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Outcome of Patients with Delayed Brain Metastases Following Initial Ipilimumab plus Nivolumab Treatment of Disseminated Melanoma

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Abstract

Introduction: Patients with metastatic melanoma have an elevated risk of developing brain metastases. Treatment with immune checkpoint inhibitors appears to decrease this risk.

Methods: A retrospective analysis of uncommon patients with delayed onset of brain metastases following first-line ipilimumab plus nivolumab treatment for metastatic cutaneous melanoma was performed. Patient characteristics and outcomes were analysed, as was the effectiveness of salvage therapy.

Results: Of 75 metastatic melanoma patients who received first-line ipilimumab/nivolumab treatment, 7 (9.3%) developed subsequent new brain metastases. The incidence was 13.8% in patients receiving standard regimen of ipilimumab/nivolumab and 7.1% in patients receiving the alternate dosing schedule. Median time to onset of brain metastases from the start of therapy was 4.8 months. The median survival was only 8.4 months, despite attempted salvage therapy.

Conclusion: Treatment with ipilimumab and nivolumab seems to result in a reduced incidence of brain metastases in metastatic melanoma patients. Most of these recurrences were identified during the first year of immunotherapy. The apparent reduction of the brain metastasis by the alternate ipilimumab/nivolumab dosing regimen requires further confirmation. All patients with delayed onset brain metastases died. Thus, more effective treatment options for brain metastases that occur during immunotherapy are badly needed.

Keywords: central nervous system, immune checkpoint inhibitor, immunotherapy, stereotactic radiosurgery

Introduction

Patients diagnosed with advanced cutaneous melanoma are at significant risk of developing melanoma brain metastases (MBM). Melanoma results in the third highest number of cancer patients who develop brain metastases, trailing only more common cancers, such as lung and breast cancer [1]. However, the actual percentage of metastatic melanoma patients who eventually develop brain metastases, termed incidence proportion percentage, is currently the highest of all cancers [2]. In the past, approximately 28-40% of melanoma patients presented with brain metastases at the time their metastatic disease was diagnosed [2,3]. In a more recent

literature review, 33% of patients still were found to have MBM at the time of initial diagnosis of metastatic cutaneous melanoma [4]. Historically, another 25%-44% of metastatic melanoma patients developed the delayed onset of MBM, even if brain metastases were not present at the time treatment was initiated [4-7]. Development of either initial or delayed MBM was associated with increased morbidity and mortality [8-10]. Approximately 50% of metastatic melanoma-related deaths resulted from central nervous system (CNS) progression [11].

Recent advances in cancer therapy, especially the development of targeted therapy (TT) and immune checkpoint inhibitor (ICI) therapy have markedly improved the survival of patients with metastatic melanoma [12-15]. Even in patients with existing MBM, both ICI and TT have demonstrated intracranial responses [16,17]. However, the combination of CTLA-4 and PD-1 blockade (ipilimumab plus nivolumab) appears to provide more durable activity in the CNS when compared to TT [18,19]. Due to these treatment advances, the frequency and timing of brain metastases appears to be evolving. Our own institutional data has shown that the incidence of delayed brain metastases following any form of ICI-based cancer immunotherapy appeared to be low (~7%) [20].

As the incidence of melanoma brain metastases appears to be decreasing following immunotherapy, we identified small number of patients with onset of brain metastases after initial ipilimumab plus nivolumab treatment to further evaluate their characteristics and clinical outcomes.

Materials and Methods

Patient Enrolment

Study candidates were identified by a retrospective chart review of a Health Insurance Portability and Accountability Act (HIPAA)-compliant IKnowMed medical record program (McKesson, Houston, TX). A search of this data base was conducted to identify patients treated by a single physician (WS) with ipilimumab and concurrent nivolumab. These records were individually accessed to verify that each patient had metastatic cutaneous melanoma. Patients who were treated with ipilimumab plus nivolumab for other cancers were excluded. Additional exclusion criteria included a diagnosis of non-cutaneous melanoma (e.g. acral-lentiginous, ocular, or mucosal melanoma). Patients who already had melanoma brain metastases (MBM) at the time of their initial diagnosis of metastatic melanoma were excluded from this analysis. Patients who received ipilimumab and nivolumab as 2nd or later lines therapy for metastatic disease were also deemed ineligible. Patient records were individually accessed and relevant data extracted into a spreadsheet for analysis (Microsoft Excel version 16.83, Redmond, WA). After data entry, the spreadsheet was de-identified. Since this was a retrospective review of existing data, there was no plan to modify treatment based on the results or contact patients directly. This study design was reviewed by the Western IRB chair and deemed exempt from full Institutional Review Board (IRB) review.

Data Collection

Details recorded including age at the start of ICI treatment, gender, and comorbidities. Description of the primary site and initial sites of metastatic disease were used to define the melanoma stage at the time of diagnosis. Pertinent pre-treatment variables, such as lactate dehydrogenase levels, PD-1 ligand (PDL1) expression, tumor mutational burden (TMB) was recorded. The “driver” mutation status identified by Next-Gen molecular sequencing (including BRAF, NRAS, NF-1, KIT mutations, or “quadruple negative”) was also recorded.

Treatment Regimens

All patients in this series were treated with first line ipilimumab plus nivolumab therapy. Patients were treated either with standard regimen (ipilimumab 3 mg/kg with nivolumab 1 mg/kg every 3 weeks) [21], or the alternate dosing regimen (ipilimumab 1 mg/kg with nivolumab 3 mg/kg every 3 weeks) [22]. Doses were generally rounded up to the nearest vial size, as the toxicity and effectiveness of these agents is similar across a broad dose range. The number of induction and maintenance doses administered were recorded. Detailed information regarding the treatment course was collected, including the treatment start and end dates and subsequent treatments administered following the initial ICI therapy.

Response Assessment

Information about the best objective response rate (BORR) at one year after the initiation of therapy was recorded, as well as data on ICI toxicity and steroid usage. The study evaluated the response to treatment assessed one year from the start of ipilimumab plus nivolumab therapy using the RECIST 1.1 criteria [23]. This assessment categorized patients as having a complete response (CR) if there was no detectable disease, a partial response (PR) if there was more than a 30% reduction in disease, stable disease (SD) if there was less than a 30% reduction or less than a 20% increase in disease, and progressive disease (PD) if there was more than a 20% increase in the index lesion or the presence of new lesions. This assessment considered both primary and metastatic lesions. The date of progression, MBM response status and date and cause of death (if applicable) were noted. If patients were alive, the date of the last follow-up was recorded. Data analysis concluded on September 11, 2023.

Statistical Analysis

Progression-free survival (PFS) and overall survival (OS), from the date of treatment start to the date of progression or date of

death, was analyzed via the technique of Kaplan and Meier [24]. Descriptive statistical measures, including the median and standard deviation were calculated via the Excel spreadsheet.

Results

From 2017 to 2022, 171 patients were treated at our institution with ipilimumab plus nivolumab combination therapy. This included 75 patients who received ipilimumab plus nivolumab therapy as first-line therapy for metastatic cutaneous melanoma.

Of these 75 patients, 29 received the standard ipilimumab plus nivolumab regimen (38.7%) while 45 patients received the alternate regimen (60%). An additional patient received the standard regimen and then was switched to the alternate regimen (1.3%), due to insurance requirements. Overall, 32 patients achieved a CR (42.6%) following ipilimumab plus nivolumab treatment. This included 13 patients who received standard dosing regimen (40.6%), and 19 patients received the alternate dosing regimen (59.4%). Four of the 29 patients who received the standard regimen developed delayed MBM (13.8%). Only 3 of the 45 patients who received the alternate dosing regimen developed delayed MBM (7.1%)($p>0.05$). The demographics of these 7 patients that developed delayed onset MBM following the start of ICI treatment are shown (Table 1).

All seven patients were Caucasian. Their median age was 63 (± 17.5 SD) years old (range 35-86). Four patients were female (57.1%), and 3 patients were male (42.9%). Of the patients who developed delayed onset of brain metastases, 4 patients had BRAF V600 mutation (57.1%), 1 patient had an NRAS Q61R mutation, 1 patient had a NF-1 R1362* truncation mutation, and 1 patient had a KIT A829P mutation. At the initial start of ipilimumab plus nivolumab treatment, 6 patients had normal lactate dehydrogenase (LDH) levels (85.7%), and only 1 patient had an elevated LDH levels. Two patients were receiving steroids during initial CKI therapy (28.6%). All 7 patients experienced some degree of immunotherapy related toxicity, such as fatigue, rash, fever, headache, nausea, diarrhea, and colitis. Five of these 7 patients also received other forms of treatment after diagnosis of MBM, such as BRAF/MEK inhibitors (3), whole brain radiation therapy (WBRT) (3), surgical resection (2), radiosurgery (1), and nilotinib (1) (Table 2). The remaining two patients deteriorated so quickly that they did not receive further therapy.

Patient Outcomes:

Individual patient treatment outcomes for the seven patients are shown (Table 2). The median length of time from treatment initiation to diagnosis of MBM was 4.8 months (± 7.7 months) (Figure 1). Only one patient developed CNS progression more than 1 year following the start of treatment.

This BRAF mutant patient had an unusually complicated clinical course. Initial ipilimumab plus nivolumab therapy resulted in the development of fevers and hepatic toxicity, leading to early cessation of treatment. The patient subsequently received multiple cycles of treatment with TT after multiple episodes of systemic disease progression. Following eventual CNS progression, the patient had surgical resection of a CNS lesion with stereotactic radiotherapy to the resection cavity. Subsequently, there was development of additional multifocal brain metastases. At this time, the patient was retreated with ipilimumab plus nivolumab with addition of whole-brain radiotherapy, prior to eventual demise due to brain metastases.

We evaluated treatment response and survival in patients with delayed CNS progression. Median progression-free survival (PFS) was only 4.8 ± 4.4 months from the date of CNS progression (Figure 2A). There were no clinical responders to salvage therapies (Table 2). The development of delayed-onset brain metastases had a very adverse effect on patient outcomes. The median overall survival (OS) from the diagnosis of MBM in these 7 patients was 8.4 ± 10.6 months (Figure 2B). All patients with delayed-onset MBM died due to their CNS disease, rather than from systemic progression.

UPN	Age	Sex	Primary Site	Site of Metastases	Stage	Initial LDH	PD-1 (%)	TMB (#/mb)	Mutation	Comorbidities
1	63	F	Trunk	LN, liver, retroperitoneum, lung	IVC	207	1	11	NRAS Q61R	GERD
2	59	M	Extr	lung	IVB	120			NF-1 R1362* truncation	Asthma
3	75	M	Trunk	LN	IVA	209	5	20	BRAF V600K	Nonmelanoma skin cancers, hypertension
4	86	F	UNK	groin, liver	IVC	362		3	BRAF V600E	COPD, HTN, ovarian cancer
5	67	M	Trunk	LN	IVA	131	<1	>10	KIT A829P	Hypopituitarism, hypogonadism, SCCHN
6	35	F	Trunk	lung, axilla	IVB	205	0	5	BRAF V600E	Back pain, seizure, stomach ulcer, sleep apnea, DVT
7	44	F	Trunk	adrenal gland	IVC	198		5	BRAF V600E	Low back pain

Abbreviations: UPN, unique patient number; LDH, lactate dehydrogenase; TMB, tumor mutation burden per megabase; C, Caucasian; Extr, extremity; UNK, unknown primary; LN, lymph node; GERD, gastroesophageal reflux disease; DVT, Deep Vein Thrombosis; PE, Pulmonary Embolism; HTN, hypertension; COPD, Chronic Obstructive Pulmonary Disease; SCCHN, squamous cell carcinoma of the head and neck.

Table 1: Patient Demographics.

UPN	Regimen	I+N doses	Nivolumab maintenance doses	BORR	PFS (mo)	OS (mo)	CKI Toxicity	Other treatment	Time from Tx start to brain mets (months)	Current Status
1	Standard	4	0	PD	1.4	5.2	Rash, headaches, nausea, diarrhea, ulcerative colitis	-	1.4	DOD-CNS
2	Standard	1	3	PD	4.8	5.3	diarrhea	-	4.8	DOD-CNS
3	Alternate	2	0	PD	1.4	8.4	diarrhea	WBRT	0.7	DOD-CNS
4	Alternate	4	2	PD	1.6	6.9	nausea	BRAF/MEK inhibitors	1.8	DOD-CNS
5	Alternate	4	5	PD	6.2	8.7	hot flashes, fatigue, rash, diarrhea	Nilotinib, WBRT	6.2	DOD-CNS,SYS
6	Alternate	3	1	PD	13.4	35.1	hepatitis, fever	BRAF/MEK inhibitors, RT	23.0	DOD-CNS
7	Standard	1	3	PD	7.1	9.8	fevers	BRAF/MEK inhibitors	7.1	DOD-CNS

Regimen:
Standard: Ipilimumab (3 mg/kg) + Nivolumab (1mg/kg) every 3 weeks i.v. followed by nivolumab maintenance
Alternate: Ipilimumab (1 mg/kg) + Nivolumab (3mg/kg) every 3 weeks i.v. followed by nivolumab maintenance
Abbreviations: UPN, unique patient number; I, ipilimumab; N, nivolumab; CKI, checkpoint inhibitor; PFS, progression free survival; OS, overall survival; Tx, treatment; CR, complete response; PR, partial response, SD, stable disease; PD, progressive disease; SCCHN, squamous cell carcinoma of the head and neck; RT, radiation therapy; WBRT, whole brain radiation therapy; BRAF/MEK, Braftovi/Mekinist; DOD-SYS, died of disease-systemic progression; DOD-CNS, died of disease-central nervous system progression.

Table 2: Patient treatment outcome.

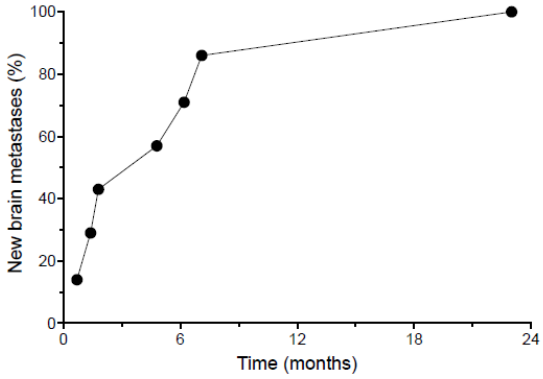

Figure 1: The median length of time from treatment initiation to diagnosis of MBM.

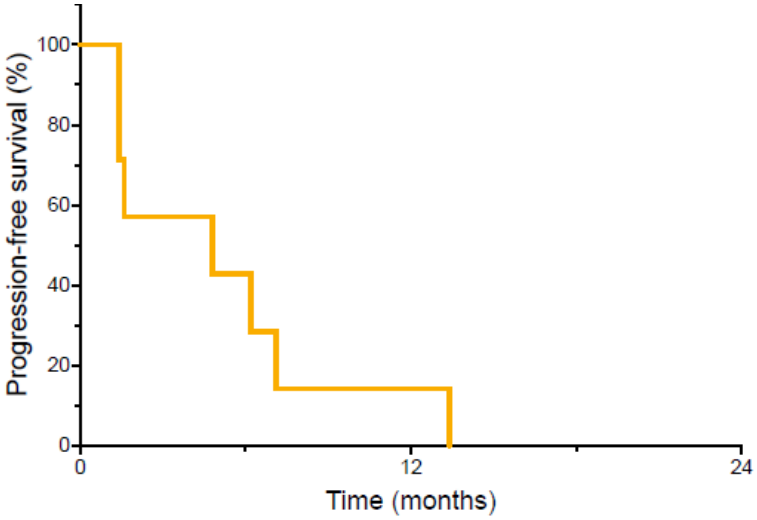

Figure 2A: Median progression-free survival (PFS) was only 4.8 ± 4.4 months from the date of CNS progression.

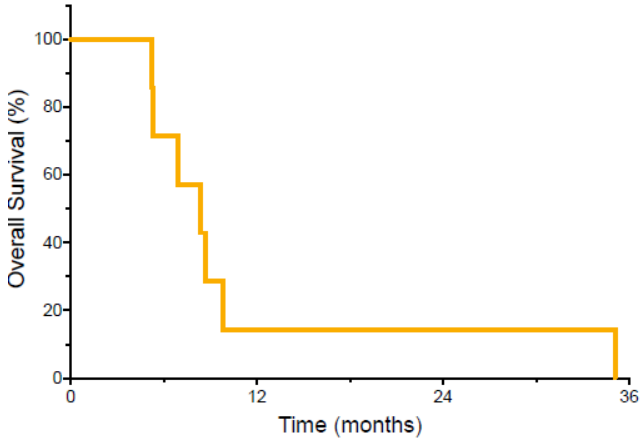

Figure 2B: The median overall survival (OS) from the diagnosis of MBM.

Discussion

Historically, the development of brain metastases in metastatic melanoma patients has had an ominous significance. Patients who developed brain metastases had a very high mortality and only a brief median survival (2-3 months) [4-7].

In the chemotherapy era, the alkylating agent temozolomide was postulated to have increased CNS activity, compared to the parental drug, dacarbazine. This was believed to be due to lipophilicity and increased CNS penetrance [25]. However, in a randomized comparison of temozolomide and dacarbazine in metastatic melanoma patients without brain metastases at diagnosis, the frequency with which brain metastases developed with either drug was not statistically different [6]. Within 3 years of starting therapy, approximately 30-45% of the enrolled patients in both arms had developed MBM [6]. Patients with MBM have historically had a 5-year survival rate of under 10% [26]. Most of the long-term survivors only had a solitary, surgically respectable lesion.

Over the past decade, the treatment landscape for metastatic melanoma has significantly improved with the development of immunotherapy employing immune checkpoint inhibitors [27]. These agents demonstrated a higher response rate and lower adverse effects in comparison to chemotherapy [28]. In addition, durable, complete remissions were observed in many patients treated with ICI [21].

Combination immunotherapy has also been shown to have significant clinical activity, even in patients who have asymptomatic MBM when diagnosed at initial diagnosis of metastatic melanoma. Ipilimumab plus nivolumab treatment has resulted in a significant percentage of patients with asymptomatic initial brain metastases achieving a durable complete remission, with almost 50% alive at 3-5 years [18,19,29]. Response of larger, symptomatic lesions is more infrequent [18,19].

Targeted therapy (TT) such as the combination of BRAF and MEK inhibitors has also demonstrated significant clinical activity in metastatic melanoma patients with somatic mutations in BRAF V600. However, only about 15-20% of patients without CNS metastases treated with BRAF/MEK inhibitors achieved 5-year progression free survival, despite ongoing therapy [30-32]. TT also has demonstrated clinical activity against asymptomatic MBM. However, long-term responses and remissions were uncommon [33]. Progression-free and overall survival following TT were further reduced in patients with poor performance status, >3 metastatic sites, and elevated LDH [19,34-36].

A large German multicentre study comparing immunotherapy and TT in BRAF-mutant patients suggested a reduction in the development of MBM in patients treated with immunotherapy [33]. At 24-month median follow-up, the incidence of MBM in patients receiving targeted therapy was 30.3% opposed to 22.2% following immunotherapy. This study concluded that the use of immunotherapy reduced or delayed the development of MBM. It should be noted that this study included patients treated with a variety of different regimens.

We have previously shown a 7% incidence brain metastases following any form of initial checkpoint inhibitor based immunotherapy for metastatic melanoma [20]. In our current study, only 9.3% of metastatic melanoma patients treated with first-line ipilimumab plus nivolumab treatment ever progressed in the CNS. Thus, we proposed that ipilimumab plus nivolumab-based immunotherapy significantly reduces the risk of subsequent MBM. This observation needs to be confirmed in a larger prospective data set. It should also be noted that none of our patients developed meningeal carcinomatosis.

When we compared patients who received the alternate ipilimumab plus nivolumab dosing regimen to those that received the standard regimen, there appeared to be a 2-fold lower risk of developing MBM. Due to the small patient numbers, this difference did not reach statistical significance. This apparent difference may be due to a lower rate of treatment interruption due to toxicity. Thus, our results should be considered hypothesis generating. Our results further suggest that the incidence of delayed MBM may be an additional important endpoint to consider in the development of future clinical trials for metastatic melanoma.

Due to the decreasing frequency of brain metastases following ICI therapy, we evaluated the clinical course and outcome of the uncommon patients who progressed in the brain following ipilimumab plus nivolumab therapy. Our current study revealed that the interval between treatment initiation and CNS progression was generally less than a year. Thus, periodic screening for development of CNS metastases, especially during the first year of immunotherapy, seems prudent.

For patients with delayed CNS progression following ipilimumab and nivolumab combination therapy, immunotherapy along with various other available treatment modalities such as TT and radiotherapy seemed to have limited efficacy. This underscores a critical need for continued research and development of more effective therapeutic options to manage and treat CNS metastases in melanoma patients.

Conclusions

Patients with metastatic melanoma treated with the combination immunotherapy were found to have a low incidence of delayed onset brain metastases. Only 9.3% of patients treated with first-line ipilimumab plus nivolumab ever developed CNS progression. The alternate ipilimumab plus nivolumab treatment dosing schedule

may result in further decreases in the frequency of delayed onset brain metastasis. The latter observation requires confirmation in a larger number of patients. Most CNS progression occurred within the first year after starting immunotherapy, highlighting the need for more frequent monitoring during this interval. Despite the effectiveness of combination immunotherapy in reducing development of MBM, outcome of these rare patients was quite poor. Patients did not appear to benefit from additional immunotherapy, targeted agents, surgery or radiotherapy. Further research is essential to provide more effective treatment options for this challenging patient population. Limitations of this study include a relatively small patient sample. However, all patients were treated in a consistent fashion by a single physician.

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Ethical Considerations: This retrospective data analysis project was reviewed by the Western IRB Chair and deemed exempt from full board review.

Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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