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Melanoma Brain Metastases: Is it Time to Reassess the Bias?

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Summary

Melanoma patients with brain metastases are typically excluded from clinical trials due to historically dismal survival (<4 months) and concerns about blood brain barrier drug penetration. The pleural cavity is another location with potential decreased drug penetrance, yet malignant effusion patients are not excluded. Here we discuss whether new technologies for local control of brain metastases have altered survival patterns. We also report our findings from a retrospective chart review of 251 metastatic melanoma patients diagnosed after 2005, and evaluate our findings in the context of eligibility for clinical trials with novel agents. We found that median survival of malignant effusion patients was significantly shorter than brain metastasis patients (two versus eight months, $p < 0.0001$). Only one pleural effusion patient lived >9 months, whereas 41 (39.4%) brain metastasis patients survived beyond this time. We conclude that with the advent of effective means for providing local control for brain metastases, survival of these patients has improved, and they often succumb to extra-cranial disease. Exclusion of melanoma brain metastasis patients from clinical research programs is no longer justified and alternative investigational approaches, possibly combining local and systemic therapies, are urgently needed for these individuals.

Keywords

melanoma; brain metastases; prognosis; clinical trial design

Introduction

Historically, patients with brain metastases from melanoma have been felt to have a uniformly dismal prognosis (<4 months). For this reason, and due to concerns about drug

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penetration through the blood brain barrier (BBB), these patients have been excluded from most clinical trials. [1] However, advances in imaging and treatment of the brain appear to be leading to improved prognosis in these patients, and recent data suggest that there is activity of some new melanoma therapies within the brain. This review will detail data reported in the literature and from our own institution that suggests that a reassessment of absolute exclusion of brain metastasis patients from clinical trial eligibility is warranted.

Historical Cohorts of Brain Metastasis Patients

In general, once melanoma metastasizes, therapeutic options have been limited. Although recent advances in development of novel therapies will likely expand the repertoire of active drugs for this disease, for many patients the best treatment option will involve participation in a clinical trial.[2–4] The brain is a common site of disease spread in melanoma patients; 10–40% of patients are diagnosed with brain metastases during their lifetime and >75% have brain metastases at autopsy. [1, 5–8] Unfortunately, for many of these patients with brain metastases, clinical trials are not an option due to protocol exclusion criteria.

Brain metastases have traditionally been considered the most ominous of all visceral metastases in malignant melanoma. Overall, historical melanoma patient cohorts have reported a median survival of patients with brain metastases in the order of 2.5 – 4 months despite use of whole brain radiation therapy (WBRT) and surgery.[5–6, 8] For example, in a retrospective chart review by Sampson et al. of 6,953 metastatic melanoma patients seen at Duke University Medical Center, 702 patients were found to have clinically significant brain metastases, associated with an overall median survival of 113.2 days, with brain metastases directly contributing to death in an estimated 94.5% of these patients. [5] In another review of 100 patients with cerebral metastases published in 1998, median overall survival was 2.5 months.[6] Davies et al. reviewed charts from 330 patients with melanoma brain metastases treated between 1986 and 2004, and found a median survival of 4.5 months. [9] Staudt et al. found a median overall survival of 5 months for 265 patients with brain involvement treated between 1986 and 2003. [10]

These studies generally rely on older series of patients, which may not be representative of outcomes in the current era of imaging and treatment. This era has been characterized by increased use of imaging, improved quality of imaging, and less morbid treatment of brain lesions once they are diagnosed.

Improved Imaging and Treatment

The National Comprehensive Cancer Network (NCCN) now recommends that magnetic resonance imaging (MRI) of the brain be included in the work-up of stage IV melanoma and clinical trials stipulate frequent brain imaging as well, with the goal of providing early intervention for small brain lesions. Routine use of MRI in recent years has improved early detection of brain metastases, and MRI has been shown to be more sensitive for detecting brain metastases than CT scans.[11] Schellinger et al found that the primary advantage of MRI over CT in the staging melanoma patients is in detecting small lesions, while others have found that MRI is primarily necessary for the detection of infratentorial lesions. [11–12] In addition, more modern generations of scanners and scanning techniques continue to improve sensitivity. [13] While the impact of this early detection of metastases on melanoma patient prognosis cannot be definitively determined, earlier detection should translate into longer survival after diagnosis, even if this is only due to lead time bias. Smaller lesions are detectable by MRI than by CT scans, and treatment of smaller lesions results in improved local control of central nervous system (CNS) disease. [11, 14]

Treatment strategies have also changed over the past years. Stereotactic radiosurgery (SRS) is an effective method of improving local control for limited brain metastases. SRS has become the preferred method for treating smaller metastases, as the local control rates are high and the procedure is well tolerated. [15]

Improved Prognosis

The Davies study, referenced earlier, examined the impact of era of diagnosis on outcome. [9] They found a significant increase in survival after 1996 with a hazard ratio on multivariate analysis of 0.75 (95% CI 0.59–0.95, $p=0.02$). With more frequent brain imaging and SRS, median survival has been extended to up to 10.6 months after gamma knife surgery in some series. [15] The German series reported recently by Staudt et al. included a multivariate analysis revealing that 83 patients who received neurosurgery or SRS had a median overall survival of 9 months. [10] Patients with single brain metastases in this series who were treated with neurosurgery or SRS rather than WBRT had improved survival. Similarly, Eigentler et al noted a significantly improved survival of patients who underwent treatment of brain metastases with SRS or surgery, although unlike the study by Davies and colleagues, when comparing patients by era of diagnosis in this patient series, there did not appear to be a statistically significant difference in survival in this series between patients treated in earlier years and patients treated more recently. [16] In highly selected patients who were referred to the National Cancer Institutes for immunotherapy, the median survival for patients with brain metastases was 16.1 months. [17] We note that some of these newer series exclude patients with overwhelming brain metastases, not amenable to therapy with SRS due to size and/or number, that were included in the older cohorts.

Blood Brain Barrier

The newer melanoma brain metastases series strongly suggest that that survival is no longer as dismal as previously thought, and that further investigation of pharmacologic agents that penetrate the blood brain barrier (BBB) in this patient population is warranted. Additionally, in the setting of brain metastases, the integrity of the BBB itself might be compromised, based on clinical observations that the administration of drugs thought to not have CNS activity can indeed result in favorable brain tumor response. This is likely due to increased permeability of tumor blood vessels, as reviewed by Provenzale et al. [18]

Drug development strategies, however, have traditionally not included timely evaluation of drug efficacy in the brain metastasis population. One example is the development of ipilimumab for melanoma patients. This monoclonal antibody likely causes systemic immune responses that affect brain metastases. In the pivotal phase III study of ipilimumab demonstrating a survival benefit, patients with untreated brain metastases were generally excluded; however, 82 patients (12.1%) did have a history of brain metastases, 73 of whom had prior local therapy for CNS disease. [4] This relatively small clinical experience, combined with case reports from a subsequent ipilimumab compassionate use study, suggested that ipilimumab may indeed have central nervous system activity. [19–20] Based on these observations, a phase II clinical trial was conducted specifically administering ipilimumab to patients with untreated brain metastases, which demonstrated that ipilimumab has similar activity in both brain and extra-cranial lesions. [21] This study, however, was initiated years after the initial ipilimumab trials.

A second example is the study of temozolamide and sorafenib in melanoma brain metastases patients. [22] Both drugs can cross the BBB. Initial studies with sorafenib alone and in combination with chemotherapy excluded patients with active brain metastases. [23–24] Temozolamide has known CNS activity, albeit with a low response rate in melanoma. [25–26] Prior studies had shown a response rate in brain metastases of 4.4% only. [27] In the

combination study of temozolamide and sorafenib for patients with or without brain metastases, activity was seen in patients without a history of prior temozolamide therapy. Despite a generally low progression free survival of 3.5 months and a 23% six month progression free survival rate in the brain metastases cohort, these results were considered favorable and thought to be due in part to local therapies that were allowed on this study, such as SRS.[22]

While most initial clinical trials with novel agents exclude patients with untreated brain metastases, a recent trial with GSK2118436, an inhibitor of mutated BRAF, is an exception to the long-standing paradigm. A phase I/II study of this agent included a subset of patients with untreated brain metastases.[28] At the 2010 meeting of the European Society for Medical Oncology, Long et al reported that nine of the ten patients with untreated cerebral metastases enrolled in this trial had shrinkage of their brain lesions.[28] This study, thus, demonstrates that asymptomatic brain metastases, similar to asymptomatic metastases in other sites, can be treated systemically on clinical trials, and that drug activity is not necessarily different than in other metastatic locations.

These examples of clinical trials for melanoma brain metastases are generally the exception rather than the rule, and other than the GSK trial, these studies were conducted after the drugs had demonstrated activity in non-cranial melanoma metastases, resulting in a delay of months to years in access to novel regimens for patients with brain metastases. Given the dramatic progress made in the past decade with local therapies for brain metastases, for many of our patients, lack of access to drugs that are systemically active can result in their demise.

The Yale Experience: Brain metastasis versus Pleural Effusion

The pleural cavity is another site with possible decreased drug penetration, yet patients with malignant pleural effusions are not excluded from clinical trials. For example, some pleural infections cannot be treated with systemic therapies due to decreased drug penetrance into the pleural cavity.[29–32] Given the shared features unique to both the pleural cavity and the brain in terms of drug penetrance, we compared survival in brain metastasis patients to that of patients with metastases to the pleural cavity.

With Institutional Review Board approval, we reviewed 251 charts of patients with stage IV unresectable melanoma treated at our institution between 2005 and 2010. Parameters studied during this review included location of primary melanoma and histologic details of the primary melanoma (ulceration, regression, lymphovascular invasion, Breslow thickness, and number of mitotic figures per high powered field), date and location of metastases, therapies for systemic disease, and therapies for specific metastases (i.e. brain or pleural cavity). These patients received a variety of systemic therapies including chemotherapies, biological therapies, and immunotherapies. Specific therapies, such as ipilimumab, were noted.

Of these 251 patients, we identified a small cohort of 19 patients (7.5%) who developed malignant pleural effusions and studied the overall survival from the time of diagnosis of malignant effusion. Determination of malignant effusion was made by positive cytologic sampling, or in the case of negative cytology, the presence of positive pleural biopsy or large pleural based metastases on imaging. 104 (41.4%) patients had brain metastases and no pleural effusions. Brain metastases were diagnosed based on brain imaging, either as clinically indicated for symptoms or for routine surveillance, thus in many cases small, asymptomatic lesions were diagnosed. Survival from time of diagnosis of metastatic effusion was compared to survival from the time of diagnosis of brain involvement in patients who developed brain metastases. Two patients with concurrent malignant effusions and active brain metastases were excluded from survival analysis, while four patients who

had malignant effusions and treated brain metastases, who died of complications of effusions while the brain metastases remained quiescent, were included in the survival analysis of the pleural effusion patients.

The two cohorts had similar distributions of all clinical co-variables, including age, gender, location of primary melanoma, and Breslow thickness, with the exception of receipt of chemotherapy. The brain metastases patients had their brain lesions treated with multiple modalities including SRS, WBRT, and surgical resection, as detailed in .

Compared with the brain metastasis cohort, patients with malignant effusions were less likely to receive chemotherapy ($p=0.03$) and immunotherapy ($p=0.62$). Of the clinical co-variables listed in Table 1, the only significant difference between the two cohorts was receipt of chemotherapy. Five pleural effusion patients were unable to receive any systemic therapy at all, and survived an average of 1.2 months. Patients with malignant effusions were more likely to have higher LDH elevations; 50% of patients with a known LDH value had an LDH > 400 u/L versus 20.5 % from the brain metastasis cohort with a known LDH value ($p = 0.0102$).

Survival of patients with malignant pleural effusions was significantly shorter than that of patients with brain metastases ($p < 0.0001$). There was a dramatic difference in median overall survival from the time of diagnosis of malignant pleural effusions and time of diagnosis of brain metastasis (two versus eight months). The survival curves for these two groups are depicted in Figure 1.

Recent series reporting survival for metastatic melanoma with brain involvement demonstrate that the survival has improved with frequent imaging and improved methods of local control, compared to older series. Here we confirm these findings and also demonstrate that survival of patients with melanoma brain metastases is significantly longer than that of patients with malignant pleural effusions. A thorough review of the literature did not reveal large series of patients with malignant effusions from melanoma. Reports of isolated case studies were found. [33–35] It is well established that malignant effusions in general portend a poor prognosis with survival estimated at 3 – 10 months from diagnosis of effusion regardless of primary malignancy. [36–38] Melanoma is known to cause malignant effusions, but poor outcomes and a worse prognosis, such as our results indicate, have not been well documented. These patients were also less likely to receive chemotherapy due to their overall poor performance status, resulting in rapid clinical demise, and improved modalities for local control of malignant effusions are urgently needed. Despite the poor prognosis of patients with malignant effusions, these patients are not specifically excluded from clinical trials with systemic therapy.

Due to the complexities in determining the precise cause of death in patients with metastatic disease, we could not accurately quantify the fraction of patients with brain metastases who died specifically from their brain disease. Many of these individuals, however, had excellent control of their brain metastases with local therapy and succumbed to uncontrolled systemic disease.

Conclusions

Our findings confirm improved survival of patients with melanoma brain metastases compared to survival in older cohorts. Furthermore, we show that the brain is no longer the most formidable site of metastatic dissemination. Given the frequency of brain metastases in melanoma patients and advances in local control of CNS disease, all drugs in development should undergo thorough pharmacologic evaluation for penetration into the normal brain parenchyma and into melanoma brain metastases. One potential approach to clinical

development of drugs for this rather common problem is the inclusion of patients with active brain metastases in initial trials of drugs with known CNS penetration or activity, such as the trial conducted with GSK2118436.²⁸ This approach is further supported by previous studies with a carefully selected patient population, which suggested that treating asymptomatic brain metastasis patients with systemic therapy and frequent brain imaging, while deferring immediate radiation therapy, is safe.^{39–40} These trials enrolled patients with little to no symptoms, low CNS disease burden (1–3 brain metastases), and an excellent performance status. Another possible approach is early activation of separate trials or separate arms on phase II or III trials for patients with brain metastases that allow concurrent use of investigational agents and local therapy to the brain as needed for growing lesions or symptomatic brain lesions, particularly in situations in which BBB penetration of the drug is questionable. This would alleviate the concern that metastases in a critical location in the brain might not respond to systemic therapy, and if untreated, can result in debilitating symptoms. Different criteria for evaluation of drug activity in the brain metastasis arm will need to be developed and applied, as standard radiologic criteria for response might not reflect activity, particularly when cerebral edema might cause lesions to enlarge, especially when immune-based therapies are being studied. Our retrospective chart review, combined with recent clinical trial experience, clearly indicates that the prognosis of melanoma brain metastases is no longer so poor that exclusion of these patients from our clinical research programs is justified and that the bias against inclusion of these patients be reassessed.

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Figure 1. Kaplan-Meier Curves demonstrating the overall survival from time of diagnosis of metastatic pleural effusion or from time of brain metastases, respectively. Patients with pleural effusions had significantly shorter survival than patients with brain metastases ($p < 0.0001$).

Table 1

Clinical Characteristics of Metastatic Pleural Effusion and Brain Metastasis Cohorts.

Clinical Characteristic	Pleural Effusion Cohort N=19 (100%)	Brain Metastasis Cohort N=104 (100%)	Differences by chi-square (X ²)
Age			
<40 years old	1 (5)	16 (15.4)	1.7 (p=0.19)
≥40 years old	18 (95)	88 (84.6)	
Gender			
Male	12 (63.2)	67 (64.4)	0.01 (p=0.92)
Female	7 (36.8)	37 (35.6)	
Type of Primary			
Cutaneous	14 (73.4)	92 (88.5)	2.1 (p=0.15)
Non-cutaneous	2 (10.5)	3 (2.9)	
Unknown primary	3 (15.8)	9 (8.7)	
Breslow (mm)			
≥2	8 (42.1)	47 (45.2)	0.001 (p=0.97)
<2	4 (21.1)	24 (23.1)	
Unknown	7 (36.8)	33 (31.7)	
LDH (units/Liter)*			
Normal (≤242 u/L)	7 (36.8)	37 (35.6)	0.43 (p=0.51)
Elevated (>242 u/L)	11 (57.9)	41 (39.4)	
Unknown	1 (5.3)	26 (25.0)	
Pleural Effusion Cytology			
Positive	13 (68.4)	NA [‡]	NA
Negative [†]	2 (10.5)	NA	
Unknown	4 (21.1)	NA	
Local Therapy for Effusion [§]			
None	5 (26.3)	NA	NA
Thoracentesis/Needle Drainage	6 (31.6)	NA	
Drainage Catheter/Tube	8 (42.1)	NA	
Pleurodesis	2 (10.5)	NA	
Pleural effusion first site of metastasis			
Yes	7 (36.8)	NA	NA
No	12 (63.2)	NA	
Chemotherapy			
Yes	6 (31.6)	60 (57.7)	4.5 (p=0.03)
No	13 (68.4)	44 (42.3)	
Immunotherapy (including Ipilimumab)			

Clinical Characteristic	Pleural Effusion Cohort N=19 (100%)	Brain Metastasis Cohort N=104 (100%)	Differences by chi-square (X ²)
Yes	13 (68.4)	77 (74.0)	0.3 (p=0.62)
No	6 (31.6)	27 (26.0)	
Presence of brain metastasis //			
Yes	4 (21.1)	104 (100)	NA
No	15 (78.9)	0 (0.0)	
Stereotactic Radiosurgery			
Yes	2 (10.5)	84 (80.8)	NA
No	17 (89.5)	20 (19.2)	
Craniotomy			
Yes	2 (10.5)	27 (26.0)	NA
No	17 (89.5)	77 (74.0)	
Whole Brain Irradiation			
Yes	2 (10.5)	32 (30.8)	NA
No	17 (89.5)	72 (69.2)	

* at the time of diagnosis of effusion or brain metastasis

[†] Determination of malignant effusion in patients with negative cytology was made based on the presence of positive pleural biopsy or large pleural based metastases on imaging.

[‡] NA is not applicable.

[§] Some patients received more than one local therapy for their effusion.

// This analysis includes only the four malignant pleural effusion patients who had treated brain metastases and died of complications of effusions while their brain metastases remained quiescent.