Chapter

Intracranial Metastatic Melanoma

Hiu K.C. Tang and Joon W. Ho

Abstract

Central nervous system (CNS) metastases are a common manifestation of malignant melanoma, with a median overall survival of as little as 4.7 months based on a study of patients diagnosed between 1986 and 2004 prior to the era of effective systemic therapy. Yet most of the clinical trials exclude patients with intra-cranial metastases. CNS involvement often causes neurological deficits and functional impairment. Localised therapies, such as surgical excision and stereotactic radiotherapy are applicable to only a minority of patients. There are evidences of clinical benefits for immunotherapy than best supportive care and when given alongside radiotherapy provides a better overall survival than radiotherapy alone. This chapter evaluates the efficacy and toxicity of these treatments against advanced melanoma patients with brain metastases.

Keywords: melanoma, metastatic melanoma, melanoma brain metastases MBM, immunotherapy, radiotherapy, stereotactic radiotherapy, brain metastases, CNS metastases

1. Introduction

Central nervous system metastases are a common and often lethal manifestation of malignant melanoma, with a median overall survival of as little as 4.7 months based on a study of patients diagnosed between 1986 and 2004 prior to the era of effective systemic therapy [1]. Although both cutaneous and mucosal melanomas have a high propensity for CNS dissemination, this is almost unheard of with uveal melanoma despite the close anatomical proximity of the eye and brain [2]. CNS involvement often causes neurological deficits and functional impairment. Localised therapies, such as surgical excision and stereotactic radiotherapy, are applicable to only a minority of patients. However, stereotactic radiation therapy is able to overcome the relative radio-resistance of melanoma by delivering extremely high doses of radiotherapy with little damage to surrounding brain tissue [3]. It is also increasingly appreciated that stereotactic radiotherapy may drive immunogenic cell death and this can lead to regression of non-irradiated lesions via immune priming and the 'abscopal' effect [4]. Radiotherapy can upregulate tumoural PD-L1 expression and can lead to increased T-cell infiltration of tumours with increased proinflammatory cytokine levels [5, 6]. This potential synergistic interaction between stereotactic radiotherapy and immunotherapy could be exploited and this is being explored in current clinical trials (PERM trial NCT02562625). Symptomatic patients require corticosteroid therapy to reduce peri-lesional vasogenic oedema and control neurologic symptoms in

the short-term. It is suspected that high-dose corticosteroids prevent immune activation and attenuate the benefit of immune checkpoint blockade.

The blood brain barrier comprises of endothelial cells, astrocytes and pericytes. Usually the passage of molecules from blood to the brain parenchyma is limited under physiological conditions [7]. However, research has shown that activated T-cells can cross the blood–brain barrier - raising the possibility of treatment using immunotherapy [8]. The endothelial cells of the blood brain barrier in brain metastases are thought to be able to initiate an inflammatory cascade that activates immune cells [9]. Berghoff et al. have shown, using immunohistochemical analysis of melanoma brain metastases, that three-quarters of these lesions exhibit CD3+ tumour-infiltrating-lymphocytes and tumour cells were PD-1 positive in half of cases [10] (**Table 1**).

In contrast to carcinomas, such as breast and lung, melanoma brain metastases display a diffuse lymphocytic infiltrate throughout the tumour mass as opposed to a stromal infiltrate [11].These pathologic data provide strong evidence that adaptive immune responses can be active in the distinct microenvironment of the brain.

Lepto-meningeal metastases are a deadly and feared complication of malignant melanoma and also occur commonly in breast and lung cancers. They are common in haematological malignancy but much rarer in solid tumours where they usually manifest in the presence of advanced metastatic disease in multiple organ systems. Lepto-meningeal metastasis, also sometimes known as neoplastic meningitis, occurs when cancer cells disseminate to the arachnoid and/or pia mater covering the central nervous systemic tissue in the brain and/or spinal cord. They typically cause rapidly-progressive, and often fatal, neurological deficits due to infiltration of cranial nerves, spinal cord and nerve root compression (radiculopathy), symptoms of meningitis and raised intracranial pressure. Treatment is usually supportive and there is very little evidence for any anti-cancer treatment being effective although intra-thecal chemotherapy has been used as has cranio-spinal radiotherapy which is poorly tolerated in adults.

The vast majority of clinical trials for metastatic melanoma exclude patients with brain metastases, and certainly those with symptomatic lesions. Therefore, there is a paucity of clinical evidence to guide decision making in terms of therapeutic options for this patient population. The current clinical evidence base comprises small, retrospective studies. The majority of patients with metastatic melanoma will develop brain or lepto-meningeal metastases at some point in their disease trajectory [12], therefore this chapter will provide a good summary to help clinicians to understand and manage this group of patients.

Drug	Target	FDA approval date	Treatment schedule
Ipilimumab	CTLA-4	March 2011	3 mg/kg administered intravenously every 3 weeks
Pembrolizumab	PD-1	December 2014	2 mg/kg administered intravenously every 3 weeks or 200 mg every 3 weeks/400 mg every 6 weeks
Nivolumab	PD-1	September 2014	3 mg/kg administered intravenously every 2 weeks or 240 mg every 2 weeks/480 mg every 4 weeks

Table 1.
Immunotherapy and treatment schedule.

2. Immune checkpoint inhibitors for metastatic melanoma

The therapeutic options for patients with metastatic melanoma, previously restricted to dacarbazine chemotherapy (DTIC, alkylating agent) [13] and immunotherapy with high-dose intravenous interleukin-2 [14], have expanded to include immune checkpoint inhibitors and BRAF targeted therapy in recent times and the outlook has become somewhat less guarded with long-term survival being achieved in a proportion of patients. Importantly, in terms of randomised, comparative large-scale clinical trials no such evidence exists for DTIC or IL-2 despite FDA approval in 1975 and 1998 respectively. Immune checkpoint inhibitors are monoclonal antibodies that disrupt the CTLA-4/CD28 and PD-1/PD-L1 interactions, and by so doing, lead to improvements in T-cell priming by dendritic cells and cytotoxic T-cell effector function respectively. These treatments, such as ipilimumab (anti CTLA-4) and pembrolizumab (anti-PD-1), attenuate T-cell inhibitory signals and generate enhanced, sustained and powerful anti-melanoma immune responses that can be associated with durable disease control. It is noteworthy that the first systemic therapy proven to confer a survival advantage in metastatic melanoma was the anti CTLA-4 antibody ipilimumab and this was the first time in a randomised clinical trial that an increase in overall survival had been achieved in this disease [15]. The comparator group in this trial was treatment with an HLA-A2 restricted gp100 peptide vaccine not placebo and patients had received prior chemotherapy or IL-2. Toxicities of ipilimumab can be severe and unpredictable and in the pivotal study, the treatment-related death rate was 2.1% although this has diminished over time as physicians' experience and patient education improves. However, with ipilimumab monotherapy only approximately one in five patients achieve long-term overall survival and patients with high volume metastatic disease, elevated serum lactate dehydrogenase levels, low serum albumen, rapidly progressive course and brain metastases seldom derive benefit benefit [16]. In previously untreated metastatic melanoma patients, high-dose ipilimumab monotherapy (10 mg/kg) in combination with dacarbazine chemotherapy outperformed chemotherapy in terms of overall and progression-free survival and to a lesser extent objective response rate [17]. From the clinical perspective, the United Kingdom [18] National Institute for Health and Care Excellence (NICE) approved Ipilimumab for the treatment of metastatic melanoma in 2012 [19], followed by Pembrolizumab and Nivolumab that target the PD-1 axis in 2015. Combination immunotherapy with concurrent ipilimumab and nivolumab has also been available since 2017 for the treatment of metastatic melanoma with favourable outcome compared to ipilimumab monotherapy. This clinical trial was, however, not sufficiently powered to definitively determine if combination immunotherapy was superior to nivolumab monotherapy [20]. Ipilimumab and nivolumab can achieve objective radiologic responses rates of approximately 60% and the likelihood of 5-year overall survival is 53%. These agents, especially anti PD-1 monotherapy, are better tolerated than chemotherapy [21], and demonstrated a better progression-free survival outcome with lower toxicities [22].

In a randomised Phase II clinical trial, patients with ipilimumab and targeted therapy (if BRAF mutant) refractory advanced melanoma had improved progression-free survival when treated with pembrolizumab compared with investigators choice of cytotoxic chemotherapy with a likelihood of 6-month progression-free survival of 34% versus 16%. Serious treatment-related adverse events were far less common with immunotherapy – 11% versus 26% with chemotherapy. The likelihood of radiologic response was 5 times higher with pembrolizumab (21%) than chemotherapy (4%) [23].

Selection of patients who are most likely to benefit from immune checkpoint blockade remains largely an elusive goal, although potential biomarkers are emerging and these include a high somatic mutational burden with resultant abundant neo-epitopes for immune recognition [24], a greater diversity within the faecal microbiome and the presence therein of specific bacterial species [25], the level of PD-L1 expression on tumour cells and tumour-associated leukocytes [26] and density of CD8 T-cell tumoural infiltrate [27]. Identification of predictive biomarkers for immunotherapy would allow futile treatment and associated toxicities to be avoided in patients unlikely to benefit.

Ipilimumab was the first checkpoint inhibitor to be used in patients with CNS metastases. In 2012, Margolin et al. published a phase 2 study involving 72 melanoma patients with CNS metastases who received intravenous ipilimumab. Intra-cranial disease control (defined as objective response or stable disease for at least 3 months) was achieved in 24% of the patients who were asymptomatic and not receiving corticosteroids and 10% in those with symptomatic, steroid-requiring lesions [28]. However, in a real-world study of ipilimumab for metastatic melanoma patients in the UK, median overall survival for those with brain metastases was 3.5 months [16]. This was followed by another open-label phase 2 trial using intravenous Pembrolizumab [29]. Of 18 patients enrolled into that study, 22% achieved disease control intracranially. Recently, Tawbi et al. published in the New England Journal of Medicine a larger trial involving 94 patients being treated with combination immunotherapy [30]. In patients with small (less than 3 cm) asymptomatic brain metastases, the intracranial clinical benefit rate (objective response or stable disease for at least 6 months) was 57%, there were also higher chances of grade 3 and 4 toxicities (55%). The rate of radiologic complete response within the brain is notable at 26% and this may be a surrogate marker of long-term survival. Intra-cranial responses were achieved rapidly with a median time to response of 2.3 months. The rate of intra-cranial response was in fact slightly numerically higher than that of extra-cranial metastases. Similar findings were noted in Long's study including patients with lesion size up to 40 mm with an intra-cranial response rate of 46% (in pre-treated patients) and 56% in systemic-therapy naïve patients and 53% of patients were free of intra-cranial progression at 6 months, using ipilimumab and nivolumab. However, combination immunotherapy was of marginal benefit in patients with progression after prior local treatment for brain metastases, neurologic symptoms or lepto-meningeal disease with a single partial intra-cranial response amongst 16 patients, only 13% were free of intra-cranial progression at 6 months and median overall survival was poor at 5.1 months (similar to that of historic patients treated with supportive care with or without whole brain radiotherapy) [31]. Ipilimumab monotherapy, even at doses as high as 10 mg/kg with associated toxicities, was also ineffective in patients with neurologic symptoms with an intra-cranial response rate of 5% and median overall survival of 3.7 months as described by Margolin et al. [28] Anti PD-1 monotherapy appears to be a valid treatment option with intra-cranial response rates of 22–26% and median overall survival of 18 months [32]. However, the durability of responses when patients have brain metastases remains uncertain, and by way of comparison, median overall survival for patients without brain metastases treated with pembrolizumab was 24 months and 38.6 months in treatment-naive patients [33].

When taken as a whole, most clinical trials of immunotherapy appear to show potential clinical benefit to melanoma patients with CNS metastases, with combination immunotherapy possibly providing the best clinical outcomes but at the cost of higher toxicity.

3. Targeted therapy for intracranial metastatic melanoma

Approximately 45 to 50% of patients with metastatic cutaneous melanoma harbour missense mutations involving the BRAF proto-oncogene (codon 600) and in these patients MAP kinase targeted therapies such dabrafenib with trametinib or encorafenib with binimetinib are a valid treatment option with high rates of radiologic response including intra-cranial responses. There is no randomised clinical trial evidence to guide the selection of 1st line systemic therapy in BRAF mutant patients, concurrent treatment with MAP kinase inhibitors and immune checkpoint inhibitors remains a highly experimental approach albeit with some early signals that combination treatment can be safely delivered and there is no clinically useful predictive biomarker for immunotherapy benefit. This remains a nuanced clinical dilemma for the oncologist and patient. RAF and MEK inhibitors have direct anti-proliferative effects on the melanoma cells and do not rely on using the immune system as an effector and their effectiveness is not blunted by immunosuppressive therapies such as corticosteroids. Therefore, many patients with melanoma brain metastasis have received targeted therapy in the first line setting with rapid tumour control and neurological improvement in the majority but durability of response is limited with typical intra-cranial progression free survival of 6–8 months. Rapid progression of metastatic disease, and particularly CNS metastases, when refractoriness to RAF and MEK inhibitors inevitably develops often leads to a sharp decline in performance status and many patients are unable to receive or benefit from immunotherapeutic approaches in the second line setting. In fact, an Australian retrospective study found that only 35% of patients discontinuing front-line targeted therapy for progressive disease went on to receive subsequent lines of systemic therapy [34]. There is also biological evidence that the increased melanoma differentiation antigen expression, enhanced dendritic cell function and increased CD8 T-cell infiltration driven by RAF–MEK inhibitors early on in treatment (2 weeks) is lost at the time of tumour progression, creating an 'immune desert' environmental that is hostile to the effects of immune checkpoint inhibitors. Therefore, where small asymptomatic brain metastases are present or when brain lesions have been treated with ablative radiotherapy, immunotherapy should be the preferred initial treatment.

4. Whole brain radiotherapy and stereotactic radiosurgery for intracranial metastatic melanoma

Radiotherapy is widely used to treat intracranial melanoma, i.e., brain metastasis, in order to control disease, alleviate symptoms and even improve survival. The two main forms of radiotherapy are stereotactic radiosurgery (SRS) and whole brain radiotherapy (WBRT). Radiotherapy planning, dose and schedule, and outcomes differs between SRS and WBRT.

4.1 Whole brain radiotherapy

As the name implies WBRT involves the irradiation of the entire intracranial contents, tumour and normal brain tissue alike. WBRT is often used when intracranial disease is extensive, such as large and/or multiple brain metastasis or leptomeningeal disease, and when radical treatment is not possible. Even with WBRT, overall survival is poor in the order of 6 months and patients are unlikely to survive long enough to

develop late toxicity of irradiation of normal brain such as neurocognitive impairment. Treatment set up typically involves a pair of opposing photon beams, from the patients left and right, which converge in the mid-plane to deliver dose throughout the cranium. 20Gy in five daily fractions and 30Gy in ten fractions over two weeks are two commonly used conventional WBRT schedules worldwide with the latter the standard schedule in the United Kingdom [35]. Clinical trials did not demonstrate any benefit in improvement of neurological function or overall survival with dose escalation over conventional WBRT [36]. Despite widespread use worldwide over decades, only two clinical trials compared WBRT with best supportive care. The first, published in 1971, reported no difference in survival between WBRT and oral prednisolone alone but the study was conducted in the pre computed tomography era and hampered by a small cohort and inadequate statistics [37]. The QUARTZ trial reported in 2016 is a multi-centred, statistically powered trial conducted on patients with non-small cell lung cancer (NSCLC) with brain metastases unsuitable for radical treatment. There was no significant difference in overall survival and quality of life between patients treated with WBRT compared to dexamethasone and best supportive care alone. Overall survival was in the order of 9 weeks which is a reflection of poor prognosis with brain metastases and the limited effect of WBRT. Subgroup analysis indicated that patients under 60 or with five of more brain metastases might derive a survival benefit from WBRT [38]. Although this trial was limited to NSCLC, it is likely that similar results will be observed with WBRT to brain metastases from other cancer types. WBRT is no longer default option in managing brain metastases unsuitable for radical treatment given the lack of clear benefit in survival or quality of life, potential toxicity and inconvenience to the patient. Instead, the clinician should consider patient factors, such as age, performance status, systemic disease status and patient wishes, in tailoring a patient-centred management plan which includes best supportive care.

4.2 Stereotactic radiosurgery

Patients with limited brain metastases such as solitary or oligometastatic metastases or small volume disease, could benefit from treatment such as neurosurgery and SRS which are more targeted and radical than WBRT. These treatment modalities can achieve superior long-term control compared to WBRT. For instance, local control rate after SRS is in the order of 70–90% at 1 year [3, 39–42]. Decision to treat with SRS or neurosurgery should be made in a multi-disciplinary setting. A brain metastasis that is solitary, accessible, or large volume causing pressure symptoms is an ideal candidate for neurosurgery whereas lesions that are small in volume, surgically inaccessible or multiple are suitable for SRS. Patient factors such as surgical and anaesthetic risk and comorbidities need to be taken into account too [43]. Outcomes after neurosurgery and SRS are similar; a meta-analysis reported non-significant difference in local control between SRS and neurosurgery at 1 year, and non-significant difference in overall survival at 1 and 2 years [44].

Unlike WBRT, SRS is focused high dose radiotherapy on the brain metastases with steep dose fall off to reduce irradiation of normal brain. Multiple brain metastases up to a total of 20 ml can be treated. The volume limit is intended to limit collateral dose to normal brain. Treatment set up involves the patients being immobilised either with a stereotactic frame or custom-made thermoplastic mask which serve to minimise movement and error during treatment delivery. Small lesions such as those under

2 cm can be treated with 20 Gy in a single fraction while larger lesions or those close to critical structures such as the brain stem or optic chiasm are treated with lower dose of 15–18 Gy in a single fraction or a fractionated schedule such as 27Gy in three fractions. Acute toxicities of SRS include headache, nausea, fatigue and risk of seizure and are often self-limiting and managed with steroids.

The addition of WBRT to SRS reduces the risk of intracranial recurrence but this does not translate into a survival benefit [3, 42, 45]. Intracranial recurrence, either with local recurrence of previously treated lesion or distant recurrence of new lesions, can potentially be treated with repeat SRS which obviates the need for upfront WBRT. WBRT also increases the risk of late neurotoxicity such as leukoencephalopathy and neurocognitive impairment which can manifest many months after treatment and result in significant detriment in quality of life and function [42, 45, 46]. Late neurotoxicity is a significant concern especially for patients who will otherwise have long term systemic disease control, such as patients with melanoma with good response to immunotherapy. The addition of WBRT to SRS is therefore not the standard of care in the United Kingdom. Instead, radiological surveillance with MRI to detect recurrence is performed after SRS [10].

4.3 Radiotherapy and immunotherapy

Radiotherapy can disrupt the blood–brain barrier allowing the entry of drugs into the central nervous system circulation. Concurrent radiotherapy and immunotherapy might have a synergistic effect stimulating the immune response resulting in greater anti-cancer effect. Several retrospective studies have reported excellent outcomes with concurrent radiotherapy and immunotherapy for melanoma. One study on reported overall survival of 56 months with SRS and immunotherapy compared to 24 months and 14 months with immunotherapy alone and SRS alone respectively, while another study reported significantly longer overall survival (15.9 months vs. 6.1 months) and lower cumulative incidence of neurologic death (9% vs. 23%) with SRS and immunotherapy compared to SRS alone [47, 48]. The synergistic effect of radiotherapy and immunotherapy on the immune response in theory could result in more severe acute toxicity, however these studies also report good safety profile with low incidences of grade III or greater toxicity. Treatment scheduling and long-term outcomes and toxicities of combined immunotherapy and radiotherapy are areas of ongoing research interest.

5. Conclusions

The landscape of systemic treatments of MBM patients has undergone tremendous evolution over the past decades and there has been major improvement in outcome for this disease.

Immunotherapy is a relatively safe option for MBM patients with anti-PD-1 having least toxicity and associated with no reported treatment related death. On the other hand, Ipilimumab is associated with increase in immune related toxicities but Ipilimumab and Nivolumab has shown increase in overall survival when comparing with monotherapy. Also, combination with radiotherapy and immunotherapy provides a higher response rate but potential increase in CNS toxicities. More studies are needed to determine the progression free survival, patient's satisfaction and quality of life as well as assessing the cost effectiveness of the treatments.

Combination of immunotherapy with cytotoxic chemotherapy or targeted therapy may also be a potential therapeutic approach, but further understanding of drug mechanism is required.

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Conflict of interest

The authors declare no conflict of interest.

Author details

Hiu K.C. Tang* and Joon W. Ho
Nottingham City Hospital, Nottingham, UK

*Address all correspondence to: ht8000@my.bristol.ac.uk

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