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Intrathecal administration of tumor-infiltrating lymphocytes is well tolerated in a patient with leptomeningeal disease from metastatic melanoma: A case report

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Abstract

Patients with leptomeningeal disease (LMD) from melanoma have very poor outcomes and few treatment options. We present a case of intrathecal (IT) administration of autologous tumor infiltrating lymphocytes (TIL) in a patient with LMD from metastatic melanoma. The patient developed LMD after previous treatments with surgery, high-dose bolus interleukin-2 (HD IL-2), and systemic TIL infusion and experienced radiographic progression after intrathecal IL2 (IT IL-2) therapy. The patient received weekly treatment with increasing numbers of IT TIL followed by twice-weekly IT IL-2. The patient received three IT TIL infusions and did not experience any toxicities beyond those expected with IT IL-2 therapy. Analysis of cerebrospinal fluid (CSF) demonstrated increased inflammatory cytokines following the intrathecal treatments. Subsequent imaging demonstrated disease stabilization, and neurological deficits also remained stable. The patient expired five months after the initiation of IT TIL therapy with disease progression in the brain, liver, lung, and peritoneal and retroperitoneal lymph nodes, but without LMD progression. These results demonstrate the safety of intrathecal administration of TIL in melanoma patients with LMD and support the feasibility of conducting a prospective clinical trial to determine this therapy's clinical benefit among these patients.

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Conflict of Interest:

All authors were employed by The University of Texas M.D. Anderson Cancer Center in 2011 at the time of patient's treatment. Dr. Radvanyi is currently an Adjunct Member of the H. Lee Moffitt Cancer Center & Research Institute as well as employed by Lion Biotechnologies. Seth Wardell is now an employee of Lion Biotechnologies. Dr. Patrick Hwu now serves on the Lion Biotechnologies Advisory Board and Dr. Chantale Bernatchez serves as a consultant.

Introduction

The treatment of advanced melanoma has improved dramatically in the last decade. However, improving outcomes in patients with central nervous system (CNS) metastases remains a critical challenge, particularly among those with metastatic spread to the leptomeninges (leptomeningeal disease, or LMD). The median survival of patients with LMD is only 6-10 weeks, which is significantly worse compared to patients with three or more parenchymal brain metastases. (1, 2) Treatment options for patients with LMD are very limited, and there is minimal evidence of clinical benefit. (3, 4)

Multiple immunotherapies can achieve durable disease control in patients with metastatic melanoma. However, little data is available about the safety and efficacy of these treatments among patients with LMD. Here we describe, to our knowledge, the first intrathecal administration of autologous tumor infiltrating lymphocytes (TIL) in combination with intrathecal interleukin-2 (IT IL-2) in a metastatic melanoma patient with LMD. Our results demonstrate the safety and feasibility of this therapy and provide support for prospective clinical testing in this challenging patient population.

Case Presentation

At initial melanoma presentation, a healthy 52-year-old male was diagnosed with a cutaneous melanoma to the right cheek on shave biopsy (Clark's level reported at least III, Breslow thickness at least 0.84 mm). He underwent wide local excision (residual melanoma depth 1.49mm) and sentinel lymph node biopsy, which revealed melanoma in three out of four parotid lymph nodes. He subsequently underwent a partial parotidectomy and cervical lymphadenectomy (1/35 lymph nodes positive), followed by adjuvant radiation therapy.

He enrolled in a vaccine trial (MEL-48) and received four weekly injections but developed fever and pulmonary infiltrates in week 5 and was taken off protocol. The patient was followed clinically with surveillance scans every 2 months until CT scans revealed indeterminate lung nodules, which progressed on subsequent scans. TIL were harvested from a pulmonary wedge resection. MRI of the brain also revealed new metastases, and were treated with craniotomy followed by stereotactic radiosurgery to the postoperative cavity. The patient then received one cycle of high-dose bolus IL-2 (HD IL-2), but repeat MRI of the brain showed multiple new lesions in both cerebral hemispheres. He required whole-brain radiotherapy (37.5 Gy in 15 fractions) followed by consolidative gamma knife radiosurgery to residual enhancing disease. His systemic disease also had progressed, with new liver, spleen, omentum, and axillary lymph nodes involvement as well as enlarging bilateral pulmonary metastases.

The patient enrolled in an IRB-approved clinical trial of autologous TIL and received lymphodepleting chemotherapy (Cytosan + fludarabine) per protocol. The infused total number of TIL was 35×10^9 and was followed by two cycles of HD IL-2. Repeat imaging demonstrated a mixed response, with lesions progressing within the spleen and lymph nodes but with a decrease in the size of the liver and lung metastases. CNS imaging showed a nearly complete regression of the patient's known metastatic lesions.

Development of lower-extremity weakness and numbness of the lower extremities 4 months later at time of a splenectomy prompted an MRI of the spine which revealed paraspinal muscle metastases and multiple enhancing nodules in the distal cord and nerve roots at the lumbar level, consistent with LMD. An Ommaya reservoir was placed, and the patient was initiated on IT IL-2 therapy. (5) At that time, CSF analysis showed a single large atypical cell in a background of peripheral blood, making further analysis impossible. The patient received a total of 13 IT IL-2 doses over 5 weeks, with the anticipated side effects of elevated intracranial pressure (ICP), causing nausea, vomiting, headaches and change in mentation. Opening pressure at first IT IL-2 injection was 12 cm H₂O, with values as high as 64 cm H₂O during the induction period. For symptom control, the patient required 26 additional Ommaya taps to remove CSF during this time frame. Over the course of the IT IL-2 treatment, the number of taps for symptoms of elevated ICP decreased. During the IT treatment, cytology of the patient's CSF confirmed LMD with two samples containing melanoma cells in the spinal fluid (positive HMB45 immunostain). Meanwhile, the patient's systemic extracranial disease progressed rapidly as well.

One month after initiation of the IT IL-2, the patient experienced progressive weakness of the bilateral lower extremities, and an MRI of the spine revealed worsening LMD in the lumbar area, requiring palliative radiation to T12-S1.

A repeat MRI of the spine 3 weeks after radiation treatment showed further progression of the LMD, but the systemic disease remained grossly stable.

A compassionate-use investigational new drug application (CIND 10-0060) was approved by the FDA for the intrathecal administration of autologous TIL. The first IT treatment consisted of 0.3×10^9 TIL, with no symptoms during or after the injection, and no new neurological symptoms observed. The TIL consisted of 96% CD8+ T cells. On days 1 and 4 after the IT TIL 1.2 MiU of IT IL-2 were given, with no toxicities beyond those expected with IT IL-2 treatment, including nausea, vomiting, headache, chills and transient changes in his mentation. He required CSF removal for elevated ICP (opening pressures ranging from 25 to 30 cm H₂O) on days 2, 3 and 5 after IT IL-2. The patient went on to receive 1×10^9 IT TIL the next week, and 3×10^9 IT TIL the week after, with two doses of IT IL-2 given each week during this time. For symptom control, the patient required 17 additional taps. Three weeks after the first IT TIL administration he was retreated with systemically administered autologous TILs (89×10^9 cells) and received one additional dose of IT IL-2 a few weeks later.

Cancer progression outside the CNS led to small bowel obstruction, eventually requiring resection. Repeated MRI of the spine during that time showed stabilization of the LMD, with no progression of neurological symptoms, but increased generalized weakness. Table 1 reflects the treatment schedule and correlates the clinical and radiological examination.

Repeat imaging one month later revealed progression in the lung and liver as well as peritoneal and retroperitoneal metastatic deposits. CNS imaging demonstrated multiple new parenchymal brain metastases but continued stabilization of LMD. The patient was treated with one dose of ipilimumab (3 mg/kg); one week later, he received another dose of IT IL-2.

Unfortunately, our patient's performance status deteriorated, and both ipilimumab and IT IL-2 treatments were stopped. The patient continued to undergo palliative removal of CSF via Ommaya reservoir. Five months after the first IT TIL infusion, the patient passed away at home.

Laboratory Data

T cells can secrete large amounts of cytokines when activated, and it was unclear whether the large number of IT T cells would lead to a “cytokine storm,” poor tolerance and significant side effects. As noted, clinically we found no evidence of such an event after any of the IT TIL treatments. Levels of IFN- γ , IL-10, IL-12 p70, IL-13, IL-1 β , IL-2, IL-4, IL-6, IL-8, TNF- α and TGF- β were measured in the CSF at baseline and daily for four days post-infusion for each of the three IT TIL infusions (**Fig. 1A**). No appreciable elevation in the levels of IL-4, IL-12 p70, IL-13 or TGF- β were detected when measured after any of the IT TIL infusions (data not shown). IFN- γ levels, presumably produced by activated T cells, peaked after each IT TIL infusion and returned to baseline levels within 4 days. The exception was noted after the last dose, in which levels were still elevated at the last time point recorded (4 days after IT TIL infusion #2; 105 pg/ml). The peak concentration of IFN- γ induced by each TIL infusion decreased as the number of infused TIL increased (724 pg/ml after 0.3×10^9 TIL; 610 pg/ml after 1×10^9 TIL; and 474 pg/ml after 3×10^9 TIL) (**Fig. 1B**). In contrast, TNF- α and IL-1 β levels peaked higher with each dose of IT TIL infused and remained markedly elevated at the last time point assessed (**Fig. 1C and D**). IL-10 measurements also increased after IT TIL infusion. They reached the highest peak after the second infusion and returned to baseline levels but remained high after the last infusion (**Fig. 1E**). Levels of IL-6 and IL-8 also increased significantly after each IT TIL, peaking after the last infusion and remaining high at the last time point monitored, especially with IL-8 (**Fig. 1F and G**). Interestingly, levels of IL-6 and IL-8 peaked at a lower concentration after the second IT TIL dose in comparison to the first IT TIL infusion when levels of IL-10 were highest, potentially suggesting a downregulation by IL-10. This result was not observed following the third IT TIL infusion. Although the IT infusion of increasing amounts of TIL did induce the production of inflammatory cytokines in the CSF, our patient did not experience any unexpected side effects from the IT TIL infusion.

Discussion

To our knowledge, this is the first case report describing the intrathecal administration of autologous TIL in a patient with LMD from melanoma. The patient tolerated the therapy well and experienced no side effects beyond those expected from the concurrent administration of IT IL-2. Radiographic imaging demonstrated stabilization of the patient's LMD following IT TIL treatment, which notably had progressed on prior IT IL-2 treatment alone. These results suggest that such treatment could potentially have clinical benefit.

For LMD arising from melanoma, current treatment options are limited to systemic therapy or radiation and do not change the extremely poor prognosis. Furthermore, experience with IT chemotherapy is sparse and has not been satisfactory in treating melanoma, and only limited case reports exist on the treatment with immune-stimulating agents. (6, 7)

The rationale for adding IT TIL to this patient's treatment regimen was based on the results of the systemic administration of autologous TIL in conjunction with high-dose IL-2. Multiple centers, including our own institution, have reported significant response rates in patients with metastatic melanoma. (8, 9) We also have previously reported that IT IL-2 can be administered safely in a specialized center with personnel trained to remove CSF via Ommaya reservoir to relieve symptoms due to increased intracranial pressure. Twelve of the 46 patients experienced a response, as defined by a negative CSF cytology of 4 weeks duration. (5) Median overall survival was 3.8 months (0.5-90 months) for the entire cohort and was increased to 11.5 months (7-90 months) in responders, with no death attributed to treatment. The fact that—including the patient reported here—only a small number of patients treated with IT IL-2 will achieve a durable survival led us to decide to add IT TIL to his treatment. This patient did not experience any unexpected side effects from the IT TIL infusion, an outcome that supports the feasibility of such an approach. Notably, the clinical result is consistent with observations reported in another patient treated with IT CD8+ cytotoxic lymphocytes (CTL). (10) In contrast to our case, only CD8+ CTL generated in vitro using autologous dendritic cells were used. Moreover, the IT CTLs were supported by systemic low-dose IL-2 administration, which is different from our IT IL-2 approach. Both of these cases benefitted from IT lymphocyte infusion, which resulted in at least a transient delay or reduction in the burden of the LMD. However, the treatment was unable to control the parenchymal brain disease.

IT IL-2 appears to be necessary to maintain the prolonged viability of the IT-administered cells as is the case in systemic therapy with TIL. But, as previously described, it also has an antitumor effect by itself. (8) Despite the fairly short half-life of IL-2 (only about 4 to 8 hours), its effects include a rapid induction of tumor necrosis factor alpha (TNF α) and soluble IL-2 receptor and a rapid influx of neutrophils and a prolonged presence of leukocytes. (11) We also observed TNF α levels rising after administration of IT TIL and IT IL-2, and this phenomenon may potentially explain the need for maintenance of IT IL-2.

We also demonstrated that levels of several cytokines present in the CSF are consistently increasing following IT TIL and returning to baseline prior to the subsequent IT TIL infusion. However, changes in cytokine levels in the CSF differ depending upon the cytokines tested. In our patient, we observed fluctuations in the pro-inflammatory cytokines IFN γ and TNF α following IT TIL infusion comparable to fluctuations previously observed with infusion of IT CD8+ CTL. (10) In addition, although the levels of TNF α are comparable between the two studies, we observed much higher levels of IFN γ following IT TIL as compared to the CD8+CTL infusion. In contrast to the report by Clemons-Miller, we observed vacillations in the levels of IL-10 following IT TIL infusion, whereas in their analysis, IL-10 levels did not change following CTL infusion. (10)

One important concern involving patient selection for IT therapy is the status of the patient's systemic disease and performance status. Our patient suffered from very rapidly growing systemic disease, which was responsible for his worsening performance status and ultimately his death. Parenchymal disease of the brain does not respond to any intrathecal therapy and warrants management prior to or during IT therapy with other available treatment modalities. Taken together, this suggests that patients who are candidates for IT

TIL therapy should have a good performance status, controlled systemic disease or at least treatment options available. At this point, it is also unclear how well the recent FDA agents will be able to treat or prevent the occurrence of LMD, and only a few case reports show that systemic treatment has a beneficial effect on LMD. (12-14)

Although we cannot rule out that the patient might have derived some benefit from the initial IT IL-2 administration and radiation therapy, it appears that the addition of IT TIL might have contributed to the temporary LMD stabilization, especially since the TIL have the phenotype we previously associated with clinical response. (9) Based on this case, and taken together with our experience with IT IL-2 and systemic TIL administration, we believe that the IT TIL treatment approach for selected patients with LMD from melanoma merits further investigation in a clinical trial. We are currently developing a clinical protocol to evaluate safety and efficacy in a larger cohort of patients. Importantly, CSF analysis will be crucial to identifying predictors of clinical outcomes and to suggesting additional rational strategies.

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Figure 1. Cytokine response in the CSF in response to IT TIL + IL-2

(A) Cerebral spinal fluid (CSF) was obtained from the Ommaya at the time points indicated.

(B-G) The blue bars indicate the IT TIL treatment date with the number of cells infused shown on the right Y axis. CSF was taken prior to each IT TIL infusion. The left Y axis shows the level of cytokine detected in the CSF. A Luminex[®] assay was used to determine the cytokine levels on the days shown. The cytokines shown are IFN γ (B), TNF α (C), IL-1 β (D), IL-10 (E), IL-6 (F), and IL-8 (G).

Table 1

	November/December 2010	January 2011	February 2011	March 2011	April 2011	May 2011	June 2011
IT TIL	NA	1/24/2011: 0.3×10^9 cells, 1/31/2011: 1×10^9 cells	2/7/2011: 3×10^9 cells	NA	NA	NA	
IT IL-2	11/20/2010: 1 st dose, 1.2 million units	ongoing	ongoing	ongoing, last dose 3/14/2011	NA	one dose 5/16/2013	
Systemic TIL	NA	NA	2/27/2011: 89×10^9 cells, previously 5/10/2010: 35×10^9	NA			
Ipilimumab	NA	NA	NA	NA	NA	one dose 5/17/2011 at 3mg/kg	
MRI Brain	No new parenchymal metastases or LMD	1/20/2011: no new parenchymal metastasis or LMD	Stable	Stable	Stable	Development of at least 10 metastatic parenchymal lesions	
MRI Spine	LMD distal cord and nerve roots, lumbar level	1/20/2011: Progression of LMD	Stable	Stable	Stable	Stable	
CT CAP	Stable pulmonary, hepatic and peritoneal disease	1/20/2011: New pleural effusion, stable pulmonary and hepatic metastasis, progression of peritoneal implants	Pulmonary and hepatic progression	Progression of bilateral pulmonary and hepatic metastases. Development of intussusception and small bowel obstruction	No imaging	Progression of bilateral pulmonary, hepatic, peritoneal and retroperitoneal metastases	Patient passes at home end of June 2011.
Neurocognitive Testing	1/3/2010: Mildly reduced repetition span and immediate recall in the context of intact learning and retention for verbal and nonverbal information. Mild word retrieval difficulties. He performed within normal limits across measures assessing processing speed, executive functioning, and motor dexterity.	1/21/2011: Low average to mildly impaired psychomotor speed and auditory attention span, moderately impaired encoding, memory consolidation and retrieval processes with greater evidence of memory retrieval than memory consolidation deficits.	Stable	Stable	Stable	5/15/2011: Decline in all reported parameters at time of systemic tumor progression	
Neurological Examination	Cranial nerves III-XII intact, upper extremity strength intact. 5/5. Hip flexion: R 4/5 L 2/5. Knee	Cranial nerves III-XII intact, upper extremity strength	Cranial nerves III-XII intact, upper extremity strength	Cranial nerves III-XII intact, upper extremity strength	Cranial nerves III-XII intact, upper	Further decline, overall generalized weakness, more	

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	November/December 2010	January 2011	February 2011	March 2011	April 2011	May 2011	June 2011
	extension R 4/5 L 3/5, Knee flexion R 4/5 L 3/5, Foot dorsiflexion R 5/5 L 4/5, Foot plantar flexion R 5/5 L 4/5, Toe dorsiflexion R 5/5 L 4/5	intact, 5/5, Hip flexion R 4/5 L 2/5, Knee extension R 4/5 L 3/5, Knee flexion R 4/5 L 3/5, Foot dorsiflexion R 5/5 L 4/5, Foot plantar flexion R 5/5 L 4/5, Toe dorsiflexion R 5/5 L 4/5	intact, 5/5, Hip flexion R 4/5 L 2/5, Knee extension R 4/5 L 3/5, Knee flexion R 4/5 L 3/5, Foot dorsiflexion R 5/5 L 4/5, Foot plantar flexion R 5/5 L 4/5, Toe dorsiflexion R 5/5 L 4/5	intact, 5/5, Hip flexion R 4/5 L 2/5, Knee extension R 4/5 L 3/5, Knee flexion R 4/5 L 3/5, Foot dorsiflexion R 4/5 L 3/5, Foot plantar flexion R 4/5 L 3/5, Toe dorsiflexion R 4/5 L 3/5	extremity strength intact, 5/5, Hip flexion : R 3/5 L 1/5, Knee extension R 3/5 L 2/5, Knee flexion R 4/5 L 3/5, Foot dorsiflexion R 4/5 L 3/5, Foot plantar flexion R 4/5 L 3/5, Toe dorsiflexion R 4/5 L 3/5	pronounced lower extremity, ECOG 3	