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The significance of BRAF V600E mutation status discordance between primary cutaneous melanoma and brain metastases

The implications for BRAF inhibitor therapy

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Abstract

To compare BRAF V600E status of primary melanoma and brain metastases to assess for discordance by cross-sectional study, and to evaluate clinical implications on BRAF inhibitor therapy.

Brain metastases are common in patients with advanced melanoma. Between 40% and 60% of melanomas demonstrate BRAF mutations, BRAF V600E being most common. Selective BRAF inhibitor therapy has shown improvement in outcome in patients with melanoma. It has been demonstrated that not all metastatic lesions carry the same BRAF mutation status as the primary, but the frequency in which discordance occurs remains unclear. Establishing this may have implications in the use of BRAF inhibitors in patients with melanoma brain metastases.

Patients who underwent metastectomy for melanoma brain metastases were identified using our local histopathology database. A review of histology of the primary lesion and the metastasis was performed for each patient, assessing for BRAF mutation status discordance.

Fourty-two patients who underwent a brain metastectomy following excision of a melanoma primary were identified over a 7-year period. Median survival was 9 months. The median Breslow thickness for the primary lesion was 3.4 mm. Six patients (14%) had discrepancy between the BRAF status of a melanoma primary and metastatic lesion. Of these 6 patients, 3 had a BRAF mutation positive primary with a BRAF mutation negative metastatic lesion, while the other 3 had a BRAF mutation negative primary with BRAF mutation positive metastasis.

There is an important discordance rate in the BRAF mutation status of melanoma primaries versus brain metastases.

Abbreviations: MEK = mitogen-activated protein kinase kinase, PIPE = patient information profile explorer.

Keywords: BRAF inhibitor, brain metastases, brain neoplasm, dabrafenib, melanoma, proto-oncogene proteins B-raf, vemurafenib

1. Introduction

The incidence of malignant melanoma continues to rise worldwide, with approximately 200,000 new diagnoses of melanoma per annum, leading to roughly 46,000 mortalities.[1] While malignant melanoma only accounts for 4% of skin cancers, it is responsible for 80% of all skin cancer-related deaths.[2] In patients with advanced melanoma, brain metastases are unfortunately a common and serious event, being a major cause of morbidity and mortality. Compared with lung, breast, renal, and colorectal cancer, melanoma has the highest risk of metastasising to the brain.[3] It is estimated that up to 75% of patients with stage IV disease will develop brain metastases,[4] which in turn will account for up to 50% of melanoma-related mortalities.[5] Melanoma brain metastases have a very poor prognosis, with mean survival estimated to be 3 to 5 months.[6,7] Management of melanoma brain metastases is traditionally palliative. Aggressive treatment options, such as metastectomy and stereotactic radiosurgery, do exist and have been shown to almost double survival to 8 months, but there is a strict selection criteria for determining the patients who may expect to benefit such as those having a single surgically accessible metastasis in the context of absent or stable extracranial metastases together with good performance status.[8] Whole brain radiation therapy is typically reserved for patients with multiple brain metastases or who have had failed surgical treatment, but is not associated with significant survival benefit.[9] Malignant melanoma is notoriously refractory to chemotherapy regimens, with systemic chemotherapy historically having little impact on survival. A recent study advocated for the use of immunotherapy in melanoma brain metastases, reporting that both nivolumab monotherapy and a combination of nivolumab and ipilimumab are active in melanoma brain metastases. However, the study concluded by saying that patients with symptomatic brain metastases,

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leptomeningeal metastases, or prior local therapy responded poorly to nivolumab alone. From this, the authors state that combined immunotherapy may be considered as upfront therapy in melanoma brain metastases.[10]

BRAF is a human gene responsible for producing the protein B-Raf, which is involved in signaling direct cell growth.[11] The V600E mutation describes an amino acid substitution at position 600 in BRAF from a valine (V) to a glutamic acid (E). The presence of BRAF mutations in some human cancers has been well demonstrated.[12] Between 40% and 60% of malignant melanomas demonstrate BRAF mutations, with over 90% of these being the V600E variant.[13] BRAF V600E mutations are associated with an increased sensitivity to BRAF inhibitors. The selective BRAF inhibitors vemurafenib and dabrafenib have demonstrated clinical efficacy in patients with BRAF V600E-mutant malignant melanoma metastases,[14] with vemurafenib in particular showing significant improvements in both progression-free survival and overall survival.[14,15] A recent multicenter phase 2 study across 32 hospitals advocated for dual BRAF and mitogen-activated protein kinase kinase (MEK) inhibition in patients with BRAF V600E mutation-positive melanoma brain metastases, reporting that this may allow for medical debulking of the metastatic lesion and potentially result in avoiding or deferring the need for radiotherapy or corticosteroid use.[16,17] These outcomes highlight the importance of identifying patients who may benefit from BRAF inhibitor therapy.

With regards to patient selection for BRAF inhibitor therapy, it is typically reserved for patients with stage III or stage IV melanoma, with allocation of therapy based on the BRAF mutation status of 1 tissue block, together with the assumption that all metastatic lesions will harbor the same BRAF mutation status as the primary. Previously, a degree of discordance between the BRAF V600E mutation status of the primary melanoma and the metastatic lesion has been shown, though studies are limited and the discordance rates are variable. Patients with a BRAF V600E mutation negative primary melanoma may still manifest a BRAF V600E mutation positive metastases, and similarly, those with a positive mutation status in the primary may be shown to have no such mutation in the distant disease.[18] Discrepancies of BRAF mutation status between melanoma primaries and metastases have been shown to range from 18% to 26%.[19] Further investigation of the degree to which this discordance exists may have implications in the management of metastatic melanoma as the decision to offer or to withhold BRAF inhibitor treatment in patients with metastatic melanoma based purely on the mutation status of the primary may be flawed.

2. Aims

We set out to identify all patients who underwent surgical removal of melanoma brain metastasis in our center, and to compare BRAF V600E mutation status of the primary melanoma with the brain metastasis. From this, we aimed to evaluate the impact of any discordances on current clinical practice in the use of BRAF inhibitors. We also aimed to evaluate survival post-metastectomy to assess the validity of neurosurgery as a treatment option for brain metastases in advanced melanoma.

3. Methods

3.1. Data collection

Patients who underwent brain metastectomy for a melanoma primary in Beaumont Hospital, a tertiary referral center for neurosurgery, were identified over an 8 year period using the electronic pathology database. From January 2007 to December 2015, 124 patients with a history of cutaneous melanoma underwent resection of a brain metastasis. The histopathology reports were obtained via the Patient Information Profile Explorer (PIPE) to identify cases where the histopathology reports for both the primary melanoma and the brain metastasis were available. These were reviewed to ensure that the histopathology for the metastectomy specimens was performed by a consultant neuropathologist and that the appropriate genetic testing had been performed. A total of 42 patients met these criteria. Data collection was performed using patient records, PIPE, and our in-house radiology and pathology databases. Information gathered included the age of the patient both at initial diagnosis and metastatic diagnosis, cancer subtype, Breslow depth, and BRAF V600E mutation status and survival post-metastectomy. Ethical approval was granted by the Beaumont Hospital Research Ethics Committee.

3.2. Determination of BRAF V600E mutation status

In all cases, analysis of the exon 15 sequence of the BRAF gene with flanking intronic sequences was performed following successful PCR amplification. This was performed using a BigDye Terminator Cycle Sequencing Kit along with an ABI PRISM Genetic Analyser. Sequencing was confirmed by immunohistochemistry after staining with the BRAF V600E-mutation specific antibody VE1.

3.3. Statistical analysis

Descriptive statistics were used to display both patient and tumor characteristics. Patient survival was defined as the time from metastectomy to death in months. Continuous variables were described by median and nominal values as a percentage. All statistical analysis was performed using SPSS Statistics Version 24.

4. Results

Of the 42 patients who underwent a metastectomy for a melanoma brain metastasis following resection of a primary cutaneous melanoma, 22 (52%) were women and 20 (48%) were men, with an age range of 21 to 84 years at diagnosis, and a mean age of 48 years at diagnosis (Table 1). All 42 patients were

Table 1

Patient demographics and survival.

	BRAF V600E mutation positive primary tumor	BRAF V600E mutation negative primary tumor
Total number of patients	19	23
Male to female ratio	47:53	48:52
Mean age at diagnosis of brain metastases, y	47 (range 26–84)	49 (range 21–76)
Median time from diagnosis of primary to diagnosis of brain metastases, mo	25 (range 1–81)	35 (range 5–124)
Median survival time post-metastectomy, mo	8 (range 1–25)	10 (range 3–38)

Table 2

Tumor characteristics.

Number of specimens		
	BRAF V600E mutation positive primary tumor	**BRAF V600E mutation negative primary tumor**
Primary cutaneous lesions	19	23
Melanoma brain metastases	19	23
Breslow thickness (number of patients)		
	BRAF V600E mutation positive primary tumor	**BRAF V600E mutation negative primary tumor**
<1 mm	0 (0%)	2 (8.5%)
1–2 mm	8 (42%)	8 (35%)
2.1–4 mm	8 (42%)	11 (48%)
>4 mm	3 (16%)	2 (8.5%)
Median Breslow thickness (mm)		
	BRAF V600E mutation positive primary tumor	**BRAF V600E mutation negative primary tumor**
	2.9 (range 1.5–13)	3.9 (range 0.6–11)
Tumor location (number of patients)		
	BRAF V600E mutation positive primary tumor	**BRAF V600E mutation negative primary tumor**
Head and neck	7 (37%)	5 (22%)
Trunk	9 (47%)	13 (56%)
Upper limb	0 (0%)	2 (9%)
Lower limb	3 (16%)	3 (13%)
Presence of extra-cranial metastases (number of patients)		
	BRAF V600E mutation positive primary tumor	**BRAF V600E mutation negative primary tumor**
Extra-cranial metastases	11 (58%)	7 (30%)
No extra-cranial metastases	8 (42%)	16 (70%)
Melanoma subtype (number of patients)		
	BRAF V600E mutation positive primary tumor	**BRAF V600E mutation negative primary tumor**
Nodular melanoma	10 (53%)	13 (57%)
Superficial spreading melanoma	8 (42%)	7 (30%)
Lentigno maligna melanoma	1 (5%)	3 (13%)

Caucasian. The median time from diagnosis of cutaneous melanoma to the diagnoses of melanoma brain metastases was 30 months (range 1–124 months).

Pathology reports for 84 specimens from 42 patients (42 primary cutaneous melanomas and 42 melanoma brain metastases) were identified and reviewed (Table 2). The median Breslow thickness for the primary lesion was 3.4 mm (range, 0.6–13 mm).

Of the 42 primary cutaneous lesions, 23 (54%) were BRAF V600E mutation negative, while the remaining 19 (46%) were BRAF V600E mutation positive (Table 3). Six (14%) of the 42 patients demonstrated a BRAF V600E mutation status discordancy between the primary lesion and brain metastasis. Of these, 3 (7%) had a BRAF V600E-positive primary with a negative metastasis, while the remaining 3 (7%) were shown to have a BRAF V600E-negative primary with a positive melanoma brain metastasis.

Table 3

BRAF V600E mutation status discordance.

BRAF V600E mutation status of primary cutaneous lesions (number of patients)	
BRAF V600E mutation positive	19 (46%)
BRAF V600E mutation negative	23 (54%)
Discordance between primary cutaneous lesion and brain metastases (number of patients)	
No discordance	36 (86%)
BRAF V600E-positive primary with negative brain metastases	3 (7%)
BRAF V600E-negative primary with positive brain metastases	3 (7%)

Median survival time post-metastectomy for melanoma brain metastases was 9 months (range, 1–38 months). BRAF V600E mutation positive primary tumors were noted to have a slightly worse prognosis, with a median 8 months survival, compared with the 10 months survival of BRAF V600E mutation negative patients. Of note, a higher proportion of patients in the BRAF V600E positive primary tumor group had extra-cranial metastases (Table 2). None of the patients included in this study received BRAF inhibitor therapy.

5. Discussion

We confirm a 14% discordance in V600E status between primary cutaneous melanoma and paired melanoma brain metastases. Our data would strongly suggest that the current strategy of allocating BRAF inhibitor treatment based solely on the mutation status of the primary lesion is incorrect, resulting in some patients with a BRAF V600E mutation-negative primary who may harbor mutation positive melanoma brain metastases not receiving BRAF inhibitor treatment. This is an important finding as these patients could potentially gain months of survival from receiving such therapy.[15,20] With an objective response rate of around 50%, and 90% of treated patients show some evidence of tumor regression,[19] it is important to consider that 7% of patients might fail to receive the potential benefit of BRAF inhibitor therapy.

Equally important to consider is that the prescribing of BRAF inhibitors to patients with a BRAF V600E mutation-positive

primary may offer them little benefit if the metastatic lesion is mutation-negative. It has been clearly shown that patients with BRAF V600E mutation-negative melanoma do not benefit from BRAF inhibitor therapy.[21] In fact, BRAF inhibitors used to treat BRAF V600E mutation-negative tumors may contribute to disease progression, through enhanced cell proliferation.[22]

We recommend that for patients with melanoma brain metastases who are candidates for metastectomy, the decision to allocate BRAF inhibitor therapy should be based on the BRAF V600E status of the metastatic lesion rather than on the V600E status of the primary melanoma. Our findings of BRAF V600E mutation discrepancy may go some way towards explaining the variability of clinical response observed among patients treated with BRAF inhibitors.[15,19]

Our study also lends validity to metastectomy as a treatment option for melanoma brain metastases. All of our patients were post-metastectomy, and demonstrated an increased overall survival compared with what would be expected from patients with untreated melanoma brain metastases.[7] This is supported in the literature, where overall survival has been seen to range from 6 to 22 months post-metastectomy, compared with a median of 4 months without resection.[23] It is important to be aware that, unfortunately, only a minority of patients (10%) with brain metastases are deemed candidates for surgical resection, with the ideal patient having a small number of superficial metastases in areas of the brain where surgery will not result in unacceptable impairment of function.[20] Nonetheless, our data adds further support to the role of neurosurgery in melanoma brain metastases, where carefully selected patients may see a significant increase in their overall survival.

Our study is not without limitations. Despite a broad search, our study included a relatively small number of patients where histopathology reports for both the primary cutaneous lesion and the metastatic lesion were available. Nonetheless, our findings highlight that every opportunity to ensure appropriate allocation of BRAF inhibitor therapy should be taken. Appropriate surgical candidates not only stand to benefit from the impact of resection on survival, but the additional information obtained from the assessment of the metastatic lesion may guide the patient towards BRAF inhibitor therapy which previously may have been denied. With a greater understanding of the degree of discordance between the primary and metastatic lesion, determining the BRAF V600E mutation status of melanoma brain metastases is essential to ensure appropriate allocation of treatment.

6. Conclusion

Our findings show that the discordance of BRAF V600E mutation status between primary and metastatic brain lesions in advanced melanoma is important. Recognition of this discordance may result in more appropriate allocation of BRAF inhibitor therapy to patients who otherwise might be denied therapy, and may potentially extend survival by months in patients with advanced melanoma.

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