Development of the Metronomic Biofeedback Pump for leptomeningeal carcinomatosis: technical note

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Patients with leptomeningeal carcinomatosis face a particularly grim prognosis. Current treatment consists of intrathecal delivery of methotrexate (MTX) or cytosine arabinoside (Ara-C) via Ommaya reservoir or lumbar puncture. Yet despite these interventions, the median survival after diagnosis is only 4–7 months. To address inherent shortcomings of current treatments and provide a more effective therapeutic approach, the Pharmaco-Kinesis Corporation has developed a novel type of implantable pump capable of delivering intrathecal chemotherapy (i.e., MTX) in a metronomic fashion with electronic feedback. The Metronomic Biofeedback Pump (MBP) consists of 3 components: 1) a 2-lumen catheter; 2) a microfluidic delivery pump with 2 reservoirs; and 3) a spectrophotometer monitoring MTX concentrations in the CSF. Using an animal model of intraventricular drug delivery, the authors demonstrate that the MBP can reliably deliver volumes of 500 µl/min, consistently measure real-time intrathecal MTX concentrations via CSF aspiration, and provide biofeedback with the possibility of instant control and delivery adjustments. Therefore, this novel approach to chemotherapy minimizes toxic drug levels and ensures continuous exposure at precisely adjusted, individualized therapeutic levels. Altogether, application of the MBP is expected to increase survival of patients with leptomeningeal carcinomatosis, and appropriate Phase I and II trials are pending.

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LEPTOMENIGEAL carcinomatosis (LC) is a condition in which cells from a primary solid or hematological tumor metastasize, invade the subarachnoid space, and spread throughout the CNS via the CSF, resulting in seeding of the leptomeninges in a diffuse and multifocal manner along the surface of the brain and spinal cord. It usually represents a late event of cancer progression and is most commonly observed in patients with advanced breast and lung cancer, as well as in melanoma. The most frequent symptoms include multiple cranial nerve deficits, motor deficits, altered mental status, headache, and radicular pain.3,16

In the US, approximately 1%–8% of cancer patients are diagnosed with LC, but on autopsy it is detected in 19% of those in whom disseminated disease presents with neurological signs and symptoms. The incidence of LC has been reported to be increasing, due to longer overall survival in patients treated with novel antineoplastic agents. There is currently no cure and outcome is invariably fatal. The median survival of patients with LC receiving current therapy is a mere 3.6 months, 4 months, and 7 months from the time of diagnosis in the cases of melanoma, small-cell lung cancer, and breast carcinoma, respectively.4,17

The treatment of LC rarely involves systemic chemo-
therapy because most agents do not penetrate the blood-
brain barrier (BBB) at concentrations that are sufficiently
high to exert therapeutic activity. Instead, current options
for treating LC are limited to intrathecal chemotherapy,
either via repeated lumbar punctures or via a surgically
placed Ommaya reservoir with intraventricular catheter.
Lumbar injections are difficult for a patient to tolerate,
and it is not entirely clear to what extent chemotherapy
instilled into the lumbar thecal sac can spread to the brain
and the cervical and thoracic spinal cord. Therefore, the
currently preferred method is the Ommaya reservoir,
which delivers chemotherapy directly to the ventricular
system and has been shown to be more effective than the
lumbar puncture.1,6
To date, only 2 chemotherapeutic agents are commonly
used for delivery via the Ommaya catheter: methotrexate
(MTX) or cytosine arabinoside (Ara-C), which traditionally
have been given as single-dose injections 2 days per
week during an induction phase, followed by less frequent
injections during subsequent consolidation and mainte-
nance phases. However, because of the short half-life and
rapid clearance of these medications, more frequent dos-
ing has been applied also, but this latter approach is more
taxing on the patient. A more recent approach involves
a liposomal formulation of Ara-C, called DepoCyt (Sigma-
Tau Pharmaceuticals, Inc.) that provides for a longer
half-life of the drug and allows for less frequent injections
(once every 2–4 weeks).8
Still, treatments via Ommaya reservoir have inherent
limitations that minimize therapeutic efficacy and impair
patient convenience, with inherent complications related
to placement and delivery.1,2,6 Therapeutic efficacy is ham-
pered by a lack of clear understanding of the amount of
drug delivered and the steady-state levels achieved in the
CSF. Moreover, despite individualizing the dosage based
on patient body-size measurements, the toxicity and effi-
cacy outcomes of chemotherapy vary considerably among
patients. This occurs due to the highly variable inter-
individual pharmacokinetics of anticancer agents, as well
as unpredictable changes in CSF flow dynamics that may
interfere with and disturb therapeutic levels of drug ex-
as unpredictable changes in CSF flow dynamics that may
allow highly individualized, continuous exposure at precisely maintained therapeutic levels. Moreover, it allows the physician to have full control of
the device, with options to modify the treatment regimen
promptly according to changing conditions.
In this report, we demonstrate the capabilities of the
MBP with in vitro and in vivo experiments that simulate
and accomplish intraventricular delivery of MTX. The re-
results from the in vitro experiments are compared with a
computer simulation model to visualize the accuracy of
the delivered dosages. Our in vivo experiments in swine
present the use of a spectrophotometer as a real-time
feedback sensor to monitor MTX levels in CSF, enabling
pharmacokinetically guided delivery of chemotherapeutic
agents with the goal of maximizing therapeutic outcomes.

Methods
The MBP Implantable Infusion System
The MBP is part of a multicomponent system that
includes the following subsystems. 1) The MBP itself, which
is an implantable infusion pump with sampling and di-
agnostic capabilities. 2) A 2-lumen catheter reservoir ar-
rangement that enables both local delivery of medications
and the sampling of biological fluids from the delivery site.
(Alternatively, both lumens can be used to deliver 2 differ-
ent therapeutic agents for combination therapy purposes.)
3) An external wireless transmitter and receiver with pro-
gramer and data collection system (i.e., a graphical user
interface [GUI]) that communicates with the MBP via
remote wireless connection, and is used to program and
display sensor data from the MBP.

The MBP Subsystem
The enclosure of the MBP is made of a medical-grade,
 lightweight titanium alloy that is widely used in many long-
term implant devices and enables MRI compatibility. Two
cmicropumps regulated by valves, whose flow rates can be
calibrated to approximately 500 µl/min, enable simultane-
ous pumping of drugs from reservoirs to the brain, and
acquire CSF samples for analysis by the onboard sensor.
The MBP contains two 5-ml reservoirs, which can be con-
figured for standard metronomic and biofeedback applica-
tions or for polypharmacy use. The standard metronomic
and biofeedback option has one reservoir for drug delivery
and another for storing sample fluid. The polypharmacy
application has each reservoir containing a different drug,
which can be selected on demand by clinicians. The micro-
fluidics card allows for delivery of medication from the
chemotherapy reservoir, or to transport CSF for sam-
ping. A 4-wavelength spectrophotometer (355, 365, 395,
and 470 nm) is used to determine concentrations of MTX
in CSF in real time, based on the characteristic ability of
MTX to absorb ultraviolet light at 370 nm.20 The 4-wave-
length spectrophotometer has been tested and is shown
to be effective in monitoring MTX concentrations in real
time. This will measure the distribution and elimination
of drugs, and enable physiological feedback on treatment
response. Sensors allow for autonomous operation and
improve device safety. The MBP is equipped with pressure sensors to measure reservoir volume, detect channel blockages, and monitor intracranial pressure (ICP). A flow-rate sensor controls the drug delivery rate, and bio-sensors detect medication concentration. A thermistor is included to monitor temperature fluctuations.

Specialized Catheter System

The MBP uses a specialized 2-lumen multipiece catheter. This subcutaneous catheter connects the MBP to a delivery location such as a lateral ventricle for the treatment of LC. The 2 noncommunicating lumens are used as follows: one lumen is used to deliver medication from the pump to the treatment site, and a second lumen is used for transporting biological fluid samples from the treatment site back to the pump, where they are analyzed and contained for later removal. In clinical use, the catheter will be implanted much like a ventricular shunt catheter, the main difference being that the proximal end of the catheter will be connected to the MBP, which in turn is implanted above the pectoralis muscle.

Communication Components

The MBP is equipped with a low-power wireless radio, operating in a Federal Communications Commission–approved medical implant wireless band intended for application in implanted medical devices, such as pacemakers, implanted cardioverter defibrillators, neurostimulators, and drug pumps. It is composed of an internal wireless system and integrated antenna, as well as an external antenna for transmitting and receiving data. The MBP can be monitored and controlled by the physician full control of the device and the ability to update treatment regimens according to changing conditions.

The MBP Programmer and Data Collection Base Station

The MBP uses a medical-grade wireless chip and protocol, which enables it to transfer and receive data and commands after implantation. To schedule the delivery of drugs, as well as the sampling of biological fluid from the treatment site, a wireless base station is used. This base station communicates with the MBP via a connected wireless antenna. The base station runs a GUI from which schedules can be set and reviewed for CSF sampling and drug delivery. Sensor data can also be viewed in near real time, and schedules for periodic sensor data collection can be set. In addition, the GUI allows the user to view the status of the device remotely. Items such as battery life, medication level, catheter clogging, and patient activity can be monitored through the base station.

In Vitro Simulation of CSF System

To simulate the CSF system in vitro, 3 containers were serially connected via flexible fluidic tubing. The main container, simulating the fluid compartment surrounding the brain (referred to as the brain reservoir), was initially filled with 200 ml of saline (0.9% sodium chloride). This brain reservoir, representing the cranial cavity, was kept at a constant volume of 200 ml, and continuously stirred by a magnetic stirrer to achieve uniform distribution. A second reservoir, which is referred to as the source reservoir, was also filled with saline. This reservoir was connected to the brain reservoir container via soft tubing and a piezoelectric pump (Bartels Mikrotechnik). This reservoir acts to simulate the natural CSF creation of the ventricles. Saline was pumped from the source reservoir to the brain reservoir at a rate of 400 μl/min; this rate was chosen to simulate the natural CSF creation rate of the ventricles.

A third container acted as the CSF sink, and is referred to as the sink reservoir. It was connected to the brain reservoir via additional soft tubing and provided a location for excess CSF to drain. Because the brain simulation container is airtight, its internal pressure increases when saline is pumped in from the source container, and it adjusts by compensatory outflow to the sink container. The sink reservoir thus simulates the absorption of CSF by the body. Altogether, the setup of this 3-reservoir fluidic circuit was intended to represent the fluid system surrounding the brain, inclusive of natural turnover of CSF within the CNS.

Delivery of MTX to the In Vitro CSF System

Lyophilized MTX sodium powder (Ben Venue Labs, Inc.) was reconstituted with 0.9% sodium chloride solution to 2.5 mg/ml and loaded into the MBP, which was connected to the brain container of the CSF in vitro system via 2 noncommunicating fluid tubes. The arrangement was bidirectional, with one tubing path for delivery of MTX and the other for sampling. The MTX was delivered to the brain reservoir according to the remotely programmed schedule, and it was quickly mixed using the magnetic stirrer. The presence of the simulated CSF source caused the MTX in the brain container to be gradually diluted and eliminated to the CSF sink, just as it would be in the human body. In parallel, samples from the brain container (500 μl every 10 min) were collected by the MBP, and the MTX concentration was determined by the onboard spectrophotometer. Absorbance was also measured using a Beckman DU730 spectrophotometer for comparison and validation.

Fully Implantable Design

The MBP is designed to be fully implantable and battery operated, much like a pacemaker, to lower the risk of infection and to allow the drugs to infuse over extended time periods. This improves patient quality of life by reducing time spent in the hospital and allowing more mobility and comfort. Self-sealing silicone septa allow access to the MBP medical reservoirs. An enclosure containing protruding ports can easily be felt through the skin for transcutaneous drug refill.

In patients, the future implantation technique for the MBP will be similar to a ventriculoperitoneal shunt. A right frontal curvilinear incision and bur hole will be made for the catheter placement, with a horizontal incision made approximately 2 cm superior to the nipple line as the pocket for the pump itself. A shunt passer will be tunneled from a postauricular nick to the chest incision. Two fer-
rules in the pump are used to hook up the double-lumen catheter, which is moved superiorly through the shunt passer to the postauricular nick. A short shunt passer will be passed from the right frontal bur hole to the postauricular nick, and the catheter will be passed up to the frontal bur hole. The double-lumen ventricular catheter will be passed into the frontal horn of the lateral ventricle, and tied to a reservoir that connects the ventricular device with the one directed to the pump.

Animal Experiments

All animal protocols were approved by the Institutional Animal Care and Use Committee (IACUC) at Cedars-Sinai Hospital in Los Angeles, California. Four 15- to 18-week-old male swine were obtained from S&S Farms. One animal per day underwent operation. All animals were anesthetized using propofol infusion, and maintained under anesthesia throughout the length of the procedure. After anesthesia, the pig was placed in a lateral position, and the lower back was prepared and shaved in a sterile fashion. The lumbar drain insertion site was localized using a lateral C-arm x-ray, approximately 2 cm superior to the iliac crest. A Codman lumbar drain was inserted using an 18-gauge Tuohy needle. For the ventriculostomy placement, a preoperative CT scan was obtained. First, by using the axial, sagittal, and coronal views of the CT scan, an entry site, proposed trajectory, and depth of catheter insertion were determined. At the frontal skull, a linear scalp incision at the insertion site was made and a hand-held perforator was used to make a frontal bur hole. The dura mater was opened with a pinpoint cautery, and a ventricular Codman catheter was inserted. Once CSF was verified, the catheter was tunneled and connected to the pump.

Results

The MBP Setup

The MBP is a fully implantable infusion pump with Wi-Fi biofeedback capabilities, designed to deliver chemotherapeutic agents locally and metronomically in a long-term therapy regimen. As outlined in Fig. 1, the MBP is fully implantable in the chest (above the pectoralis muscle similar to a pacemaker) or in the abdominal cavity (similar to a pain management infusion pump). The enclosure of the MBP is made of medical-grade, lightweight titanium alloy, which is widely used in many long-term implanted devices, due to the alloy’s proven biocompatibility with tissue and bone. The pump is connected to a delivery

FIG. 1. The MBP components. A: The device can be implanted in the patient’s chest or placed anywhere in the abdominopelvic cavity, with a catheter connecting to a ventricle in the brain. The wireless link allows clinicians to interact with the MBP via remote computer station. B: Exterior of the MBP (catheter only partially shown). C: Arrangement of individual parts configuring the MBP. Figure is available in color online only.
target location, such as a tumor or a lateral ventricle, by a subcutaneous, dual-lumen catheter. Two micropumps inside the MBP, whose flow rates can be calibrated to approximately 500 µl/min, independently control the flow of each lumen, which enables both the pumping of drug from its reservoir to the brain and simultaneous acquisition of CSF samples for analysis by the onboard sensor. Alternatively, both lumens can be used for the concurrent delivery of 2 different chemotherapeutic agents for combination therapy purposes. In the following material, we will primarily present characteristics of the bidirectional (simultaneous delivery and sampling) option.

The MBP is capable of interfacing to a computer base station near the patient. The sensor data are transmitted over the medical implant communication service wireless radio link to the care provider’s computer for real-time monitoring, and this bidirectional link permits the user to immediately gain control of the implanted system and execute a new pumping routine. The intuitive computer interface enables clinicians to review current and past drug delivery and allows them to program individualized dosage adjustments over the course of chemotherapy.

To characterize MBP function, we designed a set of in vitro experiments to test the performance of its onboard spectrophotometer, its ability to performometronic deliveries, and its capacity to sample fluid and analyze it on board. Additional testing was performed, in which the pump was run in a closed-loop configuration, to show its ability to self-regulate the delivery of medication based on the drug concentration levels detected by the onboard sensor.

Operational Evaluation of the MBP With In Vitro CSF System

An in vitro CSF system was designed and set up as shown in Fig. 2 (and described in detail in the Methods section). The system was applied first to evaluate a comparison of metronomic versus bolus delivery of MTX over the course of 7 days. Metronomic delivery was programmed for 2 different doses given every 2 hours, with 0.298 mg or 1.49 mg injected in a volume of 0.416 ml (resulting in a total dosage of 25 mg or 125 mg, respectively, over 7 days). Bolus delivery consisted of a single dose of 12.5 mg in 5 ml every 3.5 days (resulting in 25 mg total over 7 days). In all cases, the total volume injected over the course of 7 days was the same (10 ml). The concentration of MTX achieved in the brain reservoir was measured by the MBP onboard spectrophotometer (Fig. 3).

As shown in Fig. 3, metronomic delivery of low-dose or high-dose MTX resulted in drug concentrations within the in vitro CSF that remained within a narrow concentration range, where highs and lows fluctuated by only about 20%. In contrast, bolus injections resulted in extreme variations of CSF drug concentrations that ranged from a sharp spike immediately after delivery to undetectable drug levels within 48 hours. Altogether, these results demonstrate reliable metronomic delivery of MTX, which minimizes peak toxicity levels while increasing the duration of the therapeutic range.

To verify the accuracy of onboard MBP drug measurements, we compared them to a MATLAB simulation. In this case, 12 doses (0.8 mg in 0.32 ml each) of MTX were delivered by MBP every 2 hours over a 24-hour period. In parallel, MATLAB (MathWorks) simulated delivery of 12 doses at 1.04 mg in 0.416 ml each. As shown in Fig. 4, in both cases the expected drug dosages could be confirmed, indicating a high degree of reliability of MBP drug delivery and subsequent measurements.

We also performed short-term measurements over the course of 30 minutes, with MTX injections every 10 minutes and real-time measurements of drug concentrations made by the onboard MBP ultraviolet photo sensor. We then compared the calculated expected drug concentrations to the actual, real-time concentrations of MTX. As shown in Fig. 5, there was close alignment between expected and actual drug concentrations, further verifying the high degree of reliability of MBP onboard measurements.

Functional Evaluation of the MBP In Vivo

The MBP was tested for reliability, consistency, and accuracy based on delivery of a contrast agent to a swine model in vivo. Additional objectives were to verify continuous CSF circulation from the ventricles to the lumbar thecal sac, to demonstrate the ability of the implanted MBP to continue its wireless communication while subcutaneously implanted, and to investigate how different modes of delivery would affect the concentration of the delivered agent within the cisterna magna. (See Methods section for surgical procedures and placing of the MBP).

A total of 4 animals were studied to evaluate the pump and valve mechanisms for accuracy in pumping and ability to deliver contrast agent (methylene blue). In particular, we analyzed the MBP’s flow rate and pump strength, and
its ability to deliver and maintain a predetermined concentration of agent. The sensors were tested for accuracy in reading bellows volume, as well as internal and external pressure. At the end of the studies, a pathology procedure was conducted to investigate the concentration of contrast agents within the tissue, as well as the concentration of MTX in the brain. The latter agent was included with the objective being to illustrate that it was possible to measure MTX concentrations using a spectrophotometer (rather than for pharmacological performance). In addition, the MBP was examined for damage or corrosion, and for buildup of solids within the catheter and other CSF-exposed components.

Figure 6 presents several MBP characteristics in vivo. Panel A of Fig. 6 shows the pump’s increasing strength in relation to its flow over the course of 1 hour. While the flow rate hovers around the target pump rate, in this case 500 μl/min, the bellows empty out, which generates a greater pressure differential for the pump to overcome. As a compensatory consequence, the pump strength increases for each subsequent pumping, thus in fact operating as intended. Panel B of Fig. 6 presents a comparison between expected and actually measured bellows volumes over the course of 1 hour and a total volume delivery of about 3 ml. As shown, both levels are closely aligned. Panel C of Fig. 6 displays ICP readings over a duration of 7 hours, comparing readings from the output and inlet pressure sensors. This result indicates that, although both sensors
work reliably, the inlet pressure sensor appears to produce a more stable reading and is probably a better candidate for estimating ICP in the subject.

Figure 7 displays a comparison of the programmed target flow rate (for this test, 1250 μl/min) with the actual real-time flow rate. As shown, the actual flow rate remains fairly constant over the 6-hour testing period, indicating reliable drug delivery in vivo.

Figure 8 displays a number of vital signs obtained from each pig. As shown, the majority of vital signs remained normal throughout the experimental period, indicating that placement and activation of the MBP was well tolerated by the animals. Of note, there was an increase in systolic blood pressure, which might have been secondary to the transient increase in ICP—although there was no significant decrease in pulse, consistent with Cushing’s mechanism.

At the end of the experiment, the pigs’ brains and spinal cords were harvested and analyzed for the distribution of methylene blue and MTX concentration. In the case of methylene blue, the spectrophotometer was able accurately to measure the concentration of this dye achieved in vivo (Fig. 9A). Furthermore, MBP-mediated delivery of methylene blue to pig brain resulted in diffusion of dye through the entire ventricular system; dye was detectable in brainstem, cerebellum, and spinal cord (Fig. 9B and C). During MBP-mediated MTX delivery, MTX concentrations were measured in CSF samples obtained by lumbar drain (i.e.,
the metronomic biofeedback pump distant from the catheter delivery site) over the course of several hours. As shown in Fig. 9D, high concentrations of the drug could be documented in the CSF at levels that compared favorably to what has been reported in patients (e.g., Strother et al.22). After initial buildup, MTX concentrations remained fairly constant for several hours, consistent with metronomic delivery. On termination of drug delivery, MTX concentrations began to decline rapidly.

Together, these results demonstrate that the device and all of its sensors function as expected in vivo, and are able to deliver and measure the programmed dosages of pharmacological agents accurately and effectively. The findings further demonstrate that CSF could readily be accessed from the ventricles via the double-lumen catheter, that wireless communication with the implanted MBP can easily be established, and that no significant physiological changes in blood pressure, pulse, or ICP occurred during infusion into the CSF of the animals.

Discussion
Current Limitations in LC Treatment

Treatment outcome for LC has not significantly improved over the past 10 years, and the dismal prognosis invariably remains. Traditionally, chemotherapeutic treatment for LC has consisted of MTX or Ara-C, and in recent years the use of a liposomal formulation of Ara-C (DepoCyt) has been favored.14 Newer approaches to LC treatment involve biological agents, such as trastuzumab (Herceptin; Genentech, Inc.) for Her2/neu-positive breast cancer LC, or rituximab (Rituxan, Biogen Idec and Genentech, Inc.) for lymphomatous carcinomatosis, which have demonstrated efficacy in small clinical trials and case reports.18 These monoclonal antibodies are unable to cross the BBB and therefore require direct intrathecal administration, similar to MTX and DepoCyt. More recent developments involve combination approaches with the aforementioned agents.10,13 Although some encouraging outcomes have been noted, the median survival is still far from satisfactory, and substantial additional improvements in LC therapy are required.

Use of the MBP for Treatment of LC

The MBP was designed to address the most pressing problems and limitations in treating patients with LC. Its key advantages over current treatments include the following. 1) The application of biofeedback will measure and report intrathecal drug concentrations, which will enable the clinician to promptly adjust drug dosages. 2) The rate of drug delivery can be adjusted without the need for injections, which greatly reduces the risk of infections and enables fine-tuned adjustments to maintain effective intrathecal drug concentrations. 3) The digital interface can be programmed so that predetermined drug dosages and delivery rates are adjusted automatically to balance potential fluctuations of in situ drug concentrations. 4) The option to accommodate several bellows enables delivery of various therapeutic agents from a single device, which obviates the need for multiple, repeated injections in case of combination therapy. 5) Metronomic delivery (i.e., frequent small drug doses over a short interval) is expected to reduce the incidence of complications, because it enables long-term CSF exposure to drug concentrations within the therapeut-
Potential Limitations of MBP Use

Leptomeningeal carcinomatosis is not a disease in which there is uniform spread of cancer cells throughout the CSF; and therefore local tumor deposits can cause poor circulation of a drug throughout the CNS axis. As a result, drug circulation may be limited in some regions of the CNS where there is such occlusion. While this problem also impairs conventional intrathecal chemotherapy via Ommaya reservoir or lumbar puncture, it may exert limitations on therapy with the MBP as well.

Another complicating factor in LC is hydrocephalus, which is seen in approximately 25%–40% of these patients, and currently is addressed by placing a shunt that can be adjusted at the time of intrathecal chemotherapy delivery. The MBP can be adapted for patients with hydrocephalus. Future designs will have a catheter extending from the collection bellows that can be inserted into the peritoneum.

Further problems may be posed by catheter occlusion caused by the high protein concentration and cancer cells present in the CSF. The delivery of drugs into the CSF via
the outflow ventricular catheter (which should theoretically be less prone to occlusion than a shunt catheter, based on the chronic positive pressure and outflow) is worth investigating. In comparison, the inflow catheter, where CSF is actively sucked into the MBP via negative pressure, may have a higher risk of occlusion. However, this inflow lumen features a port where external saline can be injected to unplug the catheter, thereby greatly reducing the risk of catheter occlusion.

Potential pump failure may result from malfunctions in the communication, fluid path, and control components, or the catheter. A communication malfunction may result from a number of causes, such as electromagnetic interference, failure of the wireless Internet connection, disconnected antenna, or the device being out of range, which could cause cessation of communication or reduced signal quality with intermittent communication. Clogged or leaky fluid paths, possibly due to a residue deposit, a kink, a loose connection, or a break in the tubing, may cause the pump to stall or the battery to drain faster due to overcompensation. Although such occurrences may not be entirely avoidable, their risks for the patient will be greatly reduced by having leakage, pressure, and current sensors in the MBP that will alert the physician to the existence of such problems.

Metronomic chemotherapy has been proposed as a means to potentiate the antitumor effects of chemotherapeutic drugs and to overcome drug resistance. The MBP presents a technical device aimed at achieving this goal. Although the literature provides supportive evidence that metronomic approaches indeed might be superior to bolus delivery, definitive proof for this claim has not yet been established. Therefore, future investigations using the MBP will have to include studies to evaluate the pump’s therapeutic efficacy in comparison with conventional bolus delivery of chemotherapeutic drugs.

Other Applications of the MBP

The MBP is currently designed for chemotherapeutic drug delivery into the CSF in cases of LC. However, additional future clinical applications for the brain are anticipated. Drug delivery into the CSF for the treatment of primary brain cancers such as malignant gliomas or metastatic cancers is an obvious option, because it would overcome the BBB, which represents a serious obstacle for many chemotherapeutic drugs that are delivered via intravenous or oral administration. Future potential CNS applications include direct CSF delivery of drugs for refractory fungal meningitis (e.g., coccidiomycosis, cryptococcosis), which currently is treated with Ommaya reservoir–based delivery of amphotericin; other applications may include Parkinson disease, Alzheimer disease, stroke, and other neurodegenerative diseases of the brain.

Future Studies and Regulatory Approval

Future studies will extend the in vivo Phase I nonsurvival studies described in this current report to in vivo Phase II survival studies in a pig model, and will include analysis of long-term toxicity. The data from these future studies will be used for an ISO 13485 application and the design of good laboratory practice for large-animal studies. Investigational device exemption approval will then be obtained for Phase I trials in the US and Europe for patients with LC. These initial trials will be using a concentration × time regimen for MTX and will apply accepted regimens for that agent (currently delivered via Ommaya reservoir). The goal will be to determine the accuracy and safety of the pump, and eventually to enable customized delivery of MTX via in vivo verification of real-time drug concentrations.

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References


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Conception and design: Chen, Shachar. Acquisition of data: Chen, Napolitano, Adell. Analysis and interpretation of data: Chen, Schönthal, Shachar. Drafting the article: Chen, Schönthal, Shachar. Critically revising the article: Chen, Schönthal, Shachar. Reviewed submitted version of manuscript: all authors. Administrative/technical/material support: Napolitano, Adell. Study supervision: Chen, Shachar.

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