Safety Profile of Long-Term Intraventricular Access Devices in Pediatric Patients Receiving Radioimmunotherapy for Central Nervous System Malignancies

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Background. The use of Ommaya catheters or ventriculoperitoneal shunts with programmable valves (pVP-shunts) for intraventricular drug administration is increasingly more common. Patients with primary central nervous system (CNS) malignancies and with tumors metastatic to the CNS have been treated with compartmental radioimmunotherapy (cRIT) with 124-I or 131-I labeled monoclonal antibody 3F8 or 8H9. For each injection, catheters were individually accessed 3–6 times. Thereafter catheters were accessed for periodic routine cytology. Six patients (4%) had complications including three with catheter migration in the newly-placed setting requiring surgical revision. Two patients had pericatheter cyst formation and four patients had catheter malfunctioning. Four patients required Ommaya conversion to VP shunts because of hydrocephalus secondary to disease progression. Conclusions. We report a long-term safety profile of intraventricular access devices in patients receiving cRIT. Minimal acute complications are observed despite the frequency of cerebrospinal fluid acquisition; long-term complications are rare. Programmable VP shunts appear to be a safe and effective alternative to Ommaya catheters.

Key words: CNS metastases; intraventricular access devices; ommaya; radioimmunotherapy

INTRODUCTION

The use of Ommaya catheters or ventriculoperitoneal shunts with programmable valves (pVP shunts) for intraventricular drug administration is increasingly more common. Patients with primary central nervous system (CNS) malignancies and with tumors metastatic to the CNS have been treated with compartmental radioimmunotherapy (cRIT) with 124-I or 131-I labeled monoclonal antibodies on institutional review board approved protocols at Memorial Sloan-Kettering Cancer Center for 15 years. We now summarize the safety profile of intraventricular access devices in pediatric patients receiving cRIT.

BACKGROUND

Dr. Ayub Ommaya’s invention, the Ommaya reservoir, reported in 1963, was the first subcutaneous reservoir that allowed for repeated intrathecal injections [1]. As a convenient method of accessing the cerebrospinal fluid (CSF), the device enabled the administration of antibiotics, obviating the need for painful lumbar punctures. In the 1970’s, Ommaya catheters in pediatric oncology were used with increasing frequency [2]. As an alternative to the Ommaya catheter, pVP-shunts are increasingly used, with the most common being Codman or Medronic valves. In contrast to the Ommaya catheter, the pVP-shunt requires setting adjustment and confirmation before and after drug administration, but has the added advantage of modifiable pressure settings. Placement of such devices has enabled the administration of antibiotics [3], chemotherapy [4], stem cell transplantation for neurodegenerative diseases [5], treatment for hydrocephalus or brain tumor cysts [6], and intraventricular narcotics for intractable pain [7]. With easy access to the CSF, frequent measurements of cell count, culture, cytology, or pharmacokinetic and dosimetry studies are possible. Although the indications are vast, the list of reported complications of such devices includes catheter mal-position, non-functionality [8], infection [9], development of cavum septi pellucidi [10], porencephalic cyst formation [11], and development of hemiparkinsonism [12]. Neurosurgical expertise, familiarity with the various devices, pre- and intraoperative planning, endoscopic guidance, and stereotactic techniques [13,14] all aid in minimizing such risks. Routine administration of cRIT by pediatric oncologists and nurse practitioners in the outpatient setting is possible because of these intraventricular access devices. Improved survival for patients with high risk tumors treated with salvage regimens incorporating cRIT has been noted [15], making it important to document the incidence of acute and/or long-term complications of indwelling intraventricular access devices for such patients. This analysis in patients receiving cRIT with 124-I or 131-I monoclonal antibodies has not been previously reported. We undertook this study to address this important question in a large group of pediatric patients who received cRIT.

PATIENTS AND METHODS

Since 1998, patients with high risk or recurrent CNS tumors with antigen-reactivity were eligible for cRIT. Baseline MR brain and spine, and CSF cytology were obtained. All patients had an indwelling Ommaya catheter or pVP shunt. Once devices were placed, there was no plan to remove them in the short or long term unless medically indicated.

Prior to intraventricular drug administration, all patients underwent CSF patency studies with radionuclide cisternography.
using intraventricular $^{111}\text{In}$-DTPA followed by nuclear imaging at 1–4 hours and again at 24 hours post injection. In the setting of a functional ventricular peritoneal shunt, the valve setting was adjusted 1–2 hours prior to injection, and then approximately 6 hours after injection. Such baseline CSF flow studies assured (1) device functionality, (2) that an injected drug would be therapeutically dispersed throughout the entire thecal space, and (3) that there was little or no risk of local drug-induced neurotoxicity. One hundred fifty-one patients with recurrent CNS tumors were treated. Diagnoses of primary CNS tumors included medulloblastoma, medulloblastoblastoma, atypical teratoid rhabdoid tumor, ETANTR, chordoma, and anaplastic ependymoma; tumors metastatic to the CNS included neuroblastoma, retinoblastoma, rhabdomyosarcoma, and melanoma. The 151 patients received a total of 513 cRIT injections. For patients with GD2-expressing tumors, treatment involved 2 mCi $^{131}\text{I}$-3F8 or more recently $^{124}\text{I}$-8H9 followed by four serial injections of 10 mCi $^{131}\text{I}$-3F8 per injection, with a therapeutic goal of ≥2 injections (≥20 mCi), dosimetry permitting. For patients with B7H3-expressing tumors, treatment involved 2 mCi $^{131}\text{I}$-8H9 or $^{124}\text{I}$-8H9 followed by 1–2 injections of 10–80 mCi $^{131}\text{I}$-8H9 per injection on a dose escalation study. Pharmacokinetics were studied by serial CSF sampling through the intraventricular device and blood samplings. Dosimetry was based on pharmacokinetics and region of interest (ROI) analyses on whole-body SPECT ($^{131}\text{I}$) or PET ($^{124}\text{I}$) scans. Response was determined by clinical, radiographic, and cytologic criteria, as well as progression-free survival at 6 months, and approximately yearly thereafter.

**RESULTS**

One hundred fifty-one patients with recurrent primary or metastatic CNS tumors had a ventricular access device (143 Ommaya reservoirs, 8 VP shunts with programmable valves) placed for drug administration and CSF acquisition. One hundred forty-five patients had no complications with permanent indwelling intraventricular devices, as long as 10+ years post device placement. There were no activity or athletic restrictions placed on our large group of survivors post cRIT. Although not a complication per se, one child 5 years after completion of cRIT from metastatic neuroblastoma, alarmed a school nurse, who unfamiliar with the Ommaya catheter, thought the child has sustained a head injury resulting in a bump on her head. The child and parents reassured the nurse that it was a device used for prior therapy. Another young man similarly reported having to alert his barber prior to haircuts so he would not be alarmed as well. Six patients (4%) had intraventricular device complications (Table I). This included three incidences of catheter migration in the newly-placed setting requiring surgical revision. There were no incidences of catheter migration as a long-term complication. Two patients had pericatheter cyst formation (with cyst formation before cRIT administered in one patient) resulting in elective removal and

**METHODS OF ACCESSING DEVICES**

The antibodies 3F8 and 8H9 were radiolabeled with iodogen method under the supervision of our Medical Physics team according to the FDA requirements specified by the IND. All patients had an intraventricular reservoir (i.e., Ommaya reservoir or pVP shunt) with adequate CSF flow determined by $^{111}\text{In}$-DTPA followed by nuclear imaging at 1–4 hours and again at 24 hours post injection. In the setting of a functional ventricular peritoneal shunt, the valve setting was adjusted 1–2 hours prior to injection, and then approximately 6 hours after injection. The Ommaya catheter site/VP shunt was prepped and draped. A volume of CSF equal to the volume of drug to be injected was removed, the drug injected slowly through a Millipore filter, so as not to exceed a rate of 1 ml/minute. 0.5 ml of sterile normal saline and 3 ml of autologous CSF were flushed slowly through the filter. The reservoir was manually pumped after the flush. Patients positioned in a 60’ to 90’ sitting position for at least 1 hour following injections to facilitate CSF flow. The device remained accessed with a capped 24-gauge butterfly needle so that CSF samples could be obtained for pharmacokinetic and dosimetry estimates. After cRIT injections, patients had approximately 0.5 ml CSF and 1–2 ml blood obtained for radioactivity levels at approximately, 1, 2, 4–6, 18–24, 44–48, 66–72 hours and ~5–7 days post injection. The device frequently remained accessed for up to 48 hours, thereafter requiring individual accesses for subsequent CSF sample acquisition.

**TABLE I. Complications of Intraventricular Devices**

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Diagnosis</th>
<th>Age</th>
<th>Type of device</th>
<th>Complication</th>
<th>Time frame from placement to complication</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NB</td>
<td>5</td>
<td>Ommaya</td>
<td>Soccer related head injury caused device dislodgement</td>
<td>1 week</td>
<td>Removal of device; new device placed</td>
</tr>
<tr>
<td>2</td>
<td>NB</td>
<td>3</td>
<td>Ommaya</td>
<td>Nonfunctioning; migration away from the ventricle</td>
<td>6 weeks</td>
<td>Removal of device; new device placed</td>
</tr>
<tr>
<td>3</td>
<td>NB</td>
<td>29</td>
<td>Ommaya</td>
<td>Catheter migration away from the ventricle; non functioning</td>
<td>4 months</td>
<td>Removal of device; new device placed for cRIT</td>
</tr>
<tr>
<td>4</td>
<td>NB</td>
<td>3</td>
<td>Ommaya</td>
<td>4 cm pericatheter cyst formation</td>
<td>5 months</td>
<td>Observed for 5 more months, increase in size, midline shift; permanent removal of device</td>
</tr>
<tr>
<td>5</td>
<td>MB</td>
<td>3</td>
<td>Ommaya</td>
<td>5 cm pericatheter cyst formation</td>
<td>4 months</td>
<td>Observed for 6 months; removal of device; new device placed for cRIT</td>
</tr>
<tr>
<td>6</td>
<td>RB</td>
<td>5</td>
<td>pVP shunt</td>
<td>Shunt discontinuity at the level of the thoracic inlet</td>
<td>6 years</td>
<td>Permanent removal of device</td>
</tr>
</tbody>
</table>

NB, neuroblastoma; MB, medulloblastoma; RB, retinoblastoma; cRIT, compartmental intraventricular radioimmuno therapy; pVP shunt, ventriculoperitoneal shunts with programmable valves.

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endoscopic cystoventriculostomy in both patients (Fig. 1). Both cysts developed within the first six months after device placement. There were no true catheter-related infections, whereas in other studies infectious complications are regularly reported with the administration of intraOmmaya chemotherapy. Only 1 patient had a routine CSF culture reported 1 week post sampling to have propionibacterium acnes. As the patient was not ill and the culture took 1 week to grow, it was initially thought to be a contaminant. On repeat CSF evaluation and in the absence of any intervening medical therapy, cultures remained negative. There were no catheter related hemorrhages, seizures, focal deficits, or valve malfunctioning. Four patients later required Ommaya conversion to VP shunts because of hydrocephalus secondary to progressive disease. Although more cumbersome to use given the pre- and post-adjustment procedures required for pVP-shunts, there were no complications specifically with the valves on such devices.

DISCUSSION

Indwelling intraventricular access devices are required for many routine pediatric oncology patients [16]. A thorough understanding of the types of reservoirs available helps to minimize acute or long-term risks associated with their use. We have demonstrated a remarkable safety profile for permanent indwelling devices used for cRIT administration. In our study, such devices used for cRIT are not associated with any infection risk, despite the catheters remaining accessed for up to 48 hours post injection. This is in contrast to the recognized infectious complications reported with standard chemotherapy agents. One may question whether the cRIT treatment, injected through a filter, is directly responsible for this lack of infection risk, or whether the drug itself helps eliminate microscopic or low-colonized bacteria loads. The only longer term risk of catheters in our series appears to the development of pericatheter cyst formation, albeit rare as well. Given this safety profile, we routinely recommend that such catheters permanently remain in our patients, thereby posing no risk of creating a new complication at the time of device removal. Of note, our patients have no restrictions on their athletic or activity level despite the permanent presence of this long standing device.

CONCLUSION

We report a remarkable safety profile of permanent intraventricular access devices in pediatric patients receiving cRIT. It is greatly reassuring that rare acute complications are observed, despite the frequency of device access and CSF acquisition. Long-term complications greater than 10 years post injection when catheters remain indwelling, are also rare. Programmable VP shunts appear to be a safe and effective alternative to Ommaya catheters.

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REFERENCES