Title

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Journal

JCO Oncology Practice, 16(11)

ISSN

2688-1527

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Publication Date

2020-11-01

DOI

10.1200/op.20.00146

Peer reviewed

The Treatment of Metastatic Melanoma with Leptomeningeal Disease using Intrathecal Immunotherapy

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Background:

Leptomeningeal disease (LMD) is a devastating complication of metastatic malignancy. Patients with LMD generally present with acute to subacute neurologic deficits that can be quite debilitating. Median survival from time of diagnosis is 3-4 months for solid oncology patients[1]. Cancer immunotherapy with checkpoint inhibitors (CPIs) has revolutionized cancer treatment, but there is little data about the efficacy of CPIs for treatment of LMD. Several case reports describe clinical improvement in patients with LMD treated with intravenous (IV) CPIs[2,3]. Preliminary data from a phase II clinical trial suggests that IV pembrolizumab has promising activity for patients with solid tumor malignancies and LMD[4], and two other phase II clinical trials are currently underway evaluating IV pembrolizumab monotherapy (NCT03091478) and IV ipilimumab/nivolumab combination therapy (NCT02939300).

One potential issue with IV CPI administration is that these monoclonal antibodies are large (>140,00 Da), and thus they may not effectively cross the blood brain barrier. Therefore, one hypothesis is that intrathecal (IT) CPI administration may be a more reliable and efficacious method of drug delivery. Here, we describe the use of IT immunotherapy in two patients with metastatic melanoma and LMD.

Case Presentations:

Patient One: 49M initially diagnosed with stage III unresectable melanoma of the cutaneous upper back in 2013, now with metastatic disease including LMD since

June 2019. He was initially treated with PO dabrafenib/trametinib and IV ipilimumab/ nivolumab, but he had radiographic progression of disease (Figure 1A/B) and CSF cytology confirmed the presence of malignant cells (Figure 1C). Therefore, in September 2019 he was started on a combination of IV and IT nivolumab (240mg IV nivolumab and 20mg IT nivolumab q14 days), which he tolerated well. After three cycles of IV/IT nivolumab, repeat MRI brain in October 2019 showed a decrease in the extent of LMD and intraparenchymal metastatic disease (Figure 1D/E) and CSF cytology was benign. Clinically, his seizures and balance improved and his speech was stable.

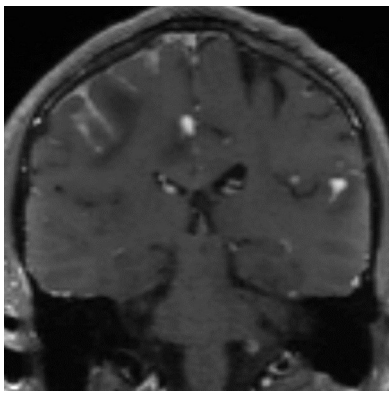
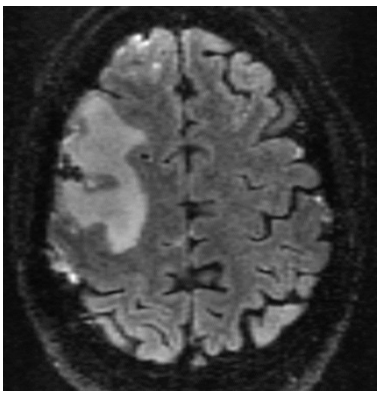
Patient Two: 39F initially diagnosed with stage IIIA melanoma of the right posterior thigh in 2007, who subsequently developed stage III recurrent disease in 2016. She underwent surgical resection and was started on IV pembrolizumab, but this was stopped due to pneumonitis four months later. Instead, she started PO dabrafenib/trametinib which she continued until progression of disease in September 2018, prompting switch to encorafenib/binimetinib. However, in October 2019, she developed left eye blurriness and left arm numbness. Brain MRI showed several 1cm brain metastases and subtle LMD (Figure 2A), which was confirmed with positive CSF cytology (Figure 2B). Therefore, she was switched back to dabrafenib/trametinib and also started on 20mg IT nivolumab q14 days. She experienced mild headaches with each IT infusion, but otherwise tolerated it well. After three cycles of IT nivolumab, repeat brain MRI in December 2019 showed possible subtle progression of LMD (Figure 2C), although comparison was limited by differences in MRI technique. CSF cytology was now benign and clinically she reported improvement in her visual symptoms.

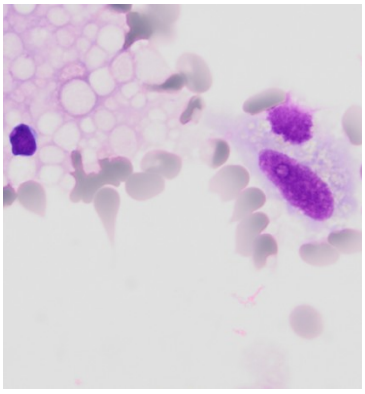
Discussion:

This is the first published case report to our knowledge that describes the use of IT immunotherapy in two patients. Both patients tolerated IT nivolumab without notable side effects, and Patient One had a particularly impressive radiographic and clinical response to treatment. These cases highlight the potential benefit of IT immunotherapy, and suggest the need for future clinical trials to evaluate the safety and efficacy of this drug administration strategy. Currently, there is a Phase I clinical trial underway at MD Anderson studying the safety of IV/IT nivolumab in patients with cutaneous or uveal melanoma and LMD (NCT03025256), with results not yet reported. In addition, it will be important to study the safety and efficacy of IT immunotherapy in other primary cancer types. We are hopeful that IT immunotherapy will be a tolerable, effective, and durable treatment option for patients with solid tumor malignancies and LMD.

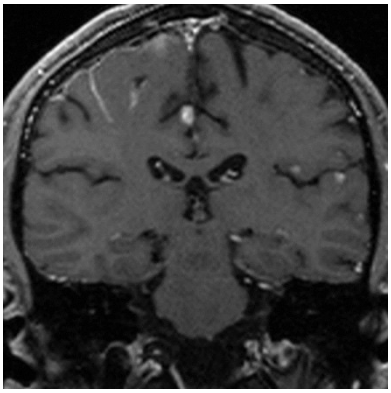
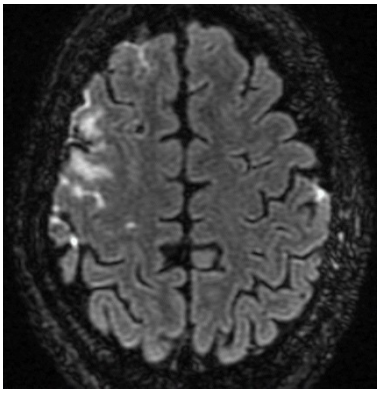
Figure 1. Patient One: Brain MRI and CSF cytology before and after IT nivolumab therapy

Patient One: Pre IV/IT nivolumab

A  **B**  **C**



Patient One: Post C3 IV/IT nivolumab

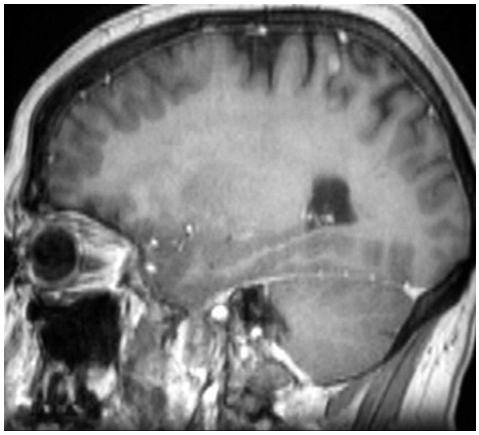
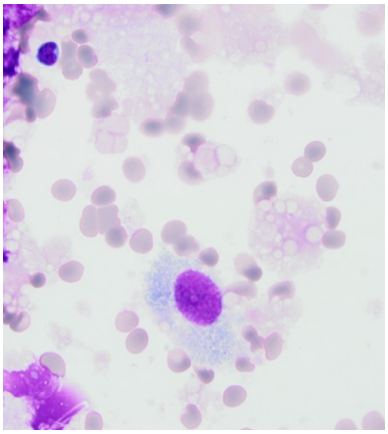
D  **E** 

Patient One: Pre IV/IT nivolumab
A) Coronal T1 post-contrast MRI and (**B**) Axial FLAIR images from September 2019 before initiation of IV/IT nivolumab. There is extensive linear and nodular leptomeningeal enhancement involving the right frontal sulci which is associated with FLAIR hyperintense marked right frontal edema. Small contralateral parenchymal metastases are also evident. (**C**) CSF cytology from July 2019 prior to initiation of IV/IT nivolumab. This 600X image shows an enlarged nucleus with prominent nucleoli on the right in comparison with an adjacent mature lymphocyte on the left.

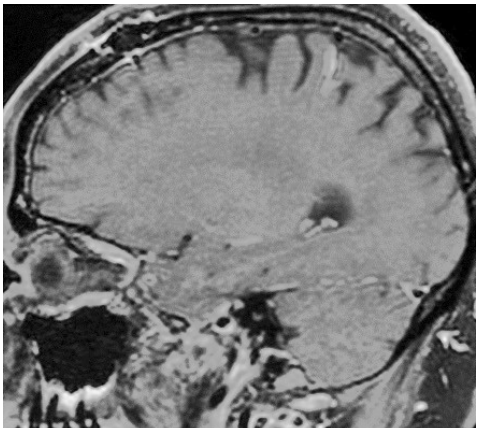
Patient One: Post C3 IV/IT nivolumab
(**D**) Coronal T1 post-contrast MRI and (**E**) Axial FLAIR images from October 2019 after three cycles of IV/IT nivolumab. There is decrease in the extent of leptomeningeal enhancement and marked decrease in of the right frontal edema and mass effect. There is also a decrease in size

Figure 2. Patient Two: Brain MRI and CSF cytology before and after IT nivolumab therapy

Patient Two: Pre IT nivolumab

A  **B** 

Patient Two: Post C3 IT nivolumab

C 

Patient Two: Pre IT nivolumab
(**A**) Sagittal T1 post-contrast MRI from October 2019 before initiation of IT nivolumab. There is intracranial metastatic disease and subtle LMD. MRI taken using 1.5T magnet, shown is a 3D BRAVO T1 cut.
(**B**) CSF cytology from October 2019 prior to initiation of IT nivolumab. This 600X image shows a single epithelioid neoplastic cell with pigmented cytoplasm, enlarged nuclei, and prominent nucleoli in comparison with an adjacent mature lymphocyte on the left.

Patient Two: Post C3 IT nivolumab
(**C**) Sagittal T1 post-contrast MRI from December 2019 after three cycles of IT nivolumab. MRI taken using a 3T magnet, shown is a 3D CUBE T1 FS image. The difference in coloration

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