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Hot Topic

The use of systemic therapies for the treatment of brain metastases in metastatic melanoma: Opportunities and unanswered questions

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ABSTRACT

The development of brain metastases is common in patients with metastatic melanoma and heralds a particularly poor prognosis. The development of the immunological agent ipilimumab and targeted treatments such as the selective BRAF inhibitor vemurafenib have revolutionised the treatment of metastatic disease. Evidence from clinical trials suggest these drugs may be effective in the treatment of brain metastases from melanoma. However efficacy may be limited by a lack of penetration of the blood brain barrier (BBB) and by multi substrate efflux pumps expressed on the BBB. The role and sequencing of radiotherapy, both whole brain and stereotactic radiotherapy, is yet to be determined but combinations of radiotherapy and systemic therapies may further increase the effects of these drugs on brain metastases. Considering the impact of brain metastases on morbidity and mortality in metastatic melanoma, future research into systemic drug therapy for the treatment of brain metastases and improvements in BBB penetrance should be a priority.

Introduction

Melanoma is the fifth most common cancer in the United Kingdom, with an annual incidence of 20 per 100,000 [1]. Of those patients diagnosed with cutaneous melanoma, 7–20% have metastatic disease at the time of presentation [1,2], with the most common sites of secondary tumours being liver, bone and brain [3]. The median overall survival is poor, averaging at 6–9 months [4,5], with only 5–22% of patients alive after 5 years [6]. Over the last 40 years overall survival has improved marginally, but this is most likely due to improvements in detection and advances in imaging techniques employed in patient follow up rather than any success of therapeutic intervention [4]. In fact, until recently treatment options for patients with advanced metastatic melanoma have proved woefully inadequate. Various treatments, including chemotherapy with the alkylating agent dacarbazine (DTIC) and cytokines such as interleukin-2 (IL-2), have elicited a response in a small percentage of patients, but have not been shown to significantly extend either progression-free or overall survival [7,8]. More recently, novel therapies for the treatment of metastatic melanoma, such as ipilimumab and vemurafenib, have demonstrated promise in the treatment of the disease.

Increased understanding of the molecular changes in melanoma has also lead to development of drugs that have improved the outcome for patients with metastatic disease. A decade ago it was discovered that 40–60% of melanomas carry a mutation of the gene, coding for the protein kinase B-raf (BRAF) [9]. BRAF is a serine/threonine kinase that acts as a member of the mitogen activated protein kinase pathway (MAPK), a cascade which functions to modulate cell growth, proliferation and migration [10,11] (Fig. 1). Mutations of BRAF lead to constitutional activation of the MAPK pathway, and are a powerful factor in driving the development of melanoma [9]. Initial trials with the non-selective BRAF inhibitor sorafenib were unsuccessful, but newer, more selective, BRAF inhibitors have demonstrated efficacy in the treatment of patients with metastatic melanomas harbouring a BRAF mutation. The first of these drugs to be licenced was vemurafenib (Zelboraf).The pivotal phase III trial, BRIM-3, compared vemurafenib to dacarbazine chemotherapy in 675 patients with BRAF mutation positive metastatic melanoma [12]. The rate of response for vemurafenib treatment was 48%, compared with 5% in DTIC, and the median overall survival improved from 9.6 months with chemotherapy to 13.2 months with vemurafenib [12].

Ipilimumab (Yervoy) is a fully humanised monoclonal antibody that competitively inhibits CTLA-4. Inhibition of this ligand, expressed on the surface of T cells, leads to prolonged T-cell

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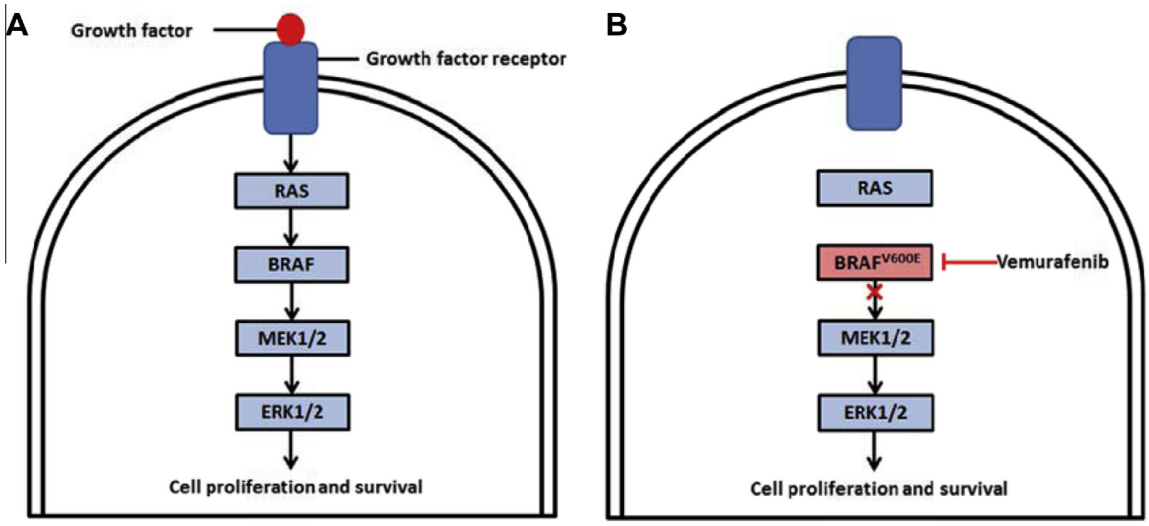

Fig. 1. The MAPK/ERK pathway. (A) Normal activation of the pathway is instigated by the binding of growth factors to a growth factor receptor, and leads to cell proliferation and survival. (B) In 40–60% of melanoma cells, mutated BRAF leads to constitutional activation of the pathway. Vemurafenib is able to inhibit the activity of $BRAF^{V600E}$, thereby preventing this process in these malignant cells. Adapted from [11].

activation and proliferation [13]. A pivotal phase III trial in patients with previously treated metastatic melanoma compared ipilimumab with or without a gp100 peptide vaccine to the vaccine alone. This study demonstrated an improvement in overall survival for those patients receiving ipilimumab compared to vaccine from around 6 to 10 months [14]. Furthermore, long term survival has been reported in a small number of patients. In the first line setting ipilimumab has also been shown to improve survival when combined with DTIC compared with DTIC alone [15].

Brain metastases in metastatic melanoma

Of patients with metastatic melanoma, 44% develop symptomatic brain metastases [16]. These lesions cause considerable morbidity, and prognosis in these patients is poor [7,17] with a median overall survival of only 4 months [16]. It is thought that as many as 95% of patients with brain metastases will die as a result of these lesions [18], and that 20–54% of all melanoma deaths result from brain metastases [16,19].

Solitary or a small number of brain metastases from metastatic melanoma can be surgically resected, a procedure which may be followed by adjuvant whole brain radiotherapy (WBRT) [20]. The rationale behind this approach is that a significant proportion of these patients will most likely have a number of undetectable micrometastases that would subsequently develop into significant intracranial masses if left untreated [21]. Randomised controlled trials have shown that this approach applied to solitary brain metastases (without specific regard to the primary tumour type) leads to fewer cases of intracranial disease recurrence, and longer overall survival compared to radiotherapy alone or no treatment [22–24]. However, the role of surgery with regard to patients with multiple brain metastases remains controversial.

To date, there have been no completed randomised clinical trials specifically focussing on the use of WBRT following local treatment of melanoma brain metastases. Data from a study in 1987 suggested that WBRT following surgical resection of a solitary melanoma metastasis led to a lower rate of relapse, however this study included 19 melanoma patients, only 3 of which formed the treatment group [25]. The answer to this question may become clearer following completion of an on-going a phase III trial headed by the Australia and New Zealand Melanoma Trials Group which is due to complete recruitment in 2016. This study includes patients with up to 3 brain metastases from malignant melanoma initially treated with surgical resection or stereotactic radiosurgery (SRS), and aims to determine whether WBRT is able to control intracranial micrometastases, and if so whether this contributes to a prolonged period of time before neurological decline [21].

WBRT is not without its side effects. Patients suffer significant post treatment fatigue, alopecia and potential cognitive decline following WBRT [26]. More recently more targeted methods of delivering radiotherapy, such as stereotactic radiosurgery, have been increasingly employed [27,28]. This technique involves using multiple convergent beams of radiation to deliver a high dose of radiation to a specific target area [27]. Studies have reported 63–75% local control at 1 year following SRS, depending on tumour size [29–32]. Data supports the use of SRS for patients with small tumours, particularly if asymptomatic at presentation to improve local control, however the role of SRS in extending survival in the presence of uncontrolled extracranial disease is less clear. A randomised trial from the RTOG demonstrated a survival benefit for patients treated with SRS and WBT compared to WBRT alone, with importantly, improved performance status at 3 and 6 months [33]. However the number of patients in the study with malignant melanoma was very small and needs to be interpreted with caution as the radiosensitivity of melanoma may be different to the majority of other solid tumours.

Whether SRS alone without the addition of WBT is sufficient to improve local brain control has also been the subject of a randomised study of patients the up to four brain metastases from various solid tumours [34]. Whilst the intracranial failure rate was higher in the SRS arm, there was no overall difference in survival or functional preservation between the two groups. Current radiosurgery techniques allow treatment of a number of metastases (up to 10) in a single session but the optimal treatment of greater than 4 brain metastases is less clear with number of metastases and total volume of metastases suggested as important prognostic signs [35].

Current trials looking at the role of SRS in brain metastases from melanoma include the melanoma gamma knife trial run by the M.D. Anderson Cancer Centre, which aims to compare the effect of SRS to WBRT in patients with more than 3 melanoma brain tumours (NCT01644591) [36].