Case Report

Intrathecal topotecan with systemic checkpoint inhibitor therapy for gastroesophageal cancer with leptomeningeal involvement: two case reports and review of the literature

Cindy M. Pabon[1]^, Debra N. Yeboa[2]^, Barbara J. O'Brien[3]^, Nazanin K. Majd[3]^, Chenyang Wang[2]^, Mariela A. Blum Murphy[1]^

[1]Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

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Correspondence to: Mariela A. Blum Murphy, MD. Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Unit 0426, 1515 Holcombe Blvd., Houston, TX 77030, USA. Email: mblum1@mdanderson.org.

Background: Leptomeningeal metastases (LM) in gastroesophageal (GE) malignancies are exceedingly rare. Historically, treatment for LM has included steroids, radiation, chemotherapy, and intrathecal (IT) chemotherapy. However, the outcomes in GE malignancies with LM remain poor. Unfortunately, clinical trials in GE malignancies have traditionally excluded those with LM, limiting advances in therapeutic strategies. Given that LM poses potentially devastating neurologic and psychologic sequelae, there is an urgent need for more effective treatments.

Case Description: Patient 1 is a 44-year-old woman with localized esophageal adenocarcinoma who undergoes neoadjuvant chemoradiation followed by esophagectomy. Seven months following surgery, she develops ataxia, weakness, and nausea/vomiting. Magnetic resonance imaging (MRI) reveals intracranial disease that is subsequently successfully resected and then treated with gamma knife (GK) radiation. Pathology confirms metastases. Three months later she is found to have LM. She receives palliative whole brain radiation therapy as well as focal radiation to the spine. Following this she transitioned to concurrent IT topotecan plus intravenous (IV) ipilumumab/nivolumab with durable response beyond 14 months. Patient 2 is a 71-year-old man with *de novo* metastatic esophageal adenocarcinoma with durable response to 5-fluorouracil plus irinotecan. Asymptomatic intracranial metastases are detected on surveillance scans 2 years after initial diagnosis for which he receives GK. Follow up MRI identifies new LM. As such, to treat the LM, he was transitioned to IT topotecan and IV pembrolizumab with good response for 6 months until death from a gastrointestinal bleed.

Conclusions: We present two cases of LM in patients with GE adenocarcinoma who had longer survival than what has been reported. They were treated with combination IT topotecan and IV checkpoint inhibition. Further studies evaluating the central nervous system tumor immune-microenvironment can help expand our understanding of how this combination has worked well in our patients and how to care for others with similar scenarios.

Keywords: Esophageal adenocarcinoma; leptomeningeal metastases (LM); intrathecal chemotherapy with concurrent systemic immunotherapy; case report

^ ORCID: Cindy M. Pabon, 0000-0002-9755-9374; Debra N. Yeboa, 0000-0002-2901-7477; Barbara J. O'Brien, 0000-0002-1188-7765; Nazanin K. Majd, 0000-0001-6451-544X; Chenyang Wang, 0000-0001-6798-0857; Mariela A. Blum Murphy, 0000-0002-4310-3590.

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Introduction

Leptomeningeal metastasis (LM) is defined as diffuse or multifocal infiltration of cancer cells into the pia matter and arachnoid membrane (1). Clinical manifestations vary based on extent and pattern of spread as well as whether parenchymal disease exists. Presenting symptoms may include cranial nerve deficits, headaches, gait abnormalities, speech changes, vision changes, nausea, vomiting, seizures, or altered awareness (2).

The most commonly associated solid tumors with LM include breast cancer, lung cancer, and melanoma (3). LM in gastroesophageal (GE) malignancies is exceedingly rare, with an estimated incidence of 0.17–0.19% (4,5). In contrast, studies indicate a 2% incidence of LM in lung cancer, 10–12% in breast cancer, and up to 12% in melanoma (2).

Historically, the prognosis of leptomeningeal disease in GE cancers is poor (5). Moreover, therapies available do not provide substantial benefit. Given that LM poses potentially devastating neurologic and psychologic sequelae, there is an urgent need for more effective treatments.

Here we present two cases of LM in patients with GE adenocarcinoma who had longer survival than what has been reported previously. They received combination intrathecal (IT) topotecan and intravenous (IV) checkpoint inhibition. Furthermore, we review and update the current literature on LM in those with GE malignancies. We present this article in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-70/rc).

Highlight box

Key findings

- Two patients with leptomeningeal metastases (LM) from their gastroesophageal malignancy have demonstrated excellent response to combination intrathecal (IT) topotecan with systemic checkpoint inhibition.

What is known and what is new?

- Historically, treatment options for solid tumor LM have included systemic steroids, radiation therapy, systemic chemotherapy, and IT chemotherapy, with a median overall survival of 2–6 months.
- Our cases and review of the literature suggest synergy between IT chemotherapy and systemic checkpoint inhibitors that may produce a more durable response than what is seen with prior treatment strategies.

What is the implication, and what should change now?

- The treatment of LM requires a multidisciplinary approach. Further investigation into the tumor microenvironment of the meninges may allow us to develop more effective strategies to harness the power of checkpoint inhibition.

Case presentation

Case 1

A 44-year-old woman presented with dysphagia and worsening acid reflux. Endoscopy identified an 11 cm esophageal mass with pathology revealing poorly-differentiated adenocarcinoma. Mismatch repair genes were intact and combined positive score (CPS) for programmed death-ligand 1 (PD-L1) was 100 via 22C3 assay. Positron emission tomography-computed tomography (PET-CT) scan identified regional nodal metastases with no distant disease. She received neoadjuvant chemoradiation with 5-fluorouracil and oxaliplatin followed by esophagectomy. Surgical pathology revealed residual disease (ypT3N1M0) for which she was recommended adjuvant nivolumab, but experienced difficulty accessing the medication in the setting of socioeconomic barriers. As such, she was transitioned to surveillance.

Seven months following surgery, the patient presented with ataxia, weakness, and nausea/vomiting. Magnetic resonance imaging (MRI) revealed a solitary 3 cm vermian brain lesion (*Figure 1A*). There was no evidence of LM on MRI. PET-CT performed concurrently did not reveal recurrence elsewhere. She underwent resection of the cerebellar lesion with gross total resection demonstrated on follow-up MRI. Pathology confirmed this was metastatic GE adenocarcinoma. She subsequently received postoperative stereotactic radiation [gamma knife (GK)] to the cavity [27 Grays (Gy) in 3 fractions]. Three months following resection and radiation, MRI brain and spine surveillance scans revealed new enhancing epidural metastases in the left lower cerebellum and right foramen magnum. This was followed by an MRI total spine that identified enhancing epidural metastasis at cervical spinal

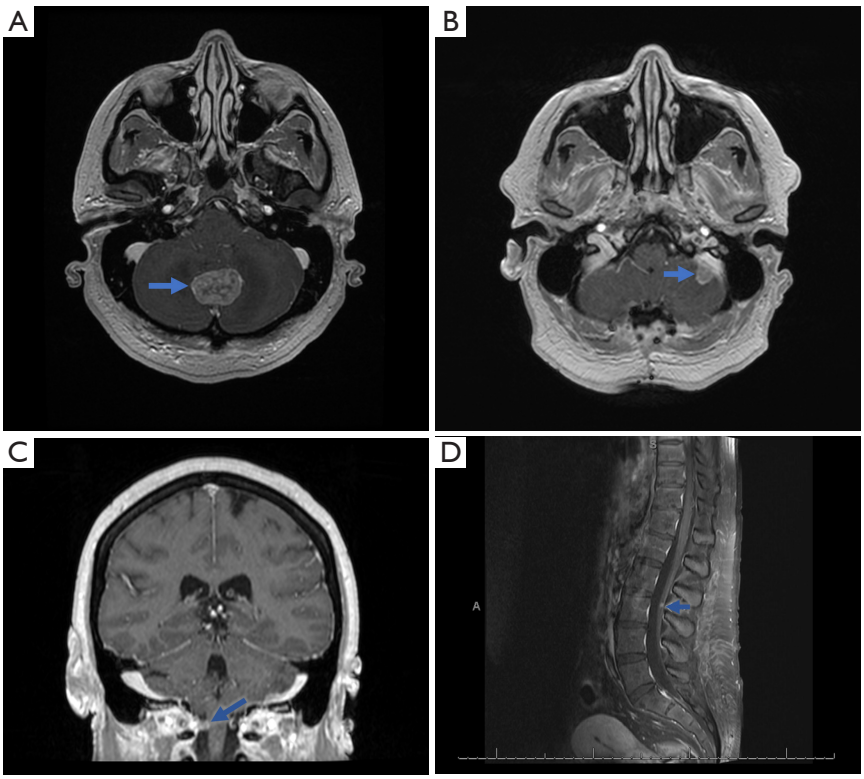

Figure 1 Central nervous system metastases detected on imaging in case 1. (A) MRI of vermis lesion (T1) (blue arrow denotes lesion). (B) MRI of dural-based lesion over left cerebellum (T1) (blue arrow denotes lesion). (C) MRI of dural-based lesion by foramen magnum (T1) (blue arrow denotes lesion). (D) MRI of dural-based lesion by cauda equina nerve roots (T1) (blue arrow denotes lesion). MRI, magnetic resonance imaging.

Table 1 LMD treatment regimen for case 1

Agent	Route	Dosing & schedule
Topotecan	IT	Based on a 28-day cycle: • Cycles 1 & 2: 0.4 mg twice weekly, followed by • Cycles 3 & 4: 0.4 mg weekly, followed by • Cycles 5 and onward: 0.4 mg every 2 weeks
Nivolumab	IV	240 mg every 2 weeks
Ipilimumab	IV	1 mg/kg every 6 weeks

LMD, leptomeningeal disease; IT, intrathecal; IV, intravenous.

cord level 5 (C5) with mild cord compression and additional disease at the cauda equina (*Figure 1B-1D*). Lumbar puncture demonstrated malignant cells, supporting the diagnosis of LM.

Once epidural lesions were noted, she received palliative whole brain radiation therapy (WBRT) (30 Gy in 10 fractions) as well as focal radiation to the spine (cervical spine and the cauda through sacrum). She continued to have good performance status. Following radiation she transitioned to IT treatment with topotecan via Ommaya reservoir, IV ipilumumab and IV nivolumab (*Table 1*).

One month after radiation, MRI of the brain began to show improvement in the enhancing disease. Two months after IT treatment initiation and 3 months after spine radiation, MRI showed resolution of LM. It was believed that a substantial contributing factor to her response was the WBRT. She continues to receive combination systemic immunotherapy with IT topotecan, 14 months after initial detection of LM. Serial cerebrospinal fluid (CSF) analyses have been negative for recurrence. She has not experienced any adverse events, with the exception of an infection associated with her Ommaya intraventricular catheter system prior to treatment which required replacement of

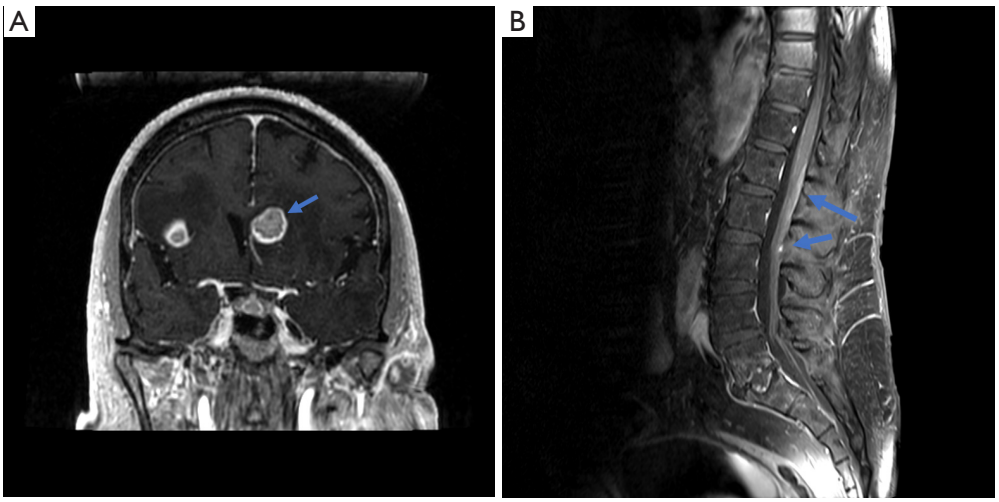

Figure 2 Central nervous system metastases identified on imaging for case 2. (A) MRI of left caudate head lesion extending to the ependymal surface of the left frontal horn (T1) (blue arrow denotes lesion). (B) MRI of spine demonstrating enhancement along intradural nerve roots and cauda equina (T1) (blue arrows specify areas of enhancement). MRI, magnetic resonance imaging.

Table 2 LMD treatment regimen for case 2

Agent	Route	Dosing & schedule
Topotecan	IT	Based on a 28-day cycle: • Cycles 1 & 2: 0.4 mg twice weekly, followed by • Cycles 3 & 4: 0.4 mg weekly, followed by • Cycles 5 and onward: 0.4 mg every 2 weeks
Pembrolizumab	IV	200 mg every 3 weeks

LMD, leptomeningeal disease; IT, intrathecal; IV, intravenous.

the Ommaya and antibiotics. The patient continues to work full-time as a nurse without limitations.

Case 2

A 71-year-old man was diagnosed with esophageal adenocarcinoma following several months of dysphagia and weight loss. Pathology showed intact mismatch repair genes and a CPS of 5. PET-CT revealed metastatic paratracheal nodes and adrenal nodules. He was treated with 5-fluorouracil and irinotecan (FOLFIRI) which he tolerated well for 29 cycles prior to progression of primary tumor and nodal disease. He underwent concurrent chemoradiation to the primary tumor with 5-fluorouracil and docetaxel, followed by maintenance capecitabine. Three months after capecitabine initiation, he progressed with a new lesion in his leg. He was restarted on FOLFIRI and received palliative radiation to the leg.

Six cycles after re-initiation of FOLFIRI, he underwent PET-CT that suggested potential brain metastasis with otherwise positive response to treatment in the body. Subsequent MRI identified six brain metastases, the largest being in the left caudate head and body, measuring 1.5 cm × 1.7 cm × 1.8 cm and extending into the ependymal surface of the left frontal horn (*Figure 2A*). The patient received palliative GK to the intracranial metastases given their large size and the thought that disease process was limited. However, MRI of the spine later revealed more widespread disease with LM along thoracic nerve roots and the cauda equina (*Figure 2B*). CSF cytology did not identify malignant cells. He had no neurologic deficits and a relatively good performance status.

As such, to treat the LM, he was transitioned to IT topotecan and IV pembrolizumab (*Table 2*).

His neuroaxis MRI restaging scans while on this regimen continued to show treatment response of intracranial GK lesions and stable LM in the spine. CSF continued to be negative for malignancy. He did not experience any immune-mediated side effects. The patient continued this regimen with no evidence of progression for 6 months before he developed an acute gastrointestinal bleed from his primary tumor and passed away.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Informed consent was obtained from the patients for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

The presence of LM may be nonspecific and challenging to diagnose. Additionally, LM may not be readily apparent on imaging studies. MRI, the preferred imaging modality, has an estimated sensitivity of 66–76% in patients with solid tumors (6). Thus, identification of LM often requires supportive laboratory/imaging findings along with clinical suspicion. Specifically, the diagnosis can be made by one of the following: (I) positive CSF cytology for tumor cells (gold standard); (II) positive radiologic findings with supportive clinical findings; or (III) symptoms with suggestive CSF in a patient with cancer (CSF may have high white blood cell count, low glucose, and high protein) (7). *Table 3* outlines published cases of GE cancers with LM (1,3,8-12).

Once diagnosed, the treatment for LM in GE cancers has not been established. In 2004, Lee estimated median overall survival (mOS) to be 4 weeks in patients with GE malignancies, following detection of LM (4). This is worse than what is reported for the general solid tumor population with a mOS of 2–4 months with current LM therapies and 1–1.5 months if left untreated (13,14). Thus, therapeutics for LM in GE cancers are palliative in nature and intended to provide symptomatic relief and stabilize/improve neurologic deficits. Historically, treatment options for solid tumor LM have included systemic steroids, radiation therapy, systemic chemotherapy, and IT chemotherapy (8).

Radiation

Several retrospective studies across different solid tumors have indicated that WBRT may provide an improvement in palliative outcomes for those with LM (15-17). Traditional palliative WBRT dosing includes 20 Gy fractionated over five treatments once a day or 30 Gy fractionated over ten treatments once a day (18). WBRT is generally well tolerated but may have acute side effects including fatigue, headache, nausea/vomiting, dermatitis along radiation field, xerostomia, and dysgeusia. Longer-lasting sequelae may include continued fatigue, pituitary dysfunction, and cognitive impairment. Oftentimes systemic steroids as well as the N-methyl-D-aspartate (NMDA) antagonist memantine may be prescribed in efforts to abate some of these effects (7).

Proton cranial spinal irradiation (pCSI) therapy is a novel treatment for LM. A clinical trial comparing WBRT plus radiation of focal disease sites to 30 Gy in 10 fractional neuro-axis radiation therapy with protons identified an OS benefit with pCSI for patients with breast cancer and non-small cell lung cancer (19). While the data is strongest in this cohort of patients, pCSI is currently being done in patients with other histologies as an extrapolation. Further data and trials with a larger range of patients will be informative to whether patients with GE cancers will share a similar benefit. Given the complexity and time required for pCSI, selection of patients who are appropriate is key because patients with symptomatic involvement or asymptomatic radiographic cord compression like in case 1 are still often best treated with local therapy in certain logistical settings. Randomized controlled data will be important to better identify whether WBRT plus local spine therapy versus pCSI will be better in the context of cases like ours where patients responded well to local therapy and the addition of IT chemotherapy. Focal GK is rarely considered in patients with LM and not standard of care. Cases where GK is offered in LM often occur under the circumstance that a patient is given the benefit of the doubt of more advanced central nervous system (CNS) disease when an acute large lesion is identified, resulting in GK, only for subsequent work-up to identify LM. Case 2 illustrates this very scenario. Further clinical trial data will be necessary to assess if there may be a future role for radiation in the context of patients who have excellent response to IT chemotherapy or CNS-penetrating systemic therapy given the evolution of these agents.

Systemic therapy

The choice of effective systemic therapy in patients with LM is limited, mainly due to poor blood-brain barrier (BBB) penetration of systemic chemotherapy and active expulsion through efflux pumps (20). Agent selection typically varies based on tumor type and biomarker expression.

There have been an increasing number of BBB-penetrant targeted therapy options for select tumors. In lung adenocarcinoma, patients with epidermal growth factor receptor (*EGFR*) mutations have seen promising results in the management of LM with 3rd generation

Table 3 Published cases of gastroesophageal malignancies with leptomeningeal involvement

Reference	Age (years)	Presenting symptom(s)	Primary tumor location	Timing of LM diagnosis	Method of LM detection	Treatment(s)	Survival outcome after treatment
Rizvi *et al.* (8)	56	Initially: dysarthria Three weeks later: nausea, diplopia headaches	Gastroesophageal junction involving the cardia and body	Recurrence	Lumbar puncture	Hospice	–
	50	Initially: frequent falls and headaches Days later: blurred vision	Gastroesophageal junction involving the cardia	Recurrence	Lumbar puncture	Died within days of recurrence	–
Alkhotani *et al.* (1)	51	Initially: left leg weakness Days later: right leg weakness plus numbness, and saddle anesthesia A week later: urinary retention, fecal incontinence, facial diplegia, bilateral sensorineural hearing loss, dysarthria, dysphagia, hypotonia, sensory loss of pinprick sensation	Gastroesophageal junction	Recurrence	MRI repeated a week after initial presentation; repeat lumbar puncture after initial negative study	Died within days of recurrence	–
Akhavan *et al.* (9)	73	Hoarseness and frontal headache	Esophagus*	Recurrence	MRI	3,000 cGy whole brain irradiation	Four weeks
Wagemakers *et al.* (10)	52	Initially: acute bilateral hearing loss Weaks later: gait imbalance, headache, nausea	Esophagus	Recurrence	Clinical diagnosis (cytology negative)	Radiation to the skull base	Sixteen weeks (from time of LM discovery)
Teare *et al.* (11)	49	Bilateral blindness, left leg weakness, frontal headache	Esophagus	At diagnosis	Post-mortem brain examination	Died within days of presentation	–
Lu *et al.* (12)	62	Asymptomatic	Gastroesophageal junction	Progression of disease	Abnormal PET-CT hypermetabolism, leading to confirmatory MRI and lumbar puncture	Unknown	Unknown
Ahmed *et al.* (3)	47	Headache with nuchal rigidity (meningitis), delirium, dizziness, nausea	Gastroesophageal junction	At diagnosis	Lumbar puncture	Systemic steroids and external beam radiation; cisplatin/5-flurouracil	Five weeks (from time of diagnosis)

*, squamous histology; all other cases reported were adenocarcinoma. LM, leptomeningeal metastases; MRI, magnetic resonance imaging; cGy, centigray; PET-CT, positron emission tomography-computed tomography.

tyrosine kinase inhibitor, osimertinib (21). Other targeted treatments in lung adenocarcinoma, such as anaplastic lymphoma kinase (ALK) therapies alectinib, brigatinib, ceritinib, and lorlatinib, have also demonstrated efficacy treating intracranial disease (22). In breast cancer, the limited success in intracranial and LM management has been in the setting of human epidermal growth factor receptor 2 (HER-2) positive patients receiving tucatinib or trastuzumab deruxtecan-containing regimens (6,23,24). In melanoma, v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*)^{v600}-mutated

Table 4 Case reports of patients treated with intrathecal checkpoint inhibitors

Age (years)	Diagnosis	Timing of LM	Treatment	Outcome
49	Stage III unresectable cutaneous melanoma	Recurrence	14-day cycle: nivolumab 240 mg IV on D1; nivolumab 20 mg IT on D1	After 3 cycles of treatment, repeat MRI showed a decrease in leptomeningeal disease and intracranial metastases. CSF cytology was benign. Clinically improved neurologic symptoms
39	Stage III cutaneous melanoma	Progression	14-day cycle: dabrafenib PO daily; trametinib PO daily; nivolumab 20 mg IT on D1	After 3 cycles of IT nivolumab, repeat MRI showed subtle progression of LM, but cytology was now benign and clinical neurologic symptoms were improving

LM, leptomeningeal metastases; IV, intravenous; D1, day 1; IT, intrathecal; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; PO, per os.

patients have historically achieved symptomatic control of intracranial or LM with encorafenib/binimetinib. However, clinical evidence is still quite limited and duration of effect is limited as well (25).

Presently, immune checkpoint inhibitors have changed the landscape of oncologic care. Phase I and II clinical trials of systemic immunotherapy are underway in various solid tumor malignancies with CNS involvement that may provide further guidance on the role of immunotherapy in this disease. In 2021, Tawbi conducted a multicenter phase II study of combination nivolumab/ipilimumab in patients with melanoma and brain metastases, including LM. This demonstrated durable OS and progression-free survival, particularly for patients who were asymptomatic at diagnosis (26). In 2023, Glitza published interim results of a phase I study of concurrent IT and IV nivolumab in melanoma patients with LM, demonstrating safety, feasibility, and an estimated mOS of 25 weeks, even if patients had prior exposure to systemic immunotherapy (27). This supports further investigation into immunotherapy for those with LM even if they are heavily pretreated. In GE cancers, systemic immunotherapies are playing an increasingly important role in the treatment of metastatic disease. However, not much has been explored in the setting of immunotherapy effects on LM within this population. For instance, CHECKMATE-648 did not specifically present or discuss cases with CNS involvement and CHECKMATE-649 explicitly excluded patients with untreated CNS metastases (28,29). Similarly, in KEYNOTE-062, patients with untreated CNS metastases and/or LM were excluded (30). More inclusive trials are needed in order to better address safety and efficacy of such agents within this population.

In 2023, Wilcox and Boire published a review exploring the pharmacology and potential for CNS penetration of several targeted agents and checkpoint inhibitors (20). Their review identified several retrospective studies and prospective trials with promising evidence for effective leptomeningeal management with systemic agents including tyrosine kinase inhibitors and immunotherapies such as nivolumab and pembrolizumab. In an era where LM therapeutic trials are still lacking, these findings suggest that we may leverage drugs with particular molecular features and degree of CSF penetration for this challenging-to-treat population.

IT therapy

Historically, IT treatment regimens have included cytosine arabinoside (ara-C), methotrexate and thiotepa. Combination IT regimens such as methotrexate/ara-C have demonstrated increased CSF cytology response rate compared to methotrexate monotherapy with improved mOS (18.6 versus 10.4 weeks, P=0.029) (31). In the early 2000s, IT topotecan was evaluated both in retrospective and prospective studies, demonstrating both safety and efficacy in the treatment of LM from various primary tumors. Additionally, it was well tolerated in comparison to other agents, with comparable outcomes, making it the most attractive of the IT therapies (32,33).

With the advent and success of checkpoint inhibitors, it has been recently questioned whether such agents may treat LM efficaciously via IT administration. In 2020, Huppert published two cases of IT administration of nivolumab in patients with cutaneous melanoma and leptomeningeal involvement (*Table 4*). Both patients had clinical response to treatment and one had an impressive radiographic response,

supporting the hypothesis that checkpoint inhibition may serve a role in the treatment of LM (34). Germany, Switzerland and MD Anderson in Houston, TX, USA have ongoing clinical trials evaluating the safety of IT checkpoint inhibitors in solid tumor patients with LM (NCT05598853, NCT05112549, and NCT03025256 respectively).

IT topotecan with IV immunotherapy

Topotecan, a topoisomerase inhibitor, has 30% CSF penetration with systemic administration (35). IT administration of topotecan has been evaluated, identifying a significantly more effective penetration to the CNS without added toxicities (32).

To our knowledge, neither IV nor IT topotecan has been studied in combination with immunotherapy in LM. However, our cases suggest potential synergy between the two. In 2019, Wang investigated teniposide, another topoisomerase inhibitor, and its role in enhancing tumor immunogenicity. Through a preclinical study, the group found that teniposide induced innate immune signaling, activated nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and stimulated interferon genes, thereby activating antitumor T cell response (36). Furthermore, through mouse models it was noted that teniposide potentiated the antitumor effect of anti-programmed cell death protein 1 (PD-1) agents, including in mice designated as immunotherapy-resistant. It is quite plausible then that topotecan has similar effects and thus augments immunotherapy response in the CSF when administered intrathecally. Another explanation for the response in our patients may be that systemic immunotherapy was sufficient in the treatment of the LM. However, presently, not much efficacy has been shown in the treatment of GE cancers with immunotherapy alone. Further studies evaluating the CSF tumor immune-microenvironment can help expand our understanding of how the combination of IT topotecan with IV immunotherapy has worked well in our patients and how to care for others with similar scenarios.

Conclusions

We anticipate further survival data of systemic and IT immunotherapy in those with LM in the years to come. If successful, this may propel further investigation into the immune environment of the meninges and how we may further harness checkpoint inhibitors for the treatment of this challenging disease. As we have seen in solid tumors, there may also be a role in combination chemotherapy with immunotherapy to augment durable, immune-based response.

Here we have presented two unique cases of LM with impressive outcomes combining IT topotecan with IV checkpoint inhibitors. To our knowledge, these are the longest reported OS records for GE cancer patients with metastasis to the leptomeninges. These cases suggest that IT topotecan combined with systemic immunotherapy can be a safe and effective regimen for LM. Further investigation into this treatment strategy should be explored.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-70/rc

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-70/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-70/coif). B.J.O.B. reports that she participates on a data safety monitoring board for Plus Therapeutics. Mariela Murphy reports that she participates in the advisory board for Astrazeneca. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Informed consent was obtained from the patients for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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