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Safety and feasibility of Ommaya reservoir for intrathecal chemotherapy in patients with leptomeningeal disease

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ABSTRACT

Aim of the study. To assess safety and feasibility of intrathecal chemotherapy (IC) and disease monitoring via Ommaya reservoir (OR) in routine clinical practice in patients with leptomeningeal disease (LMD).

Clinical rationale of the study. Leptomeningeal disease carries poor prognosis with an average survival of 3–6 months after diagnosis. OR are an accessible alternative to serial lumbar punctures for delivery of IC and disease monitoring in these patients but are not widely used, partially due to safety concerns.

Material and methods. This single-center retrospective cohort study enrolled patients who received at least one administration of IC via OR for LMD between 2017 and 2022 at a tertiary academic center. Demographics, primary malignancy, treatment type, complications, adverse events and outcomes were recorded for each enrolled patient.

Results. We identified 22 patients (17 females, 5 males) with mean age 50.9 ± 14.8 years. The primary cancers were breast (12), leukemia (3), ovarian carcinoma (3), CNS lymphoma (1), urothelial carcinoma (1), spinal melanocytoma (1), and high-grade glioma (1). A total of 208 IC injections via OR were performed [median 9 OR injections per patient (interquartile range (IQR) 5–13)]. Five patients (23%) experienced mild adverse events of grade 2 or lower by Common Terminology Criteria for Adverse Events. The overall risk of adverse events from injections was 3.4% (7/208). Eight patients (36.3%) converted into negative CSF cytology and 18 patients (82%) had clinical and/or radiological progression of their LMD (median 2 months following first injection). Eleven patients (50%) died of their LMD during follow-up. Median OS and PFS from the first injection were 5.3 months [95% CI: 4.8–NE (not estimable)] and 4.3 months [95% CI: 1.8–16.0], respectively.

Conclusions and clinical implications. Our single-center cohort study suggests that the use of intrathecal chemotherapy via Ommaya reservoir in routine clinical practice is a safe and feasible option and should be considered for treatment and frequent disease monitoring in eligible patients with leptomeningeal disease. Neurologists, especially neuro-oncologists, can significantly contribute to the care of patients of leptomeningeal disease via administering intrathecal chemotherapy.

Keywords: Ommaya reservoir, intrathecal chemotherapy, adverse events

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Introduction

Leptomeningeal disease (LMD) represents a serious neurological complication of systemic malignancies, in which tumor cells access the cerebrospinal fluid (CSF), infiltrate and disseminate into the surface of the brain and spinal cord. LMD has been considered as an end-stage disease present in about 3–8% of patients with solid tumors [1]. The most common malignancies that cause LMD are breast, lung and melanoma [2]. Common neurological signs and symptoms associated with LMD include headache, cranial nerve palsies, radiculopathies and occasionally symptoms reflective of increased intracranial pressure. Magnetic resonance imaging of the neural axis is the optimal diagnostic imaging modality and usually shows diffuse or focal leptomeningeal contrast enhancement [1]. CSF analysis is often obtained to confirm the presence of cancer cells via cytology or, more recently, via novel approaches including circulating tumor cells (CTCs) and/or circulating tumor DNA [1]. Despite advances in diagnostic techniques, LMD still carries overall poor prognosis with an average survival of 3–6 months from the time of diagnosis [3].

Treatment with systemic chemotherapy and radiation is often used for palliative purposes in these patients. Conventional systemic chemotherapy regimens, except for high-dose methotrexate, often lack efficacy against LMD as they fail to achieve therapeutically effective concentrations in the CSF due to the impermeable blood-brain-barrier (BBB) and/or blood-CSF barrier [4]. Thus, penetrating or bypassing the BBB/blood-CSF barrier and reaching effective therapeutic drug concentrations in the CSF remain critical step for treating LMD. One approach to achieve this goal is the delivery of intrathecal chemotherapy (IC) directly into the CSF via serial lumbar punctures (LP) or intraventricular administration of chemotherapeutic agents via implanted devices such as an Ommaya reservoir (OR) [5].

Ommaya reservoir allows for more convenient administration of IC, better distribution of chemotherapeutic agents throughout the neural axis, and frequent sampling of CSF for disease monitoring compared to serial LP. Nevertheless, given the potential concerns about its associated serious complications — including OR implantation-related complications, chemical and/or infectious meningitis — and the limited availability beyond tertiary academic centers, OR still has not gained widespread popularity among patients and healthcare professionals. Therefore, in this study, we aimed to assess the safety and feasibility of IC injection and disease monitoring via OR in patients with LMD in a routine clinical practice at a tertiary academic center.

Material and methods

Patient population

This is a single-center retrospective cohort study of consecutive patients diagnosed with LMD secondary to systemic or primary CNS malignancy who were evaluated and treated with IC via OR at our tertiary academic center from January 1st, 2017, to December 31st, 2022. Enrolled patients were identified using International Classification of Diseases Ninth and Tenth Revisions, Clinical Modification codes for leptomeningeal carcinomatosis (i.e., secondary malignant neoplasm of cerebral meninges). In addition, authors directly inquired neuro-oncologists at our institution for any additional eligible patient cases not identified by the above search. Eligible patients had to have LMD diagnosis confirmed by neuro-oncologist at our center based on clinical presentation, neuroimaging features, and/or CSF analysis positive for evidence of malignant cells using traditional cytology or another novel diagnostic approaches — CTCs, if available. In addition, these patients should have started treatment with IC via OR at our institution for eligibility.

Subsequently, patient charts were reviewed for: baseline demographic characteristics, Karnofsky performance status (KPS) both at initial and last IC injection (if available), type of malignancy associated with the LMD including any relevant genetic alterations, methods of diagnosis of LMD (neuroimaging and/or CSF analysis), time in months from LMD diagnosis to placement of OR, time in months from OR placement to first injection of IC, number of injections via OR per each patient, type of chemotherapeutic agents administered intrathecally, any reported intraoperative/perioperative complication with OR placement or any reported injection-related complications within 24 hours for each IC injection via OR graded according to the Common Terminology Criteria for Adverse Events (CTCAE), any documented infectious or chemical meningitis related to OR, any concurrent therapies provided along with IC (systemic chemotherapy, craniospinal irradiation), any evidence of clinical, radiological or CSF progression of the patients' LMD, time of progression in months from the first injection, and all-cause mortality for the duration of follow-up.

Clinical progression was defined as worsening of neurological symptoms and signs related to LMD following IC based on neuro-oncologists' documentation. Radiological progression was defined as worsening of neuroimaging findings of LMD following administration of IC based on our institution's neuroradiologists' interpretation. CSF progression was defined as increase or re-emergence of malignant cells burden in the CSF following initial stabilization or improvement based on cytological results and/or CTC analysis (if available). In addition, the patients' neuroimaging results were assessed for stability, partial or complete response of LMD to IC based on the neuroradiologists' interpretation. Moreover, the patients' CSF were assessed for complete resolution of malignant cancer cells defined as negative conversion following their IC based on cytology and/or CTCs.

Ommaya reservoir implantation and intrathecal chemotherapy injections

Ommaya reservoir in this cohort was placed by six neurosurgeons at our institution. OR was secured beneath the skin and connected via sterile catheter to the right frontal

horn of the lateral ventricles with tip of catheter positioned at the foramen of Monro using neuronavigation systems and/or ventricular endoscopy. Following the implantation of OR, IC injections and CSF sampling were subsequently done at our ambulatory infusion center by two neuro-oncologists (M.M., S.F.E). Most injections were done after 48 h post implantation to allow for adequate patient adjustment and to limit perioperative complications. The neuro-oncologists used aseptic techniques to insert a 23-gauge butterfly needle perpendicularly into the OR, followed by collection of CSF samples and injection of IC usually at rate of 1 mL/minute. Patients were monitored for an additional 15–20 minutes in the ambulatory infusion center to assess for any immediate symptoms or side effects.

Statistical analysis

We described and summarized demographics and baseline clinical characteristics for the entire cohort using frequency and percentage for categorical variables and mean and standard deviations (SD) or median and interquartile ranges (IQR) for continuous variables, as deemed appropriate. Time-to-progression was defined as the time lapse between the date of first IC injection and the date of the first documented clinical, radiological or CSF progression. Time-to-death was determined as the time lapse between the date of the first IC injection and the date of death or last follow-up. Kaplan-Meier method was used to assess OS and progression free survival (PFS) in this cohort. All analyses were conducted in SAS v9.4 (SAS Institute; Cary, NC).

Ethics

The Institutional Review Board reviewed and approved the study. Informed consent was waived given the minimal risk nature of this study.

Data availability

The data that support the findings of this study are available on requests from the corresponding author. The data is not publicly available because of privacy or ethical considerations.

Results

A total of 22 patients with LMD who underwent OR placement and started subsequent treatment with IC were identified from 2017–2022, with a mean age of 50.9 ± 14.8 years of this cohort, 77% of which were females (Tab. 1). Twenty patients (91%) were diagnosed with LMD based on neuroimaging, 7 (32%) of which had positive CSF analysis for malignant cells, and 2 patients (9%) were diagnosed solely based on the CSF results, given their initial negative neuroimaging findings.

Type of primary malignancy

The most common malignancy in our cohort was breast cancer, accounting for about 55% of cases. The remainder

Table. 1 Characteristics of patients with leptomeningeal disease (LMD) who received intrathecal chemotherapy (IC) via Ommaya reservoir (OR)

Variable	Total N = 22, n [%]
Age at the time of LMD diagnosis [years, mean (SD)]	50.9 ± 14.8 years
Gender	
• Male	5 (23%)
• Female	17 (77%)
LMD diagnosis*	
• Imaging-based	20 (91%)
• CSF-based	9 (41%)
• Imaging and CSF-based	7 (32%)
Type of primary malignancy	
• Breast	12 (55%)
• Bladder	1 (4.5%)
• CNS lymphoma	1 (4.5%)
• Glioma	1 (4.5%)
• Leukemia	3 (13.5%)
• Ovarian	3 (13.5%)
• Spinal melanocytoma	1 (4.5%)
Time from primary cancer diagnosis to LMD diagnosis [months, median (IQR)]	37 (24–74)
Time from OR placement to first injection, days, median	10 (7–13.5)
Total number of OR injections	208
Median number of OR injections per patient	9 (5–13)
Type of chemotherapy used for OR injections	
• Cytarabine	10 (46%)
• Etoposide	3 (14%)
• Methotrexate	10 (46%)
• Rituximab	1 (4.5%)
• Thiotepa	2 (9%)
• Topotecan	8 (36%)
• Trastuzumab	5 (23%)
Number of patients with reported complications following OR injections	5 (23%)
Headache, nausea, or emesis within 24 h following OR injections	5/208 (2.8%)
Other reported symptoms within 24 h following OR injections	2/208 (1%)
Any chemical or infectious meningitis following OR injections	0
Concurrent therapies along with IC	
• Craniospinal irradiation	8 (47%)
• Systemic chemotherapy	13 (77%)
KPS at first injection [median (IQR)]	80 (60–90)
KPS at last injection [median (IQR)]	50 (50–80)
KPS change from first to last injection [median (IQR)]	–10 (–20 to 0)

CSF — cerebrospinal fluid; IC — intrathecal chemotherapy; KPS — Karnofsky performance status; LMD — leptomeningeal disease; OR — Ommaya reservoir; *The categories of LMD diagnosis are not mutually exclusive

Table 2. Outcomes of patients with LMD receiving IC via OR

Variable	Total N = 22, n (%)
Median follow-up time from first OR injection until last injection or death [months]	5 (2–6)
CSF conversion from positive to negative testing for malignant cells	8 (36%)
Median time for CSF conversion [months]	1 (1–1)
Progression of LMD	18 (82%)
How was LMD progression determined (n = 18)	
• Clinical symptomatology only	8 (44%)
• Clinical symptomatology and neuroimaging	10 (56%)
Median time from first OR injection to progression [months]	2 (1–12)
Total number of neural axis imaging obtained following first OR injection	77
Median number of neural axis imaging obtained per patient following first OR injection	3 (2–5)
Neural axis imaging results of LMD following OR injections	35 (46%)
• Stable	18 (23%)
• Partial response	5 (6%)
• Complete response	19 (25%)
• Progression	
Death	
• Yes	11 (50%)
Overall survival	
• Median [months (95% CI)]	5.3 (4.8–NE)
Progression free survival	
• Median [months (95% CI)]	4.3 (1.8–16.0)

CSF — cerebrospinal fluid; IC — intrathecal chemotherapy; KPS — Karnofsky performance status; LMD — leptomeningeal disease; OR — Ommaya reservoir

of LMD cases was related to acute leukemia (n = 3, 13.5%), ovarian cancer (n = 3, 13.5%), primary CNS lymphoma (n = 1, 4.5%), high-grade glioma (n = 1, 4.5%), bladder cancer (n = 1, 4.5%) and spinal melanocytoma (n = 1, 4.5%). Forty-two percent of breast cancer cases with LMD (5/12) tested positive for HER2 protein. The median time from primary malignancy diagnosis to LMD diagnosis in this cohort was 37 months (IQR 24–74).

Intrathecal chemotherapy

Ommaya reservoir was placed in all patients in our cohort almost immediately following their LMD diagnosis without any apparent intraoperative/perioperative complications. The median time from OR placement to first IC injection was 10 days (IQR 7–13.5). A total of 208 IC injections was performed with a median of 9 injections per patient (IQR 5–13). The most used chemotherapeutic agents for IC injections were cytarabine (n = 10, 46%), methotrexate (n = 10, 46%), topotecan (n = 8, 36%) and trastuzumab (n = 5, 23%). Other agents included etoposide (n = 3, 14%), thiotepa (n = 2, 9%), and rituximab (n = 1, 4.5%) (Suppl. Tab. 1). Of note, 64% (n = 14) of patients received > 1 agent. Out of 208 IC injections, adverse events were reported following 7 injections only (3.4%) and were grade 2 or lower according to CTCAE. One patient experienced mild chills immediately following the injection. Other patient experienced mild nausea and emesis within 24 hours following her first injection and had mild nausea only following the second injection but did tolerate the remainder of her other nine injections, except for mild dizziness following the ninth injection. The other two patients had mild nausea only and one patient had mild nausea and headache within 24 hours of the injections. No chemical or infectious meningitis were reported. A total of five patients (23%) experienced these mild adverse events following IC injection. A total of 17 (77%) patients received either systemic chemotherapy (n = 13) or craniospinal irradiation (n = 8) along with IC. Median KPS for included patients at the time of the first and last injections was 80 and 50, respectively.

Treatment outcomes

The median follow-up time from the first IC injection until last follow-up or death was 5 months (IQR 2–6; Tab. 2). A total of 18 (82%) patients had progression of their LMD, 8 (44%) were diagnosed based on progressive clinical symptoms only, with no accompanying neuroimaging findings, and 10 (56%) were diagnosed based on both clinical symptomatology and neuroimaging findings. A total of 77 neural axis imaging studies were performed following the first IC injection, with a median number of 3 (IQR 2–5) per patient. Based on neuroradiologists' interpretation, progression, stability, partial and complete response of LMD were reported in 25% (19/77), 46% (35/77), 23% (18/77), and 6% (5/77), respectively (Fig. 1). Eleven patients (50%) died of their LMD. Median OS and PFS from the first injection were 5.3 months [95% CI: 4.8–NE (not estimable)] and 4.3 months [95% CI: 1.8–16.0], respectively (Fig. 2, 3). The median change in KPS score from first to last injection was –10 (IQR –20 to 0). Despite CSF conversion from positive to negative testing for malignant cells in 8 patients (36%) over a median of 1 month following first IC injections, 5 patients succumbed to their LMD over median of 2 months (IQR 2–5) following first injection.

Discussion

This single-center retrospective cohort study of patients with LMD who were treated with IC via OR showed that IC treatment and disease monitoring via OR was overall feasible, safe, and well tolerated with minimal adverse events. In addition, treated patients had an overall acceptable median PFS and OS compared to historical controls.

While novel systemic options and radiotherapy approaches are emerging, intrathecal chemotherapy remains one of the main therapeutic tools in LMD, and is effective against free-floating and thin linear deposits of cancer cells over the

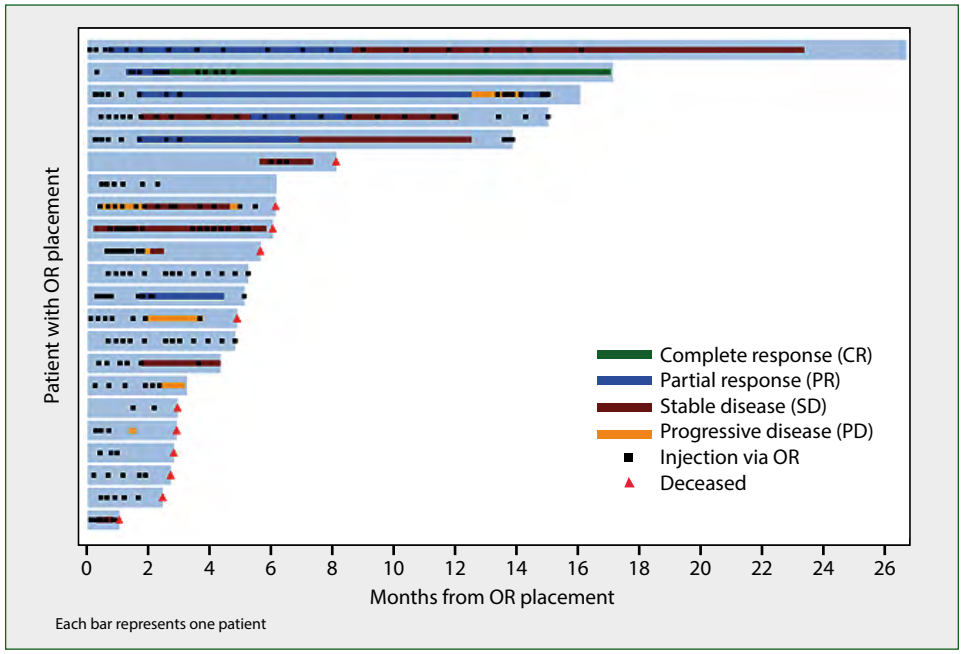

Figure 1. Swimmer plot showing the number of intrathecal chemotherapy (IC) injections via Ommaya Reservoir (OR) received by each patient along their leptomeningeal disease (LMD) disease course in conjunction with their neuroimaging results interpreted and classified as complete response, partial response, stable or progression by neuroradiology, and the survival status. Each bar represents on patient, each dot represents an IC injection via OR, and small red triangle is indicative of patient's death. IC — intrathecal chemotherapy; LMD — leptomeningeal disease; OR — Ommaya reservoir

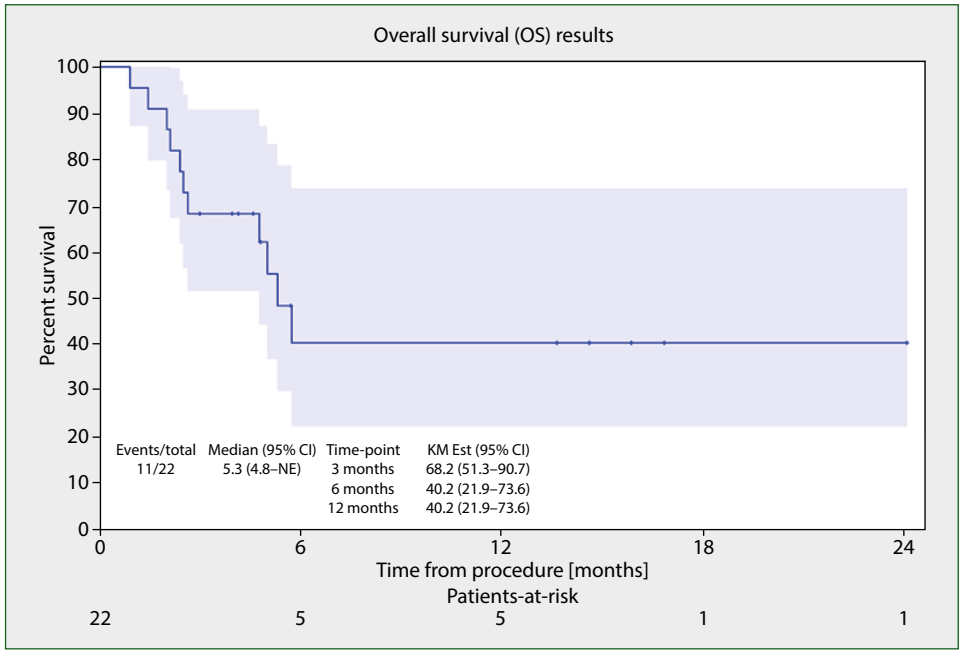

Figure 2. Kaplan–Meier survival curve showing the overall survival (OS) in our cohort of leptomeningeal disease (LMD) who received intrathecal chemotherapy (IC) via Ommaya reservoir (OR). Median OS was 5.3 months (95% CI: 4.8–NE). IC — intrathecal chemotherapy; LMD — leptomeningeal disease; NE — non-estimable; OR — Ommaya reservoir

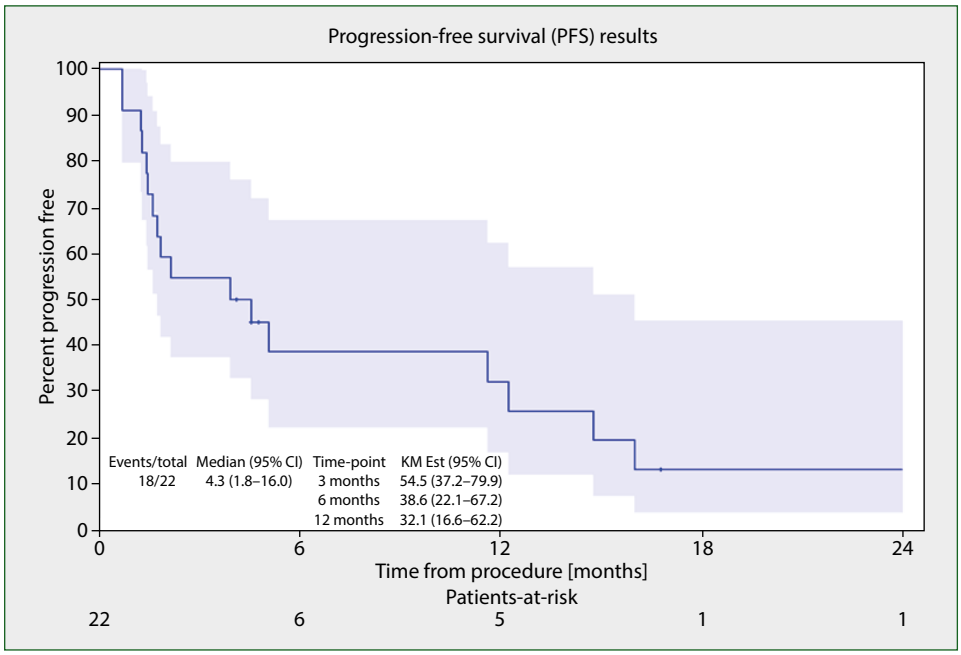

Figure 3. Kaplan–Meier survival curve showing the progression free survival (PFS) in our cohort of leptomeningeal disease (LMD) who received IC via Ommaya reservoir (OR). Median PFS 4.3 months (95% CI: 1.8–16.0). IC — intrathecal chemotherapy; LMD — leptomeningeal disease; OR — Ommaya reservoir

leptomeninges in patients with unobstructed CSF flow [2]. Ommaya reservoir has simplified the administration of various antineoplastic agents into the intrathecal space in this patient population, with recent systematic review showing that about 40% of 2200 patients with LMD who received IC had OR implantation for this purpose [6]. The currently reported OR-related complication rates in the literature are between 0–25%, which is partially related to the varying definitions of adverse events (AE) between the studies, with some including systemic AE (i.e., hematological toxicity) related to IC (an extremely rare event), as well as the inclusion of patients receiving IC via spinal intrathecal routes. For example, Lavrador [7] in his single-center retrospective cohort study of 23 patients with LMD treated with intrathecal chemotherapy via OR reported no mechanical complications related to OR injections in their cohort. In another study, Sandberg et al. [8] reported complications associated with OR implantation and placement in about 9.3% of 107 patients included in the cohort. In addition, in a 10-year retrospective single-center cohort study of 136 patients with LMD treated via OR, OR-related bacterial meningitis occurred in 18 patients (13.2%) [9]. On the other hand, our study showed that the complication rates with OR placement and subsequent IC injections were overall very low with no reported complications with OR placement. AEs were only reported after 7/208 (3.4%) OR injections performed in this study, all of which were mild grade ≤ 2 according to CTCAE with no cases of infectious or chemical meningitis. Our results suggest that utilizing OR for treating LMD and disease monitoring is overall very safe, convenient, and feasible in routine clinical practice.

Our results also showed that breast cancer was the most common primary malignancy related to LMD in our cohort, which is consistent with prior observations [10]. In addition, methotrexate and cytarabine were the most commonly used chemotherapeutic agents, similar to recent publication's results [6]. Moreover, the reported CSF conversion rate from positive to negative for malignant cells utilizing cytology and/or CTCs in our study was 36%. We started using CTCs (Biocpet, Inc.) later in the study period and most of the results reported are based on conventional cytology. A recent study showed similar CSF negative conversion rate of 30% in a cohort of 2161 patients [6]. In addition, partial and complete radiological responses of LMD were seen in 23% and 6% of our cohort, respectively. Taken together, these findings suggest that utilizing CSF analysis only for disease monitoring using cytology or CTCs may overpredict treatment response. This might be partially explained by the fact that currently available CSF analysis measures utilized for LMD monitoring assess free-floating cancer cells, but not adherent leptomeningeal cell populations. Therefore, it remains crucial that CSF analysis results from OR should be interpreted in the context of clinical symptomatology and interval neuroimaging in patients with LMD to help assess treatment response.

The median OS and PFS from the first IC injection in our study were 5.3 and 4.3 months, respectively, which are comparable to historical controls in the literature [8]. For example, median OS and PFS were 5.5 and 2.4 months, respectively, in

a recent review of about 2200 patients who received IC for their LMD [6]. Other studies utilizing IC for patients with LMD have shown OS ranging from 6.0–9.5 months [7, 8, 11].

This study has several limitations. First, the single center, retrospective nature, the design of this study, and the small number of patients included (n = 22) raise the possibility of unmeasured bias(es), including selection bias, and make it insufficient to assess for any potential rare complications that might be associated with IC via OR. Although our sample size was relatively small, a total of 208 IC injections via OR were performed with a median number of 9 injections per patient, indicating that almost all patients had sufficient repeated exposure to IC injections with no significant AEs. Second, the use of a comparator group like patients with LMD who received lumbar puncture-based IC could have strengthened the interpretation of our results and provided more robust comparison and insight related to the IC use via OR. However, given the rarity of LMD, the heterogeneity of underlying tumor histologies, our patients' preference to forego lumbar puncture and proceed with OR, and the variability in systemic therapies that patients were receiving made such design challenging to implement at our institution. Third, we only accounted for OR injections-related AEs in our safety analysis, and we did not account for the potential delayed neurological and systemic AEs related to the antineoplastic agents themselves. Fourth, the lack of any complications related to OR implantation and placement could be related to the small number of included patients, neurosurgical expertise at our institution and the use of advanced neuronavigation systems intraoperatively. Fifth, the discrepancy between CSF negative conversion and mortality possibly reflects that either CSF analysis for disease monitoring via OR may not be representative of entire CSF space, or that CSF analysis only is not yet sufficient to predict treatment response by itself. Sixth, the reliance on subjective interpretation of clinical and radiological progression by the treating neuro-oncologists and neuroradiologists, respectively, may have introduced observer bias. Use of standardized assessment tools like RANO-LM could have improved reproducibility. Nevertheless, in our study, progression — whether clinical, radiological, or CSF-based — was reported in an exploratory and descriptive manner, as the primary goal was to evaluate safety and feasibility of IC administration via OR rather than efficacy. Lastly, about 77% of patients in our cohort received either concurrent palliative irradiation or systemic chemotherapy along with the IC; thus, it is difficult to ascertain the impact of IC in our cohort on the patients' OS and PFS.

Conclusions

In summary, this single-center retrospective cohort study suggests that the use of Ommaya reservoir for administration of IC in routine clinical practice is a safe, feasible and convenient option. This approach can be considered for treatment and frequent disease monitoring of patients with LMD, especially in the era of advanced cellular and molecular techniques to assess the presence of malignant cells and circulating tumor DNA in the CSF.

Article information

Data availability statement: *Data will be made available upon reasonable request to the corresponding author.*
Ethics statement: *The Institutional Review Board reviewed and approved the study. Informed consent was waived given the minimal risk nature of this study.*
Author contributions: *Conceptualization and design: E.H, S.S and M.M. Literature review and data interpretation: E.H, M.M, and R.B. Writing of the initial draft: E.H and M.M. Manuscript revision and approval of the final version: E.H, R.H, C.C, M.M, S.F.E, E.Y, B.B, M.L, C.K, R.Z, J.M.*
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