and survival compared to treatment with SRS plus ipilimumab. A study of patients who received SRS plus a PD-1 inhibitor had a median overall survival of 20.4 months as opposed to 7.5 months in patients treated with SRS plus CTLA-4 blockade [32]. A single institution retrospective study assessed the intracranial metastasis control rate in patients treated with SRS for melanoma brain metastases within 3 months of receiving treatment with anti-PD-1 immunotherapy, anti-CTLA-4 immunotherapy, BRAF plus MEK inhibitor targeted

therapy, anti-BRAF monotherapy, or cytotoxic chemotherapy [33]. The 12-month distant melanoma metastasis control rates were 38, 21, 20, 8, and 5%, respectively. Local melanoma brain metastasis control rates were similar among the groups. Combining systemic therapy with SRS was overall well tolerated without significant increase in neurotoxicity. Multivariate analysis showed improved overall survival in patients treated with immunotherapy or BRAF targeted therapy when compared to those treated with cytotoxic chemotherapy.

3. Conclusions

Treatment of patients with melanoma brain metastases should be based upon a personalized treatment plan that may include multimodality approaches utilizing systemic therapy, surgery, and radiation therapy. The treatment approach will be impacted by multiple factors including but not limited to comorbidities, performance status, number, size, and location of brain metastases, CNS metastasis-related symptoms, steroid needs, prior therapy, the presence or absence of a BRAF mutation, and patient preference. Recent advances identifying immunomodulatory and BRAF-targeted therapies with intracranial efficacy have led to outcomes that are better than historically expected through the use of anti-PD-1 monotherapy, combined anti-CTLA-4 plus anti-PD-1 blockade, and if patients with a V600 BRAF mutation combined BRAF and MEK inhibition.

Conflict of interest

Advisory Board Member for Seattle Genetics, Regeneron, Array Biopharma, EMD Serono, and Castle Biosciences. Consultant for Aspyrian Therapeutics.

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