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CLINICAL STUDY

Complications related to the use of an intraventricular access device for the treatment of leptomeningeal metastases from solid tumor: a single centre experience in 112 patients

Fahed Zairi[1] · Emilie Le Rhun[1,2] · Nicolas Bertrand[2] · Thomas Boulanger[3] · Sophie Taillibert[4,5] · Rabih Aboukais[1] · Richard Assaker[1] · Marc C. Chamberlain[6]

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Abstract Ventricular access devices (VAD) offer several advantages compared to intralumbar injections for the administration of intra-CSF agents in the treatment of leptomeningeal metastases (LM). However, there are few prospective studies reporting on complications with the use of VADs. All complications were prospectively collected that pertained to the implantation and use of a VAD in consecutive patients with solid tumor-related LM from June 2006 to December 2013. Clinical follow-up was every 2 weeks during the initial 2 months of treatment and then once monthly. Complete neuraxis MRI was performed at baseline and then every 2–3 months. A total of 112 patients (88 women) with a mean age of 51.1 years (range 26–73) were included. Primary cancers included breast (79 patients), lung (12) and melanoma (6). All patients were treated with intra-CSF liposomal cytarabine. 72 % of the patients received concomitant systemic and intra-CSF chemotherapy. The placement of the VAD was performed under local anesthesia in all cases. The mean operative time was 15 min and no perioperative complications were reported. The mean number of intraventricular injections per patient was 9.34 (range 1–47). A total of 11 complications in 11 patients were seen including 7 infections, 1 intracranial hemorrhage, 2 instances of symptomatic leukoencephalopathy and 1 catheter malpositioning. 8 complications required an operation and 1 complication was fatal. The use of a VAD is safe and may improve patients' comfort and compliance with LM-directed therapy.

Keywords Ventricular access device · Leptomeningeal meningitis · Complications · Infection intraventricular intra-CSF treatment

Introduction

Leptomeningeal metastases (LM), also known as neoplastic meningitis, is the result of the seeding of the leptomeninges by malignant cells. Breast, lung and melanoma are the most common primary cancers [1, 2] that metastasize to the leptomeninges; 5–15 % of patients with these cancers will develop LM during the course of their cancer [3]. The incidence of LM is expected to increase due to improved diagnostic tools [4] and the fact that cancer patients live longer as anticancer therapies often with poor central nervous system (CNS) penetration have become more effective [5–9]. Currently, intra-cerebrospinal fluid (CSF) chemotherapy, combined with systemic treatment and radiotherapy, is the main treatment for LM [10]. Intra-CSF treatment offers a selective regional therapy with minimal systemic toxicity, permitting concomitant systemic treatment in an appropriate clinical context. Administration through repeated lumbar puncture (LP)

✉ Fahed Zairi
fahed.zairi@gmail.com

1 Department of Neurosurgery, Hopital Roger Salengro, Lille University Hospital, Rue Emile Laine, 59037 Lille, France

2 Department of Medical Oncology, Oscar Lambret Center, Lille, France

3 Department of Radiology, Oscar Lambret Center, Lille, France

4 Department of Neuro-Oncology Mazarin, Pitie-Salpetriere Hospital, Paris, France

5 Department of Radiation Oncology, Pitie-Salpetriere Hospital, Paris, France

6 Department of Neurology, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, USA

presents many practical drawbacks. First, the drug is delivered into the epidural or subdural space without reaching the CSF, in up to 10 % of intrathecal (i.e. intralumbar) injections [11, 12]. Secondly, drug distribution delivered by intralumbar administration is not uniform throughout the neuraxis [13], with a low and inconstant concentration of drug in the intracranial compartment, a fact that may negatively impact therapy. This appears to be especially true for short half-life agents such as methotrexate, thiotepa and cytarabine [12]. Advantages of intraventricular drug administration include a comparatively pain free procedure that may improve the patients' compliance, especially when bi-weekly administration is required. Moreover, intraventricular injections are more time efficient for the physician. Additionally use of a VAD obviates concerns about safety of drug administration in the context of thrombocytopenia [4]. Since its first introduction in 1963 by Dr Ommaya [14–17], the use of VADs has increased and permitted other intra-CSF drugs and drug schedules to be administered in the treatment of LM. However, the placement and use of VAD may result in various complications that can seriously impact the patient. There are few studies reporting the complication rates of VAD regarding their use in the treatment of LM and the majority are retrospective in design [18–20]. In this prospective study, 112 consecutive patients with solid cancer-related LM underwent placement of a VAD for intraventricular chemotherapy administration. All patients were prospectively followed and all complications related to the VAD were prospectively collected.

Methods

Inclusion criteria

In this prospective study, all patients who underwent placement of a VAD in our institution between January 2007 and December 2013, for the treatment of solid tumor-related LM were reviewed for VAD related complications. During the study period, 267 patients with LM have been treated in our institution. Criteria establishing a diagnosis of LM included [21–23] presence of malignant cells by CSF cytology or neuroradiologic findings consistent with LM (leptomeningeal or cranial nerve enhancement) and supportive clinical signs (Fig. 1). Patients in poor general condition, with rapidly progressive disease, or whose life expectancy was considered limited were not considered for placement of a VAD. For patients with what clinically was felt to be less aggressive disease and in whom the life expectancy was believed to be greater than 3 months, were offered a VAD to facilitate LM-directed treatment. A total of 129 patients were eligible for VAD placement. However, 17 patients were excluded as they presented a contra-indication for surgery such as systemic infection or bleeding diathesis. A total of 112 patients were enrolled in the study. All patients or their medical surrogate gave informed consent. The local ethics committee approved the study. A declaration to the CNIL (Comission Nationale de l'informatique et des libertés), an independent French administrative authority, was made on the 17 September 2004 in order to collect data prospectively (number of declaration: 1034071).

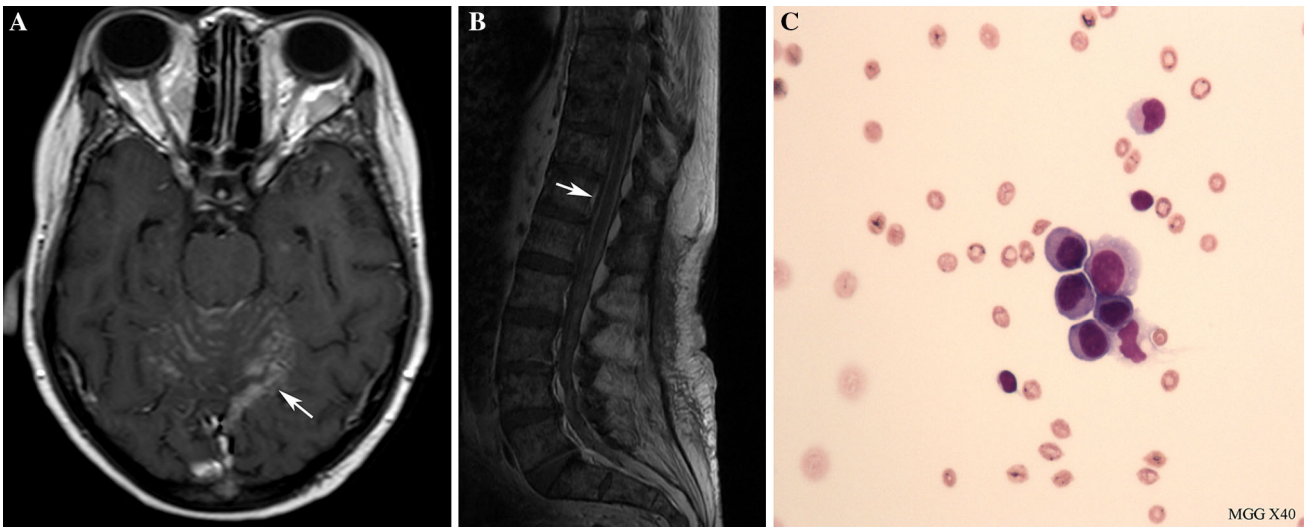

Fig. 1 Cranial axial (**a**) and spinal sagittal (**b**) T1-weighted MRI depicting an enhancement of the leptomeninges (*arrows*). Photography (MGG X 40) revealing the presence of cancer cells into the CSF (**c**)

Surgical procedure

All procedures were performed under local anesthesia by a single experienced surgeon. In the operating room, Patients were placed supine with the head slightly flexed. After performing a small shaving (4×3 cm^2), the skin was thoroughly disinfected by multiple applications of betadine. The patient was then draped in sterile condition exposing the shaved skin. A 4 cm C-shaped incision was made in front of the right coronal suture. The incision was left-sided in two patients because of the presence of a right frontal metastasis. A 14 mm burr hole was then performed anterior to the coronal suture and 2 cm from the midline, using a power drill with an automatic clutch. Then the dura was opened and the catheter was placed at a depth of 7 cm in the frontal horn of the lateral ventricle using a strict perpendicular trajectory. Once CSF flow was observed, the catheter was connected to the reservoir. The same device has been used for all patients (Sophysa© RE2010). This device is a 0.6 ml biconvex reservoir, the diameter of which permits stabilization and secure anchorage in the burr hole. After placement of the device, digital pressure (i.e. barbotage) was systematically applied to test the VAD functionality. The skin was then closed in two layers. All procedures were performed under local anesthesia without any prophylactic antibiotic medication. Neuronavigation was not used in this case series.

Chemotherapy schedules

Sustained release liposomal cytarabine (Depocyte®) was used as first-line treatment in all patients except two. Thiotepa and methotrexate were used at first- and second-progression respectively. Intra-CSF chemotherapy schedules are summarized in Table 1. All injections were performed at a single institution, by the same trained team and using a standardized protocol. A 24-gauge Huber needle was inserted in the VAD reservoir chamber after meticulous sterile preparation of the skin. First, 5–10 ml of CSF was withdrawn for cytological and biological analysis. The chemotherapy syringe was then connected to the needle using sterile technique. The chemotherapy was injected slowly over at least 1 min. Finally, the reservoir was flushed with 1 ml of sterile preservative free normal saline. Patients were advised to stay prone for 1 hour after drug administration. Oral steroids were administrated the day of and for a total of 5 days after administration of liposomal cytarabine only.

Clinical and radiological follow-up

All patients were re-evaluated before discharge to detect any procedure-related side effect. The same team performed a clinical evaluation before each intraventricular injection (i.e. every 2 weeks during the initial 2 months and monthly thereafter). Craniospinal MRI was performed at baseline, at 2 months (at the end of the induction phase) and every 3 months thereafter. Any clinical or radiological complication was prospectively collected. All patients were followed until their death.

Results

Population

A total of 112 patients were included in the study (Table 2). There were 88 women and 23 men with a mean age at diagnosis of 51.1 years (range 26–73). The mean Karnofsky performance score was 80.1 (range 60–100). The primary cancers included breast ($n = 79$), lung ($n = 12$) and melanoma ($n = 6$). 81 patients (72 %) received concomitant systemic chemotherapy, while 31 patients received intraventricular therapy only. No patient was lost to follow-up.

Surgery

The mean operative time was 15 min (range 12–22 min) and blood loss was minimal in all cases (<10 ml). The

Table 1 Summary of chemotherapy schedules

Drug	Number of patients	Half-life in CSF	Dose (mg)	Schedule
Depocyte	110	14–21 days	50	Induction/consolidation: every 14 days for 2 months Maintenance: every month until progression
Thiotepa	29	<1 h	10	Induction: twice weekly for 4 weeks Consolidation: once a week for during 4 weeks Maintenance: once a month until progression
Methotrexate	10	4.5–8 h	10	Induction: twice weekly for 4 weeks Consolidation: once a week for during 4 weeks Maintenance: once a month until progression

Table 2 Summary of main demographical characteristics

Variable	Mean value
Age (range)	51.1 (26–73)
Sex	
Male (%)	23 (20.5)
Female (%)	89 (79.5)
Karnofsky performance status (range)	80.1 (60–100)
Primary site	
Breast (%)	79 (70.5)
Lung (%)	12 (10.7)
Melanoma (%)	6 (5.3)
Other (%)	13 (11.6)

intraventricular catheter was misplaced in only a single patient, while two attempts were required for intraventricular insertion in three patients. Postoperative imaging confirmed the intraventricular placement of the catheter except for one patient who required an immediate surgical revision. One known epileptic patient manifested a seizure after surgery. As this patient had a history of seizures, and CT scanning confirmed the absence of a perioperative complication, discharge was not delayed nor was the postoperative seizure attributed to the surgery. All patients were discharged the same day as surgery.

Intraventricular injections

A total of 1046 chemotherapy administrations were performed. The mean number of injections per patient was 9.34 (range 1–47). No immediate post-drug administration complications were seen. All patients were discharged 1–2 h after intraventricular injection.

Complications

A total of 11 complications (9.8 %) occurred in 11 patients. Complications were distributed as follows: seven infections (6.2 %), two instances of symptomatic leukoencephalopathy (1.8 %), 1 intracranial hematoma (0.9 %), and 1 malpositioned catheter (0.9 %).

- *Infections* Only 3/7 instances of infection (2.7 %) were considered to be related to the surgical procedure, all occurring during the first 30 days after surgery. In all three patients, local inspection of the VAD demonstrated clear evidence of infection (Table 3). The VAD was urgently removed in all three cases. The remaining four cases of infection occurred late post-implantation and were likely related to repeated access of the VAD. One patient presented 5 months post-implantation with a subcutaneous sterile inflammatory fluid collection and was treated with local care only. The remaining three patients presented with a febrile meningeal syndrome respectively 2, 4 and 5 months post-implantation. CSF analysis confirmed bacterial meningitis in all cases (*Staphylococcus* in two patients and *Propionibacterium* in 1 patient). The VAD was removed and patients were treated antibiotics (ceftriaxone and fosfomycine) for 2 weeks. The outcome was favorable for two patients allowing subsequent intrathecal chemotherapy. One patient progressed neurologically and subsequently died.
- *Leukoencephalopathy* Two patients developed a symptomatic leukoencephalopathy requiring removal of the VAD. MRI in both revealed an edematous mass in the right frontal lobe centered about the intraventricular catheter. In both instances, CSF cultures were sterile and the catheters were removed. Both patients received oral steroids and manifested a rapid and complete resolution of symptoms. Neither patient was reimplanted with a VAD; intrathecal chemotherapy was subsequently utilized.
- *Hemorrhage* One patient with a recent history of deep vein thrombosis treated with oral anticoagulation presented with an asymptomatic intraventricular hemorrhage. 2 weeks after VAD implantation, attempted CSF aspiration was unsuccessful. A CT-scan was performed and revealed an intraventricular hemorrhage

Table 3 Initial presentation and management of patients who experienced an infection of the device

Patient	Number of injections prior to discovery of infection	Appearance of the VAD at time of documented infection	Results of CSF culture	Treatment	Outcome
1	1	Infected	*S. aureus*	DR+ antibiotics	Resolved
2	1	Infected	Negative	DR+ antibiotics	Resolved
3	1	Infected	*S. aureus*	DR+ antibiotics	Resolved
4	7	Collection	Negative	Local care	Resolved
5	4	Normal	*S. epidermidis*	DR+ antibiotics	Resolved
6	5	Normal	*S. aureus*	DR+ antibiotics	Death
7	7	Normal	*P. acnes*	DR+ antibiotics	Resolved

DR device removal, *P. acnes propionibacterium acnes*, *S staphylococcus*

that surrounded the catheter, likely causing obstruction. However, the hemorrhage was limited and has not caused hydrocephalus. After discussion with the referring oncologist, no further intra-CSF chemotherapy was administered and the patient died 76 days after the VAD placement from disease progression.

Discussion

Leptomeningeal metastases is a CNS metastatic complication occurring in 5–15 % of all patients with solid cancers [1–3]. Intrathecal chemotherapy administered by LP has been the mainstay of treatment that in combination with systemic treatment appears to modestly extend survival [10, 24, 25]. Nonetheless, intrathecal chemotherapy requires performing repeated LP, which can be uncomfortable for patients as well as both time and resource intensive for the clinic. Ventricular access devices are increasingly used for the treatment of LM, as they appear to improve patient comfort and compliance. Moreover, the intraventricular route allows a more uniform distribution of the chemotherapeutic agent in the entire neuraxis, especially into the ventricles where the tumor cells often accumulate. Indeed, a recent randomized controlled trial reported a survival benefit of the intraventricular route respect to the intra-lumbar injection [12]. This study has shown a statistically difference in terms of progression free survival in LM patients treated with intraventricular methotrexate vs. lumbar methotrexate (19 vs. 43 days; $p = 0048$). This difference was not statistically significant for patients treated with sustained-release cytarabine (29 vs. 43 days; $p = 0.35$), which is a long half-life drug compared with methotrexate (Table 1).

The main disadvantages of the VAD are complications related to its placement or use. As these complications may diminish the quality of life and shorten patient survival, the incidence of VAD complications is clinically relevant. Currently, most series reporting VAD complications in LM are retrospective and treat a heterogeneous cancer population [14, 15, 18, 26].

In this prospective study that included 112 patients treated for solid tumor-related LM, infection was the most common complication. Of the 7 cases of infection observed, 3 infections were considered to be related to the surgical procedure, as all occurred in the first 30 days after the insertion of the device. The surgery-related infection rate is in accordance with those reported in previous retrospective series. As demonstrated for ventriculoperitoneal shunts [27], shortening the operative time and applying standardized operative procedures can diminish this complication. Currently all procedures at our institution are performed by a single experienced surgeon. Although our patients did not receive prophylactic antibiotics prior to the skin incision, this strategy is often utilized and might be considered as a possible adjuvant therapy to decrease the infection rate. Indeed, it is currently recommended to administer antibiotic prophylactically prior to a neurosurgical intervention, as is commonly performed at our institution for most neurosurgical procedures. The management of surgery-related infections most often requires culture appropriate antibiotics and removal of the infected device. The four remaining infections in this prospective case series were believed to be related to repeated access of the VAD. The low infection rate (3.6 % per patient and 0.38 % per injection) seen in the current series is quite similar to those reported in recent retrospective studies [28, 29]. This finding highlights the importance of nursing care and the performance of strict sterile technique during each injection [30]. At our institution all intra-CSF chemotherapy administrations are performed by a single trained team using the same standardized protocol. The management of access-related infections is still controversial. In our series, it was decided to remove the device in all patients with proven bacterial meningitis. Some authors recommend preservation of the device and use of intraventricular antibiotic therapy [31, 32]. However, there is limited evidence in the literature to support this recommendation.

Symptomatic leukoencephalopathy is an increasingly reported complication of intraventricular chemotherapy [33–35]. It occurs as a consequence of retrograde drug movement along the catheter tract exposing surrounding white mater to elevated chemotherapy drug concentrations and resulting in white matter injury. Patients with such a complication present with signs of an intracranial mass and associated intracranial hypertension, occasionally motor weakness and rarely with seizures. MRI reveals an oedematous mass around the catheter with surrounding brain displacement. In an attempt to mitigate this complication, particular attention to measure the length of the inserted intraventricular catheter is used. Furthermore during each drug injection, chemotherapy is administered slowly after having aspirated 5–10 mL of CSF, in order to avoid ventricular overfilling and hypertension that may facilitate retrograde flow along the catheter tract. Unfortunately, CSF flow study has not been performed in patients with leukoencephalopathy. Although, no patient harboured MRI signs of CSF blockage, their contribution in the development of leukoencephalopathy, due to focal high concentration cannot be excluded. Treatment of this complication utilizes oral (or intravenous) steroids, discontinuing intraventricular injections and device removal. Intrathecal chemotherapy was utilized subsequently in our patients.

Although, intracranial hemorrhage is a serious complication of VAD insertion and use, this complication has

been infrequently reported in previous studies [10, 14–16]. Similarly in the current series only a single patient manifested this complication. Safeguarding against this complication, all patients undergo a coagulation screen prior to implantation as well as a brain MRI to rule out possible parenchymal lesions that may be in the path of the intraventricular catheter. Note, that patients treated with anticoagulation are likely to have an increased risk of intracranial hemorrhage. Despite of the proper management of anticoagulant treatment during the perioperative period, an intracranial bleeding may occur up to several days after implantation. Other series support this statement. In a retrospective series of 107 patients who underwent the placement of a VAD, Sandberg et al. [16] reported three intracranial hemorrhage, two of which occurring in patients treated with anticoagulation.

In this series there was a very low rate of mechanical dysfunction of the VAD. No case of migration or disconnection was encountered. This may reflect the design of more recent VADs that result in stabilization and anchorage of the reservoir in the burr hole and improved connections between the catheter and the reservoir. A single case of catheter misplacement that required early reoperation was seen in this series. Although, all catheters were inserted under local anesthesia without use of a navigation system, the misplacement rate is nonetheless low in the current series [14–16, 18]. This may in part be a result of the fact that a single trained surgeon inserted all catheters in a standardized way. In our series, we used a power drill with an automatic clutch for security purpose and to avoid excessive movements of the head. However, held hand drills could be alternatively used, taking attention to shape the hole to the diameter of the device.

In the current prospective series, an overall complication rate of 9.8 % (11 instances) in 11 patients in whom a VAD was placed for LM treatment. In 9/11 patients with VAD related complications, reoperation was required. Only a single complication was fatal. The complication rate in the current series is less than those reported mainly as a consequence of fewer instances of intracranial hemorrhage and mechanical VAD dysfunction. Although, insertion and access of a VAD is not technically demanding, application of standardized protocols by a trained team is required to minimize complications associated with the use of VADs.

In our study, we focused only on complications related to the VAD, and we have not reported side effects related to intra-CSF chemotherapy. The incidence of such side effects is difficult to measure as neurological symptoms may be partly due to the disease itself. In a recent retrospective cohort of 120 patients treated by liposomal cytarabine (intraventricular route, $n = 80$ and lumbar route, $n = 40$), Chamberlain [36] reported Common Toxicity Criteria $\geq$ Grade 3 neurotoxicity in 60 cycles (11.5 %) in 28 patients (23.3 %). Most toxicities were transient but 20 of them required hospitalization. Note that the route of administration did not influence the frequency of such treatment-related toxicities.

Conclusion

The use of a ventricular access device facilitates intra-CSF chemotherapy delivery in patients with LM. The device insertion as well as use improves patients comfort and compliance, hastens clinic work flow and appears to be safe with a low complication rate. An acceptable VAD related morbidity can be achieved when used by a trained team. For patient's best care, device placement should be performed by a senior surgeon and intraventricular chemotherapy administered by a trained team.

Conflict of interest None.

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