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 (i.t.) 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 IL2), and systemic TIL infusion and experienced radiographic progression after intrathecal IL2 (i.t. IL2) therapy. The patient received weekly treatment with increasing numbers of i.t. TIL followed by twice-weekly i.t. IL2. The patient received three i.t. TIL infusions and did not experience any toxicities beyond those expected with i.t. IL2 therapy. Analysis of cerebrospinal fluid demonstrated increased inflammatory cytokines following the i.t. treatments. Subsequent imaging demonstrated disease stabilization, and neurological deficits also remained stable. The patient expired 5 months after the initiation of i.t. TIL therapy with disease progression in the brain, liver, lung, and retroperitoneal lymph nodes, but without LMD progression. These results demonstrate the safety of i.t. 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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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 to 10 weeks, which is significantly worse compared with 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 are available about the safety and efficacy of these treatments among patients with LMD. Here we describe, to our knowledge, the first intrathecal (i.t.) administration of autologous tumor-infiltrating lymphocytes (TIL) in combination with intrathecal interleukin-2 (i.t. IL2) 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 1.49 mm) and sentinel lymph node biopsy, which revealed melanoma in three of four parotid lymph nodes. He subsequently underwent a partial parotidectomy and cervical lymphadenectomy (1/35 lymph nodes positive), followed by adjuvant radiotherapy.

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. TILs were harvested from a pulmonary...
wedge resection. MRI of the brain also revealed new metastases, which were treated with craniotomy followed by stereotactic radiosurgery to the postoperative cavity. The patient then received one cycle of high-dose bolus IL2 (HD IL2), 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 Institutional Review Board–approved clinical trial of autologous TIL and received lymphodepleting chemotherapy (cyclophosphamide + fludarabine) per protocol. The infused total number of TIL was 35 × 10⁹ and was followed by two cycles of HD IL2. 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 that 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 i.t. IL2 therapy (5). At that time, cerebrospinal fluid (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 i.t. IL2 doses over 5 weeks, with no toxicities beyond those expected with i.t. IL2 treatment (5). At that time, cerebrospinal fluid (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 i.t. IL2 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 i.t. IL2 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 i.t. IL2 treatment, the number of taps for symptoms of elevated ICP decreased. During the i.t. 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 i.t. IL2, 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 i.t. administration of autologous TIL. The first i.t. treatment consisted of 0.3 × 10⁹ TIL, with no symptoms during or after the injection, and no new neurologic symptoms observed. The TIL consisted of 96% CD8⁺ T cells. On days 1 and 4 after the i.t. TIL, 1.2 million units of i.t. IL2 were given, with no toxicities beyond those expected with i.t. IL2 treatment, including nausea, vomiting, headache, chill, 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 i.t. IL2.

The patient went on to receive 1 × 10⁹ i.t. TIL the next week, and 3 × 10⁹ i.t. TIL the week after, with two doses of i.t. IL2 given each week during this time. For symptom control, the patient required 17 additional taps. Three weeks after the first i.t. TIL administration, he was retreated with systemically administered autologous TILs (89 × 10⁹ cells) and received one additional dose of i.t. IL2 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 1 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); 1 week later, he received another dose of i.t. IL2. Unfortunately, our patient’s performance status deteriorated, and both ipilimumab and i.t. IL2 treatments were stopped. The patient continued to undergo palliative removal of CSF via Ommaya reservoir. Five months after the first i.t. IL2 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 i.t. 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 i.t. TIL treatments. Levels of IFNγ, IL10, IL12 p70, IL13, IL1β, IL2, IL4, IL6, IL8, TNFα, and TGFβ were measured in the CSF at baseline and daily for 4 days after infusion for each of the three i.t. TIL infusions (Fig. 1A). No appreciable elevation in the levels of IL4, IL12 p70, IL13, or TGFβ was detected when measured after any of the i.t. TIL infusions (data not shown). IFNγ levels, presumably produced by activated T cells, peaked after each i.t. 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 i.t. TIL infusion 2; 105 pg/mL). The peak concentration of IFNγ induced by each TIL infusion decreased as the number of infused TIL increased (724 pg/mL after 1 × 10⁹ TIL; 610 pg/mL after 1 × 10⁹ TIL; and 474 pg/mL after 3 × 10⁹ TIL; Fig. 1B). In contrast, TNFα and IL1β levels peaked higher with each dose of i.t. TIL infused and remained markedly elevated at the last time point assessed (Fig. 1C and D). IL10 measurements also increased after i.t. 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 IL6 and IL8 also increased significantly after each i.t. TIL, peaking after the last infusion and remaining high at the last time point monitored, especially with IL8 (Fig. 1F and G). Interestingly, levels of IL6 and IL8 peaked at a lower concentration after the second i.t. TIL dose in comparison with the first i.t. TIL infusion when levels of IL10 were highest, potentially suggesting a downregulation by IL10. This result was not observed following the third i.t. TIL infusion. Although the i.t. infusion of increasing amounts of TIL did induce the production of inflammatory cytokines in the CSF,
Table 1. Treatment and examination overview

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<tbody>
<tr>
<td><strong>i.t. TIL</strong></td>
<td>Na</td>
<td>January 24, 2011: 0.3 (\times 10^9) cells</td>
<td>January 31, 2011: 1 (\times 10^9) cells</td>
<td>February 7, 2011: 3 (\times 10^9) cells</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
</tr>
<tr>
<td><strong>i.t. IL2</strong></td>
<td>Na</td>
<td>November 20, 2010: 1st dose, 1.2 million units</td>
<td>Ongoing</td>
<td>Ongoing</td>
<td>Ongoing, last dose March 14, 2011</td>
<td>Na</td>
<td>May 16, 2011</td>
</tr>
<tr>
<td><strong>Systemic TIL</strong></td>
<td>Na</td>
<td>Na</td>
<td>February 27, 2011: 89 (\times 10^9) cells, previously May 10, 2010: 35 (\times 10^9) cells</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
</tr>
<tr>
<td><strong>Ipilimumab</strong></td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>Na</td>
<td>One dose May 16, 2011</td>
<td>Na</td>
</tr>
<tr>
<td><strong>MRI brain</strong></td>
<td>No new parenchymal metastases or LMD</td>
<td>January 20, 2011: no new parenchymal metastasis or LMD</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
<td>Development of at least 10 metastatic parenchymal lesions</td>
<td></td>
</tr>
<tr>
<td><strong>MRI spine</strong></td>
<td>No new parenchymal metastases or LMD</td>
<td>January 20, 2011: progression of LMD</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
<td></td>
</tr>
<tr>
<td><strong>CT chest, abdomen, and pelvis</strong></td>
<td>Stable pulmonary, hepatic, and peritoneal disease</td>
<td>January 20, 2011: new pleural effusion, pulmonary and hepatic metastasis, progression of peritoneal implants</td>
<td>Pulmonary and hepatic progression</td>
<td>Progression of bilateral pulmonary and hepatic metastases; development of intussusception and small-bowel obstruction</td>
<td>No imaging</td>
<td>Progression of bilateral pulmonary, hepatic, peritoneal, and retroperitoneal metastases</td>
<td></td>
</tr>
<tr>
<td><strong>Neurocognitive testing</strong></td>
<td>January 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; the patient performed within normal limits across measures assessing processing speed, executive functioning, and motor dexterity</td>
<td>January 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</td>
<td>Stable</td>
<td>May 15, 2011: decline in all reported parameters at time of systemic tumor progression</td>
<td>Patient died at home, end of June 2011</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 1.
Cytokine response in the CSF in response to i.t. TIL + IL2. A, CSF was obtained from the Ommaya at the time points indicated. B–G, the bars indicate the i.t. TIL treatment date with the number of cells infused shown on the right Y axis. CSF was taken prior to each i.t. 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 IFNγ (B), TNFα (C), IL1β (D), IL10 (E), IL6 (F), and IL8 (G).
our patient did not experience any unexpected side effects from the i.t. TIL infusion.

Discussion

To our knowledge, this is the first case report describing the i.t. 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 i.t. IL2. Radiographic imaging demonstrated stabilization of the patient's LMD following i.t. TIL treatment, which notably had progressed on prior i.t. IL2 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 i.t. 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 i.t. TIL to this patient's treatment regimen was based on the results of the systemic administration of autologous TIL in conjunction with high-dose IL2. Multiple centers, including our own institution, have reported significant response rates in patients with metastatic melanoma (8, 9). We also have previously reported that i.t. IL2 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-week 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 i.t. IL2 will achieve a durable survival led us to decide to add i.t. TIL to his treatment. This patient did not experience any unexpected side effects from the i.t. 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 i.t. CD8\(^{+}\) cytotoxic lymphocytes (CTL; ref. 10). In contrast with our case, only CD8\(^{+}\) CTLs were generated in vitro using autologous dendritic cells were used. Moreover, the i.t. CTLs were supported by systemic low-dose IL2 administration, which is different from our i.t. IL2 approach. Both of these cases benefited from i.t. 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.

Intrathecal IL2 appears to be necessary to maintain the prolonged viability of the i.t.-administered cells as is the case in systemic therapy with TIL. But, as previously described, it also has an antitumor effect by itself (6). Despite the fairly short half-life of IL2 (only about 4 to 8 hours), its effects include a rapid induction of TNF\(\alpha\) and soluble IL2 receptor and a rapid influx of neutrophils and a prolonged presence of leukocytes (11). We also observed TNF\(\alpha\) levels rising after administration of i.t. IL2 and i.t. IL2, and this phenomenon may potentially explain the need for maintenance of i.t. IL2.

We also demonstrated that levels of several cytokines present in the CSF are consistently increasing following i.t. TIL and returning to baseline prior to the subsequent i.t. TIL infusion. However, changes in cytokine levels in the CSF differ depending upon the cytokines tested. In our patient, we observed fluctuations in the proinflammatory cytokines IFN\(\gamma\) and TNF\(\alpha\) following i.t. TIL infusion comparable with fluctuations previously observed with infusion of i.t. CD8\(^{+}\) CTL (10). In addition, although the levels of TNF\(\alpha\) are comparable between the two studies, we observed much higher levels of IFN\(\gamma\) following i.t. IL2 as compared with the CD8\(^{+}\) CTL infusion. In contrast with the report by Clemens-Miller and colleagues, we observed vacillations in the levels of IL10 following i.t. TIL infusion, whereas in their analysis, IL10 levels did not change following CTL infusion (10).

One important concern involving patient selection for i.t. 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 i.t. therapy and warrants management prior to or during i.t. therapy with other available treatment modalities. Taken together, this suggests that patients who are candidates for i.t. 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-approved 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 i.t. IL2 administration and radiotherapy, it appears that the addition of i.t. TIL might have contributed to the temporary LMD stabilization, especially because the TILs have the phenotype we previously associated with clinical response (9). Based on this case, and taken together with our experience with i.t. IL2 and systemic TIL administration, we believe that the i.t. 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.

Disclosure of Potential Conflicts of Interest

All authors were employed by The University of Texas MD Anderson Cancer Center in 2011 at the time of the patient’s treatment. Dr. Radvanyi is currently an adjunct faculty member for the H. Lee Moffitt Cancer Center & Research Institute as well as being employed by Lion Biotechnologies. Dr. Patrick Hwu now serves on the advisory board for Lion Biotechnologies. C. Bernatchez is a consultant/advisory board member for Lion Biotechnologies. S. Wardell is manufacturing manager at Lion Biotechnologies and has an ownership interest (including patents) in Lion Biotechnologies. W.J. Hwu reports receiving commercial research support from Bristol-Myers Squibb, GlaxoSmithKline, MedImmune, and Merck, and is a consultant/advisory board member for Merck. No potential conflicts of interest were disclosed by the other authors.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): I.C. Glitza, C. Bernatchez, L. Vence, M. Robilis, J. Richard, C. Lacey, R. Mamsay, O.J. Fulbright, R. Ramachandran, C. Toth, S. Wardell, S.E. Woodman, W.J. Hwu, M.A. Davies, N.E. Papadopoulos, P. Hwu

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Writing, review, and/or revision of the manuscript: I.C. Glitza, C. Haymaker, C. Bernatchez, M. Rohils, C. Lacey, S.P. Patel, S.E. Woodman, W.J. Hwu, M.A. Davies, N.E. Papadopoulos, P. Hwu

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): I.C. Glitza, L. Vence, C. Lacey, R. Ramachandran, S. Wardell, N.E. Papadopoulos

Study supervision: I.C. Glitza, N.E. Papadopoulos, P. Hwu

Other (direct patient care including Ommaya taps and intrathecal dosing with intrathecal IL2): C. Lacey

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References


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