Benefit of ventriculoperitoneal cerebrospinal fluid shunting and intrathecal chemotherapy in neoplastic meningitis: a retrospective, case-controlled study

Clinical article

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Object. Neoplastic meningitis (NM) is a debilitating and increasingly frequent neurological complication of cancer characterized by infiltration of tumor cells into the leptomeninges and the subarachnoid space. Although NM is rarely curable, combined intrathecal chemotherapy and focal radiation can improve disease-related symptoms and survival. Hydrocephalus occurs in a significant proportion of patients, is associated with poor prognosis and reduced quality of life, and usually precludes the use of intrathecal therapy.

Methods. Since January of 2005, the authors have used a combined treatment approach for patients with both NM and hydrocephalus that employs a subcutaneously placed reservoir connected in series to an on/off valve and a ventriculoperitoneal shunt for both diversion of CSF and injection of intrathecal chemotherapy. They conducted a retrospective, case-controlled study from 2 independent institutions to review their experience.

Results. Twenty-four patients with NM and hydrocephalus underwent placement of a CSF reservoir-on/off valve-ventriculoperitoneal shunt (RO-VPS) construct. There was no perioperative mortality, and there were only 2 minor complications. One shunt failure and no shunt-associated infections were observed over a median of 28 weeks of follow-up. Symptomatic improvement and improved performance status were seen in 20 patients (83.3%) and were sustained over 6 months. Eighteen patients received intraventricular chemotherapy without unexpected toxicity, and cytological responses were found in 11 patients (61.1%). Median progression-free and overall survival was 14 and 31 weeks, respectively. Compared with a contemporaneous comparison group of 24 demographically matched patients with NM who underwent CSF reservoir placement only, those who received RO-VPS constructs (p = 0.02) and had primary diagnosis of breast cancer (p = 0.04) had significant advantage in overall survival.

Conclusions. A combined RO-VPS system is safe and practical to install, results in symptomatic improvement in most patients, and allows uncomplicated and effective administration of intrathecal chemotherapy in patients with NM. Cerebrospinal fluid diversion surgery should be considered in NM patients in conjunction with intrathecal and systemic treatments. (DOI: 10.3171/2011.5.JNS101768)

Key Words • ventriculoperitoneal shunt • intrathecal chemotherapy • neoplastic meningitis • leptomeningeal metastasis • on-off valve • oncology

NEOPLASTIC meningitis (NM) is an increasingly recognized complication of cancer that occurs in approximately 5%–10% of all cancer patients⁷,⁹,¹⁰,¹²,¹⁹,²⁵,²⁷ and almost 20% of those with neurological symptoms.²⁴ The incidence of neoplastic meningitis is rising,¹² most likely due to improved diagnostic techniques, increasingly successful treatment of cancer outside the nervous system, and the use of chemotherapeutic agents with little or no access to the CNS.²⁹,³² The optimum treatment strategy for NM includes focal radiation to sites of bulky or symptomatic disease, systemic chemotherapy appropriate to the stage and histology of the underlying cancer, and intrathecal chemotherapy through a subcutaneously placed ventricular reservoir.⁹ Although the median survival of patients with NM is poor—2–4 months in randomized controlled trials⁴,¹⁴,¹⁵,¹⁸—about one-quarter of patients survive for 6 months, and ap-
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proximately 12% for a year following the diagnosis of NM, using this treatment approach.

Because NM is characterized by infiltration of cancer cells throughout the leptomeninges and subarachnoid space, obstruction of CSF flow is common and leads to elevated intracranial pressure and hydrocephalus in half of patients. Without CSF diversion, patients with hydrocephalus or increased intracranial pressure can develop debilitating headaches, and cognitive, gait, sphincter, and other neurological deficits, sometimes including herniation and death. Cerebrospinal fluid diversion techniques such as ventriculoperitoneal and lumboperitoneal shunting are safe and effective in treating hydrocephalus from multiple etiologies, but these techniques have not been used extensively in patients with NM, in part due to therapeutic nihilism and in part due to concerns about peritoneal spread of cancer. Furthermore, administering intrathecal chemotherapy to patients with ventriculoperitoneal shunts is problematic because a functioning ventriculoperitoneal shunt will shunt chemotherapy out of the CSF space, making it difficult to maintain an effective concentration of chemotherapy within the CSF. To address these concerns, we have used a combined treatment approach for NM patients with hydrocephalus that employs an in-line CSF reservoir for injection of intraventricular chemotherapy, an on-off valve for CSF flow control, and a programmable ventriculoperitoneal shunt for diversion of CSF (RO-VPS). In this paper, we review our experience with this approach.

Methods

Patient Selection

Demographic and clinical outcome data from patients who underwent ventriculoperitoneal shunt placement were prospectively collected at the Brigham and Women's Hospital/Dana-Farber Cancer Institute and the Huntsman Cancer Institute, University of Utah with institutional-review-board-approved protocols. All patients treated with ventriculoperitoneal shunts were at least 18 years of age, carried the diagnosis of NM, and had symptomatic hydrocephalus. Most patients underwent lumbar puncture prior to shunt placement to demonstrate high opening pressure and/or volume-dependent neurological symptoms. Identical demographic and outcome data were collected from a contemporaneous group of patients with NM and no hydrocephalus treated at the Brigham and Women's Hospital/Dana-Farber Cancer Institute who underwent Ommaya reservoir placement without shunt placement. Patients were monitored carefully during the study period for signs and symptoms of elevated intracranial pressure, such as worsening headache, nausea, vomiting, blurry vision, mental status changes, or gait changes. If elevated intracranial pressure was confirmed via lumbar puncture and an Ommaya reservoir had already been placed, a ventriculoperitoneal shunt would be placed on the contralateral side. Informed consent was obtained from all patients for all surgical procedures.

Design of the RO-VPS Construct

The RO-VPS construct consists of a Codman Holter reservoir (Codman Inc.) connected in series with an on-off valve (Integra LifeSciences), a programmable shunt valve (Codman Hakim valve, in-line design), and distal peritoneal tubing (Fig. 1). The connection between each component is achieved via straight connectors with silk ties. The construct measures approximately 11 cm in length, compared with 3 cm for the valve only. We chose to use both an on-off valve and a programmable valve, which could be dialed from 30 mm Hg to 200 mm Hg, because of concerns that frequent adjustment of the programmable valve setting could be associated with increased risk of shunt failure. It is also important to have the on-off valve in between the Ommaya reservoir and the shunt valve because switching it off prevents the shunt valve from being exposed to external pressure when the reservoir is used for injection. During the operative procedure, a ventricular catheter is placed intracranially, and is then attached to the Ommaya reservoir. All patients received an intravenous injection of antibiotic agent (Vancomycin 1 gm at Brigham and Women's Hospital, Ancef 1 gm at the Huntsman Cancer Institute) prior to incision. After the operation, a CT scan of the head and skull radiographs (shunt series) were obtained in all cases to confirm appropriate ventricular catheter placement and the appropriate shunt pressure setting (Fig. 1). A CSF flow study (with the on-off valve closed or with the programmable valve turned up to the highest setting) was performed in all cases prior to the first administration of intraventricular chemotherapy to demonstrate appropriate CSF distribution of tracer and patency of CSF pathways.

Intrathecal Chemotherapy Protocol

As early as 48 hours after placement of an RO-VPS system, patients were treated with intraventricular chemotherapy selected by the treating neurooncology team. Prior to an intrathecal injection, the treating oncologist manually closed the on-off valve, effectively stopping the CSF flow toward the peritoneal space. The Ommaya reservoir was accessed via a 25-gauge needle, and the opening pressure was measured prior to chemotherapy administration to confirm a pressure less than 200 mm of water. The on-off valve stayed closed for 2–6 hours after the injection while the patient was closely monitored in the clinic. The valve was promptly switched open if the patient developed symptoms suggestive of increased intracranial pressure such as worsened headache, nausea, vomiting, or confusion. It was observed that over time most patients could tolerate longer duration of valve closure; as a result, in many patients the valve was kept closed for up to 24 hours. Intrathecal chemotherapy was mostly carried out in an outpatient setting and rarely was admission required after a treatment.

Data Analysis

Follow-up was performed twice weekly to once monthly depending on the patient's chemotherapy regimen and clinical course. All electronic and paper medical records were reviewed. Demographic characteristics and perioperative medical conditions were recorded, including age, sex, extent of systemic cancer, CSF chemistry,
cell count, cytology, radiographic findings, concurrent chemotherapy and radiation therapy, pre- and postoperative Karnosfky Performance Scale (KPS) scores, and progression-free and overall survival. Perioperative complications, length of hospital stay, and postoperative relief of symptoms were also extracted from the medical records. Disease progression was defined as either clinical deterioration attributed by the treating team to NM, positive results of CSF cytological analysis after initial clearing, or radiographic worsening of CNS disease. The KPS score, disease-related symptoms, and treatment-related side-effects were reported by the patient’s treating neurooncology team in the medical record. Independent-sample t-tests and log-rank tests were performed. All statistical analyses were performed with Excel (Microsoft Corp.) and SPSS 15.0 (SPSS, Inc.).

Results

Patient Cohorts

Between 2005 and 2009, 24 patients underwent surgical placement of RO-VPS constructs at our 2 institutions. Two patients were lost to follow-up. A comparison (“control”) group consisted of 26 consecutive patients who were diagnosed with neoplastic meningitis, had Ommaya reservoirs placed, and received intrathecal chemotherapy at the Brigham and Women’s Hospital/Dana-Farber Cancer Institute during the same 4-year interval. Two patients in the control group who initially underwent placement of an Ommaya reservoir alone subsequently developed symptomatic hydrocephalus and underwent placement of a ventriculoperitoneal shunt on the contralateral side. Both of these patients received intrathecal chemotherapy following the second operation and were included in the RO-VPS group. Thus, data from 24 patients were available for analyses from each group. The 2 groups were nearly identical with respect to demographic characteristics, systemic cancer spread, functional status (measured by preoperative KPS score), and treatment, apart from the type of ventricular access or shunting device they received (Table 1). A total of 29 patients were treated with whole brain radiation therapy prior to shunt or Ommaya reservoir placement, and 14 patients also received stereotactic radiosurgery for focal intracranial lesions. The distribution of patients treated with radiation therapy is similar between the 2 groups.

The median age of the patients at surgery was 57 years (range 23–75 years) in the RO-VPS group and 53.5 years (range 27–87 years) in the control group. Breast cancer was the most common primary cancer diagnosis in both groups. In the RO-VPS group, 7 patients had leptomeningeal spread of primary brain cancer (4 anaplastic astrocytomas, 2 glioblastomas, 1 medulloblastoma), as did 5 patients in the control group (2 anaplastic astrocytomas, 2 glioblastomas, 1 oligodendroglioma). At diagnosis of NM, the majority of patients (76.9%) complained of headache, although ataxia, nausea/vomiting, visual changes, and cranial nerve palsies were also frequently

![Fig. 1. Postoperative CT scan (A) and skull radiograph (B), and photograph (C) showing the RO-VPS construct. The intraventricular catheter is placed through a bur hole at the Kocher point and connected to the Ommaya reservoir (A). The RO-VPS construct is located in an extended subgaleal pocket above the pericranium (B). The 3-part apparatus (C) includes an Ommaya reservoir (1), an on-off valve (2), and a programmable shunt valve (3). All connections are tied with 2-0 silk sutures.](image-url)
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TABLE 1: Clinical and demographic characteristics of patients who underwent surgical placement of an RO-VPS construct or an Ommaya reservoir alone*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RO-VPS Group</th>
<th>Ommaya Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of pts</td>
<td>24</td>
<td>24</td>
<td>NA</td>
</tr>
<tr>
<td>age at op (yrs)</td>
<td></td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td>median</td>
<td>57.0</td>
<td>53.5</td>
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<td>27–87</td>
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</tr>
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<td>sex</td>
<td></td>
<td></td>
<td>0.67</td>
</tr>
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<td>male</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>17</td>
<td>16</td>
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</tr>
<tr>
<td>primary cancer</td>
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<td>0.74</td>
</tr>
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<td>breast</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>brain/glioma</td>
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<td>5</td>
<td></td>
</tr>
<tr>
<td>lung</td>
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<td>3</td>
<td></td>
</tr>
<tr>
<td>lymphoma</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>systemic cancer spread†</td>
<td>16 (66.7%)</td>
<td>17 (70.8%)</td>
<td>0.67</td>
</tr>
<tr>
<td>positive cytology</td>
<td>21 (87.5%)</td>
<td>19 (79.2%)</td>
<td>0.31</td>
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<tr>
<td>preop KPS score</td>
<td>53.6</td>
<td>53.1</td>
<td>0.88</td>
</tr>
<tr>
<td>preop Tx</td>
<td></td>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td>chemo</td>
<td>20 (83.3%)</td>
<td>20 (83.3%)</td>
<td></td>
</tr>
<tr>
<td>WBRT</td>
<td>15 (62.5%)</td>
<td>14 (58.3%)</td>
<td></td>
</tr>
<tr>
<td>SRS</td>
<td>9 (37.5%)</td>
<td>5 (20.8%)</td>
<td></td>
</tr>
<tr>
<td>prior craniotomy</td>
<td>11 (45.8%)</td>
<td>7 (29.2%)</td>
<td>0.07</td>
</tr>
<tr>
<td>postop IT chemo</td>
<td>18 (75.0%)</td>
<td>20 (83.3%)</td>
<td>0.27</td>
</tr>
<tr>
<td>postop systemic Tx</td>
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<td></td>
<td>0.34</td>
</tr>
<tr>
<td>chemo</td>
<td>21 (87.5%)</td>
<td>19 (79.2%)</td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>16 (66.7%)</td>
<td>13 (54.2%)</td>
<td></td>
</tr>
</tbody>
</table>

* Values represent numbers of patients (%) unless otherwise indicated. Abbreviations: chemo = chemotherapy; IT = intrathecal; NA = not applicable; RT = radiation therapy; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.
† Includes patients with other brain parenchymal metastases.

Patients who were referred to the neurosurgery clinic with a diagnosis of NM and with symptoms of hydrocephalus usually underwent RO-VPS placement within 3 days. Patients exhibited steep functional decline (as measured by KPS score) from the time of the initial diagnosis of cancer to the time when they developed symptoms of NM. This downward trend was reversed after RO-VPS placement (Fig. 2), and the beneficial effect was sustained over time. Most patients who received RO-VPS constructs had rapid relief of preoperative symptoms of headache, nausea, and gait disturbance (20 [83.3%] of 24). The mean KPS score at the first routine postoperative follow-up appointment (usually 1–2 weeks after the operation) was significantly higher than that at the preoperative evaluation (67.6 vs 53.6, p < 0.05). This improvement was sustained for the entire 6-month follow-up period of this series in 10 (41.7%) of 24 patients.

Survival After RO-VPS Surgery

Eighteen of the 24 patients in the RO-VPS group received intrathecal chemotherapy. Other concurrent postoperative treatment consisted of systemic chemotherapy in 21 patients (87.5%) and radiation therapy in 16 (66.7%). In 11 of the 18 patients who received intrathecal chemotherapy, the best cytological response to treatment was complete clearing of malignant cells on at least 2 separate, consecutive CSF samplings at least 1 week apart.
The median duration of follow-up was 28 weeks. The median overall survival was 31 weeks (95% CI 21.7–40.2 weeks, range 10–88 weeks), and 11 patients (45.8%) were alive at end of follow-up. Twenty-two patients (91.7%) eventually showed disease progression during the follow-up period. The median progression-free survival was 14 weeks (95% CI 12.2–15.8 weeks, range 4–54 weeks).

In the control group, 20 patients (83.3%) received intrathecal chemotherapy, 13 (54.2%) underwent postoperative radiation, and 19 (79.2%) had systemic chemotherapy. The median follow-up period was 14 weeks. Twenty-three patients (95.8%) showed disease progression during follow-up. The median overall survival was 19.5 weeks (95% CI 5.9–29.5 weeks, range 2.7–67.7 weeks) and progression-free survival 8.4 weeks (95% CI 1.0–13.9 weeks, range 1.8–54.6 weeks). When analyzing the length of overall survival according to primary cancer diagnosis, breast cancer patients in the RO-VPS group had significantly better survival than those in the control group (35 vs 21 weeks, p = 0.04), whereas there was no statistically significant difference in patients with other primary diagnoses (Table 2). The overall survival in the RO-VPS group altogether was also better than that in the control group, using the Kaplan-Meier method (p = 0.008, Fig. 3).

In the current study, the placement of an RO-VPS construct was associated with a very low rate of morbidity (8.3%), no perioperative infection, and no perioperative death. This is especially notable because patients with NM are potentially high-risk candidates for ventriculoperitoneal shunt placement. Prior chemotherapy and radiation therapy can result in impaired wound healing; treatment- and disease-related immunosuppression can cause increased susceptibility to infection; and prior craniotomies and the presence of malignant cells and high protein in the CSF can result in a higher failure rate for the ventriculoperitoneal shunt in these patients than in patients who do not have cancer. Our experience compares favorably with similar published reports, in which significant complications occurred in about 10% of patients.

In addition to being associated with a low complica-
tion rate, the RO-VPS constructs were effective at relieving the symptoms of hydrocephalus (in 20 [83.3%] of 24 patients) and permitted intraventricular chemotherapy to be administered in all patients in whom this intervention was deemed appropriate. In those patients in whom intraventricular chemotherapy was delivered, we saw no unusual or clinically concerning toxicity, and we observed evidence of treatment efficacy, with cytological clearing of the CSF in 11 (61.1%) of 18 patients. The observed median survival of 31 weeks in this study also compares favorably with published studies reporting a median overall survival of 8–30 weeks.4,14,15,18 The survival advantage of the RO-VPS group over the Ommaya reservoir group, with significantly better overall survival (p = 0.008).

![Kaplan-Meier curves for patients in the Ommaya reservoir group and the RO-VPS group. Patients in the RO-VPS group have significantly better overall survival (p = 0.008).](image)

**Fig. 3.** Kaplan-Meier curves for patients in the Ommaya reservoir group and the RO-VPS group. Patients in the RO-VPS group have significantly better overall survival (p = 0.008).

Conclusions

In many patients who suffer from NM, hydrocephalus and elevated intracranial pressure are responsible for rapidly declining neurological status and eventual poor outcome. Our experience suggests that CSF diversion surgery in conjunction with intrathecal chemotherapy may provide important benefits to an appreciable proportion of patients with NM. Prospective clinical studies are needed to validate this approach in patients with NM.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Kesari, Lin, Dunn, Glantz, Jensen, Friedlander. Acquisition of data: Lin, Allison, Johnson, Glantz, Jensen. Analysis and interpretation of data: Kesari, Lin. Drafting the article: Kesari, Lin. Critically revising the article: Kesari, Lin. Administrative/technical/material support: Kesari, Lin. Study supervision: Kesari, Friedlander.

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