Clinical aspects of immunotherapy and targeted therapy of advanced melanoma

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Chapter 5

Targeted treatment and immunotherapy in leptomeningeal metastases from melanoma

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ABSTRACT

Background

Historically leptomeningeal metastases (LM) from melanoma has a poor prognosis, with a median survival of only two months despite treatment. Targeted therapy and immune checkpoint inhibitors are promising new treatment options in advanced melanoma. We sought to determine the impact of targeted therapy and immunotherapy on the outcome of melanoma patients with LM, and to evaluate the influence of prognostic factors.

Patients and Methods

We analyzed a series of 39 consecutive patients diagnosed with LM from melanoma between May 2010 and March 2015 treated at the Netherlands Cancer Institute. Thirty-four of these patients also had brain metastases. Statistical analyses assessed the influence of clinical and biological characteristics on survival.

Results

Median overall survival of the entire cohort was 6.9 weeks (95% CI 0.9 – 12.8). Due to a poor performance status or rapidly progressive disease, fourteen patients received no treatment. Median overall survival of untreated patients after the diagnosis of LM was 2.9 weeks versus 16.9 weeks for treated patients ($p < 0.001$). Median survival of 21 patients treated with systemic targeted therapy and/or immunotherapy, with or without RT was 21.7 weeks (range 2 – 235 weeks). Five patients had LM without brain metastases. Three of these patients died within three weeks before any treatment was given, whereas two patients are in ongoing remission for 26 weeks (following dabrafenib) and 235 weeks (following WBRT and ipilimumab). Elevated serum LDH and S100B at diagnosis of LM were associated with shorter survival.

Conclusion

Leptomeningeal metastases from melanoma still has an extremely poor prognosis. As observed in extracranial metastatic disease, new treatment modalities such as systemic targeted therapy and immune checkpoint inhibitors seem to increase overall survival in LM, and may result in long-term remission. These new treatment options should be considered in patients with LM.

INTRODUCTION

Leptomeningeal metastases (LM) is one of the most devastating complications in solid tumors. It is clinically detected in about 5% of patients with cancer, mainly in breast cancer, lung cancer and melanoma [1]. Higher numbers are reported in autopsy series of patients with brain metastases [2, 3]. Difficulties to differentiate symptoms of LM from those caused by brain metastases (BM) may contribute to this underestimation, but limited sensitivity of diagnostic tests may also play a role. Besides, specific clinical signs are absent in at least 25% of patients at the diagnosis of LM [4]. The golden standard for the diagnosis of LM is demonstration of tumor cells in the cerebrospinal fluid (CSF). Sensitivity of CSF cytology is 50% on first lumbar puncture, and increases to 80% after repeated punctures [5]. The diagnosis can also be made by magnetic resonance imaging (MRI). MRI has a sensitivity and specificity of about 75% [6]. On clinical suspicion of LM, typical leptomeningeal contrast enhancement on MRI is considered diagnostic. Median survival of untreated patients with LM from solid tumors is only 4 to 6 weeks, usually due to progressive neurologic dysfunction [7]. Focal radiotherapy (RT) can relieve neurologic symptoms, but has no significant effect on survival [8]. Intrathecal chemotherapy (IT) is considered the mainstay of treatment of LM but its efficacy remains uncertain [5]. In LM from breast cancer, systemic treatment appeared at least as effective but less toxic than IT chemotherapy, suggesting that the blood-CSF barrier is not the crucial factor in LM [9]. Only a few series of patients with LM from melanoma have been published with reported median overall survival of 8 to 10 weeks [10, 11].

Two new treatment modalities have significantly improved survival in patients with advanced melanoma. Vemurafenib and dabrafenib, inhibitors of the mutated BRAF protein (evident in 50% of melanoma patients) have shown impressive albeit temporary responses, also in BM [12, 13]. The second new treatment strategy is the application of immune checkpoint inhibitors, like ipilimumab and nivolumab that enhance the anti-tumor T-cell response and, importantly, induce long lasting responses in a subset of patients. A complete response in a patient with LM from melanoma treated with radiotherapy and ipilimumab was reported earlier [14]. In this study we sought to determine the influence of new treatment modalities and of prognostic factors on outcome in patients with LM.

MATERIAL AND METHODS

A cohort of 39 consecutive patients diagnosed with LM from melanoma at the Netherlands Cancer Institute between May 2010 and March 2015 was analyzed. Diagnosis was based on MRI and/or CSF cytology.

Data collected included age, gender, date of diagnosis of melanoma, date of diagnosis of LM, performance status at diagnosis of LM, presence of brain metastases, number (1, 2-5 or > 5) and volume (< or > 2 cm diameter) of brain metastases, neurological signs and symptoms at diagnosis of LM, use of corticosteroids, CSF results (leukocyte count, protein, glucose, LDH), treatment for brain metastases and/or LM, date of death or last follow-up, serum blood lactate dehydrogenase (LDH) and S100B levels at diagnosis of LM.

Statistical analysis

Survival was measured from the date of diagnosis of LM to death, or last follow-up. Kaplan-Meier curves were made to estimate survival percentages. A *p*-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 22 (IBM corp., Armonk, NY, USA). Log-rank test was used to assess the influence of baseline characteristics on survival.

RESULTS

Patient characteristics

Patient characteristics at time of diagnosis of LM are summarized in Table 1. Median time from diagnosis of melanoma to LM was 3.2 years (range 0 – 29). At time of data analysis (June 2015) four patients were still alive. At diagnosis of LM ten patients (26%) had a WHO performance status (PS) of 2 (26 %) and six patients (15%) a PS of 3. The diagnosis LM was established in 36 patients (92%) by MRI and in three patients (8%) by CSF cytology. Thirty-three patients (85%) had neurological symptoms. The most common LM symptoms at diagnosis were headache (46%), nausea and vomiting (44%), gait difficulty (39%) and seizures (31%). In six asymptomatic patients, diagnosis of LM was an incidental finding at screening or follow-up MRI. Thirty-four patients (87%) also had brain metastases (BM). Ten patients (29%) were not treated for their BM. Thus, twenty-four patients (71%) were treated for BM; 16 patients received RT and 21 patients systemic therapy.

Table 1. Patient characteristics and univariate analysis of factors associated with survival

	No. of patients (%)	Median OS (95% CI)	p value
Age, years	**52.9 years (range, 26-84)**		
Sex			
Male	**23 (59)**	**6.4 (1.5 – 11.3)**	**0.8**
Female	**16 (41)**	**8.0 (0 – 17.5)**	
WHO performance status			
0-1	**22 (56)**	**18.6 (9.8 – 27.9)**	**< 0.001**
2-3	**16 (41)**	**3.6 (2.7 – 4.4)**	
Unknown	**1 (3)**		
Lactate dehydrogenase			
0-248 U/L (normal)	**19 (49)**	**18.6 (10.8 – 26.9)**	**< 0.001**
> 248 U/L (elevated)	**14 (36)**	**3.1 (1.6 – 4.7)**	
Unknown	**6 (15)**		
S100B			
0-0.10 µg/L (normal)	**9 (23)**	**24.9 (15.7 – 34.0)**	**0.03**
> 0.10 µg/L (elevated)	**23 (59)**	**5.1 (1.8 – 8.5)**	
Unknown	**7 (18)**		
Brain metastases			
Yes	**34 (87)**	**6.9 (1.1 – 12.6)**	**0.43**
No	**5 (13)**	**3.1 (1.3 – 5.0)**	
Number of brain metastases*			
None	**5 (13)**	**HR 0.5 (0.1 – 1.7)**	**0.24**
1	**2 (5)**	**HR 1.6 (0.4 – 6.8)**	**0.54**
2-5	**9 (23)**	**HR 0.5 (0.2 – 1.1)**	**0.09**
> 5	**23 (59)**	**1 (ref)**	
Treatment for LM			
Yes	**25 (64)**	**16.8 (11.6 – 22.1)**	**< 0.001**
No	**14 (36)**	**2.9 (0 – 6.0)**	
Treatment for LM*			
No treatment	**14 (36)**	**1 (ref)**	
RT	**4 (10)**	**HR 0.53 (0.2 – 1.7)**	**0.28**
Systemic	**10 (26)**	**HR 0.17 (0.06 – 0.5)**	**0.001**
RT + systemic	**11 (28)**	**HR 0.07 (0.02 – 0.2)**	**< 0.001**
Symptoms of LM			
Yes	**33 (86)**	**6.4 (2.6 – 10.3)**	**0.45**
No	**6 (14)**	**11.0 (0 – 40.0)**	

Abbreviations: HR, Hazard Ratio; LM, leptomeningeal metastases; OS, Overall Survival; RT, radiotherapy; WHO, World Health Organization

* Hazard Ratio

Treatment and survival

Twenty-five patients (64%) were treated for LM (for characteristics of treated patients see Table 2).

Table 2. Characteristics of the treated patients at time of diagnosis of LM

Patient no.	PS at diagnosis	Age at diagnosis (years)	Symptoms of LM	Treatment	Time from LM to death (weeks)
1	0	50	Cerebral	vemurafenib, WBRT	21.7
2	1	66	Cerebral	WBRT, ipilimumab	235.1+
3	2	61	Cerebral	dabrafenib+trametinib	3.1
4	1	39	Cerebral and cranial nerves	ipilimumab, WBRT	15.1
5	1	44	Cerebral	vemurafenib, WBRT	15.3
6	0	59	Cerebral	dabrafenib+trametinib, WBRT	24.9
7	1	64	None	vemurafenib, ipilimumab	26.0
8	0	64	Cerebral	WBRT, vemurafenib	18.9
9	1	47	Cerebral	WBRT	2.3
10	0	65	Cerebral and cranial nerves	ipilimumab	6.0
11	0	48	None	vemurafenib	48.4
12	1	49	Cerebral	ipilimumab, WBRT	10.0
13	0	50	None	WBRT, DTIC, ipilimumab	68.6
14	3	51	Cerebral	WBRT	3.6
15	0	50	Cerebral and cranial nerves	WBRT, dabrafenib+trametinib, ipilimumab	47.0
16	0	52	Cerebral	vemurafenib, WBRT	33.6
17	0	49	Spinal	spinal RT, dabrafenib+trametinib	61.9+
18	3	67	Cerebral	WBRT	15.9
19	2	26	Cerebral and cranial nerves	vemurafenib	3.9
20	2	49	Cerebral and cranial nerves	SRT	5.1
21	3	73	Cerebral	vemurafenib	16.9
22	1	57	Cerebral	ipilimumab	6.4
23	1	60	Cerebral and cranial nerves	ipilimumab	2.0
24	1	52	Cerebral, cranial nerves and spinal	dabrafenib, ipilimumab	16.4+
25	0	77	Spinal	dabrafenib	26.4+

+: patient alive at time of analysis

Abbreviations: LM, leptomeningeal metastases; PS, performance status; SRT, stereotactic radiotherapy; RT, radiotherapy; WBRT, whole brain radiotherapy

Treatment for LM included cranial or spinal RT in 15 patients and systemic therapy in 21 patients. No IT chemotherapy was given. Of the 21 systemically treated patients, eight patients were treated with a BRAF inhibitor (vemurafenib or dabrafenib), three patients were treated with a BRAF inhibitor in combination with a MEK inhibitor (dabrafenib and trametinib), six received ipilimumab (a CTLA-4 monoclonal antibody), two patients were treated with ipilimumab followed by a BRAF inhibitor, one patient was treated with dabrafenib in combination with trametinib followed by ipilimumab, and one patient was treated with dacarbazine followed by ipilimumab. Thus, a BRAF inhibitor was given in 14 patients, and ipilimumab in 10 patients. Fourteen patients (36%) did not receive any therapy after the diagnosis of LM due to rapid disease progression or poor performance. Of the 16 patients with a PS of 2 or 3, only six (38%) received treatment for LM (three RT and three systemic treatment). Patients with a performance status of 2 or 3 had a significantly worse median overall survival compared to patients with a performance status of 0 or 1 (3.6 versus 18.8 weeks $p < 0.001$). There was no significant difference in median survival between untreated patients with a PS of 2 or 3 and the six patients who received treatment (1.9 versus 3.9 weeks $p = 0.075$). Median overall survival for all patients was 6.9 weeks (95% CI 0.9 – 12.8) (Figure 1).

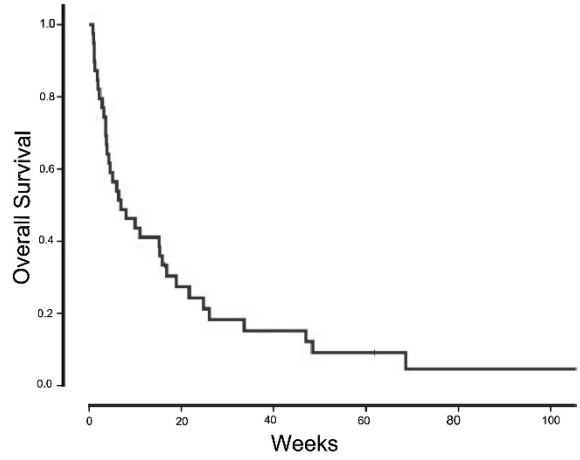

Figure 1. Kaplan-Meier curve for overall survival in weeks. Median overall survival = 6.9 weeks

There was no significant difference in survival in patients with or without neurological symptoms ($p = 0.45$). There was also no difference in survival in patients with or without corticosteroids ($p = 0.85$). Volume of BM was not significantly related to overall survival ($p = 0.54$). Of the fourteen patients who did not receive any therapy for their LM, median survival was 2.9 weeks (95% CI 0 – 6.0) versus 16.9 weeks for treated patients (95% CI 11.6 – 22.1) ($p < 0.001$). Median survival of the 21 patients treated with a BRAF inhibitor and/or ipilimumab was 21.7 weeks (range 2 – 235 weeks). Median survival of the 14 patients

in which treatment included a BRAF inhibitor (with or without a MEK inhibitor) was 24.9 weeks (range 3 – 62 weeks) (with RT 25 weeks, without RT 16 weeks). Median survival of the ten patients in which treatment included ipilimumab was 15.8 weeks (range 2 – 235 weeks) (with RT 47 weeks, without RT 6 weeks). Median survival of the four patients treated with RT only was 4.3 weeks (range 2 – 16 weeks).

Serum lactate dehydrogenase (LDH) at diagnosis of LM was available from 33 patients (85%); fourteen of these (42%) had an increased LDH (> 248 U/L). Patients with LM and an increased LDH had a significant shorter survival of 3.1 weeks (95% CI 1.5 – 4.7) compared to 18.9 weeks for patients with normal LDH (95% CI 10.8 – 26.9, $p < 0.001$, Figure 2).

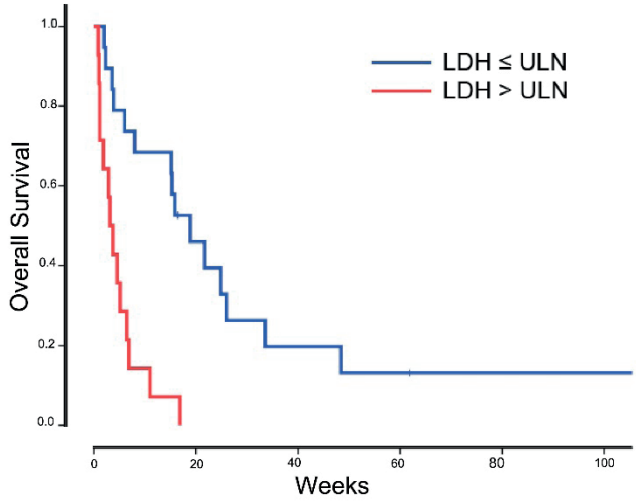

Figure 2. Kaplan-Meier curve for LDH. Median overall survival in patient group with LDH ≤ ULN = 18.9 weeks ($n = 19$), median overall survival in patient group with LDH > ULN = 3.1 weeks ($n = 14$). LDH, lactate dehydrogenase; ULN, upper limit of normal.

Patients with increased LDH were less likely to receive any treatment modality for LM; four of 14 patients with increased LDH were treated versus 18 of 19 patients with a normal LDH ($p < 0.001$). Serum S100B values were available from 32 (82%) patients at time of LM diagnosis. Nine patients (28%) had a normal serum S100B level, and 23 (72%) had an increased serum S100B level. Patients with a normal serum S100B level had a median overall survival of 24.9 weeks (95% CI 15.7 – 34.0) versus 5.1 weeks (95% CI 1.7- 8.5) for patients with an increased S100B level ($p = 0.04$). Thirty-five patients had died at time of analysis. Twenty-four patients (68%) died primarily of neurological progression, eight patients (23%) of both intracranial and extracranial progression, while three deaths (9%) were not directly tumor related. Of the twenty-four patients who primarily died of neurological progression, two patients died of progression of brain metastases, 11 patients due

to progression of LM while in 11 patients cause of death could not be attributed to LM or BM with certainty. Of the four patients still alive at time of analysis one patient was treated with local RT at L2-S5 (1x8 Gy) followed by dabrafenib and trametinib for widespread spinal LM causing a cauda equina syndrome (Figure 3). An ongoing response of 62 weeks was achieved of LM and of asymptomatic brain metastases.

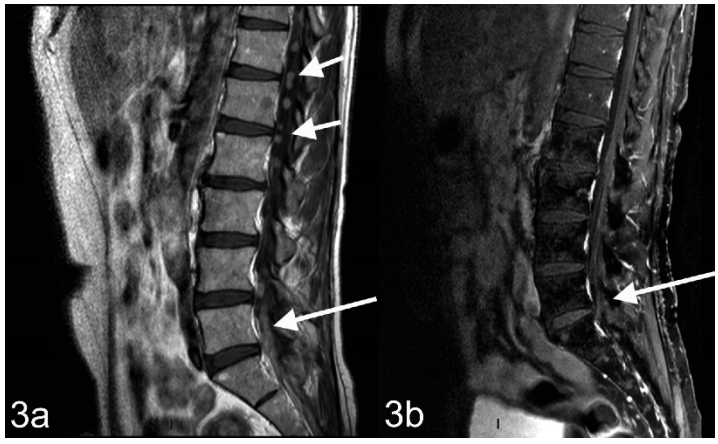

Figure 3. Post-gadolinium sagittal MRI T1-weighted images of Th11-S2, demonstrating thickening and enhancement of the cauda equine nerve roots (long arrows) and enhancing intradural nodules (short arrows) in December 2013 before RT L2-S5 and start of dabrafenib and trametinib (a), and only slight enhancement of lumbosacral nerve roots in January 2015 during treatment with dabrafenib and trametinib (Post-gadolinium sagittal MRI T1 with fat-suppression) (b).

Patient characteristics and treatment characteristics in patients with LM only

Five patients had LM without brain metastases. Three of these five patients presented with headache, vomiting, seizures and cranial nerve involvement with rapid clinical deterioration, and died within three weeks before any specific treatment was given.

The fourth patient presented with weight loss, fatigue and pain in both legs twenty-eight years after resection of a melanoma on his back. A PET-CT scan showed metastases in lymph nodes, kidneys, peritoneum, small bowel, and subcutaneously and pathologic FDG activity in the lumbar spinal canal. Additional MRI of the lumbar spine showed diffuse LM. He is currently being treated with dabrafenib, resulting in a neurological and radiological partial response for six months now. He did not receive local RT.

The fifth patient presented with progressive nausea and vomiting. Cerebral MRI showed multifocal enhancement of the leptomeninges consistent with the diagnosis of LM. She also had lymph node and lung metastases. She was treated with WBRT and 4 cycles of

ipilimumab, resulting in a complete radiological and clinical remission (see also [14]). She is free of disease for four and a half years now.

DISCUSSION

This retrospective study confirms the well-known dismal outcome of LM, and shows that for patients with melanoma, outcome is even worse compared to patients with LM from other solid tumors. More than one third of our patients had a performance status too poor for anti-tumor treatment and died in a median time of less than three weeks. The typical steep decline in the survival curve for about one third of the patients is consistent with data from literature [5, 8, 11]. A remarkable and encouraging new finding in our study are the long-term survivors when patients are being treated with targeted treatment or immunotherapy. Moreover, the median survival of 22 weeks following these new therapies compares favorably to reported results of IT chemotherapy for LM from melanoma [10, 11]. Earlier studies on immunotherapy for LM from melanoma included IT interleukin-2 (IL-2), that showed incidental responses, but also marked toxicity [11, 15]. The new checkpoint inhibitor ipilimumab has shown impressive responses in patients with advanced melanoma with a four months increase in median survival and, importantly about 20% long term survival [16]. Ipilimumab enhances anti-tumor T cell activation in the lymph nodes. As activated T-cells can cross the blood-brain barrier or blood-CSF barrier, these barriers seem less relevant for a response within the CNS. In patients with BM not requiring steroids, the intracranial response after ipilimumab approximated the extracranial response (RR 24% vs 27%) [17]. Combination with RT may increase the response by the so-called abscopal effect, i.e. increased release of tumor antigen by RT can increase antigen presentation to T cells [18]. Responses to immune checkpoint inhibitors can be delayed as first an increase of activated T cells at the tumor location is needed. In contrast, the response of metastasized melanoma to BRAF inhibitors is prompt. The response rate is about 50% in advanced BRAF mutated melanoma [19]. Although vemurafenib does not cross an intact blood-brain barrier, vemurafenib has shown to be effective in brain metastases from melanoma, but also high rates of intracranial relapse during extracranial disease control were observed [20]. Dabrafenib also does not cross an intact blood-brain barrier but similar intracranial and extracranial responses (+/- 40%) were reported after first-line treatment with dabrafenib [12, 21]. A response of LM to BRAF inhibitors as single agent has not been reported yet. In the present study an ongoing response of 62 weeks of LM outside the RT portal was documented following dabrafenib and trametinib treatment, again demonstrating that the blood-CSF barrier does not exclude successful systemic treatment of overt CNS metastases. Upregulation of the MEK pathway causes

BRAF inhibitor resistance, so combination with the MEK inhibitor trametinib probably prolonged the duration of response in our patient.

At univariate analysis, elevated serum LDH and S100B levels, both markers for tumor burden in melanoma, were associated with shorter survival. Most of the patients with elevated LDH were not treated after the diagnosis LM because of poor performance status and rapid clinical deterioration. Other possible prognostic factors, like presence and kind of neurologic symptoms, use of corticosteroids, and presence, volume and number of brain metastases were not associated with survival.

CONCLUSION

Leptomeningeal metastases from melanoma still has an extremely poor prognosis. As observed in extracranial metastatic disease new treatment modalities, such as systemic targeted therapy and immunotherapy seem to increase median survival with a few months, and may result in long-term remissions. Combining these therapies with radiotherapy might enhance their efficacy. Especially in LM patients with a good performance score and low serum LDH and S100B levels these treatment options should be considered.

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