COMMENTARY

Personalized therapeutic delivery in the neurosurgical operating room

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Effective treatments for gliomas remain elusive despite decades of work investigating the biological basis of these tumors. There have been many recent advances in knowledge that have leveraged the tools of genetics, genomics, epigenetics, and proteomics to allow investigators to more finely subclassify and make more detailed prognostic assessments (1). However, many of the barriers that prevent the implementation of clinically effective therapeutics remain unbroken: intrinsic therapeutic resistance mechanisms, biological heterogeneity within and between the same type of tumor in different patients, and the presence of blood–brain and blood–tumor barriers that prevent most systemic therapeutics from reaching their tumor targets within the CNS at effective concentrations (2). More recently, there has been substantial interest in the development of therapeutics that do not require molecular access to the CNS, for example, antiangiogenic agents (3) and immunotherapeutics (4), which act on intravascular or systemic, non-CNS targets. These novel agents are being developed mostly for the treatment of higher grade gliomas, and glioblastoma (WHO grade IV glioma, GBM) in particular, and have yet to demonstrate survival benefit in randomized trials.

For lower grade gliomas there have been few novel therapeutic options and treatment remains restricted to the conventional modalities of biopsy or surgical resection (to the extent feasible), radiation therapy, and cytotoxic chemotherapy. It is in the low-grade gliomas (WHO grade II, LGG) where an interesting molecular genetic discovery has been made: a tumor-initiating mutation in the IDH1 or IDH2 gene (5). These mutations result in a metabolic change within the Krebs cycle of tumor cells that renders the cells susceptible to depletion of NAD^+ (6). While this finding is of considerable excitement to oncologists in general, neurooncologists have recognized that pharmacological depletion of NAD^+ with use of systemically administered small-molecule inhibitors targeting nicotinamide phosphoribosyltransferase (NAMPT) is unlikely to produce meaningful clinical results in LGG as these tumors are noncontrast-enhancing and hence protected by an intact blood–brain barrier (BBB) through which most small-molecule drugs cannot pass (7).

An alternative approach to therapeutic delivery that has been of substantial interest within the neurosurgical oncology community involves the direct administration of therapeutics to target tissue intra- and/or perioperatively (Table 1). Several direct-delivery approaches have been investigated, including the use of drug-loaded biodegradable wafers applied to the surface of a resection cavity after removal of bulk tumor (8) and also the implantation of catheters through which a therapeutic is slowly delivered over a period of hours or days (convection-enhanced delivery, or CED) (9). These forms of localized delivery avoid the typical systemic toxicities associated with anticancer therapies as it is largely only tumor and/or tumor-infiltrated brain tissue that receives meaningful drug exposure. The potential utility of localized drug therapy was illustrated by the survival benefit provided in GBM, at a time when benefit of systemically administered chemotherapy was not widely accepted, by the implantation of carmustine (BCNU)-loaded biodegradable wafers at the time of surgical debulking of the tumor mass (10). Not all approaches to direct therapeutic delivery have demonstrated survival benefit, however, and the field remains under active investigation. For certain types of therapeutics, for example, viral gene therapies and targeted protein toxins, systemic administration is not an option at all, and their development depends upon improvements in the reliability of localized delivery.

Another area of active investigation within oncology, in general, and in neurooncology, in particular, involves the development of personalized therapeutics that more specifically target unique genetic or physiological changes in a patient's cancer. Well-known examples of tumor-specific therapeutics are

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Table 1. Strategies for direct delivery of therapeutics for brain tumors

Strategy	Pros	Cons
Intraventricular–intrathecal infusion	Relative ease of access Repeated administration is feasible	Poor equilibrium with brain parenchyma and brain tumor tissue
Biodegradable polymers	Potential for prolonged drug exposure over a period of weeks	Relies on diffusion, which may be an inefficient mechanism for delivering active therapeutic to a depth of more than a few millimeters
	Can be "tuned" to deliver over a short or long period of time	Can result in wound healing challenges
	Strategy has been validated clinically	
Simple injection	Can be performed intraoperatively at multiple locations	Backflow around the injection cannula
	Not very time-demanding	Poor distribution beyond the margin of the cannula May be suitable only for replication-competent viral vectors
CED	Produces more widespread drug distribution within brain parenchyma	Largely limited to hours or days
	Can be targeted to specific locations within brain and/or brain tumor	Therapeutic must be stable at room temperature during duration of infusion Communication with cerebrospinal fluid spaces may limit extent of distribution

mutation and/or dysregulation of HER2 and CDK4/6 in breast cancer, ALK kinase in non-small cell lung cancer, ABL kinase in chronic lymphocytic lymphoma, and BRAF in melanoma (11). In gliomas, there have been largely unsuccessful attempts to date to target frequently observed genetic alterations including EGFR amplification (and its consequent EGFRviii mutation) and alterations in signal transduction, including aberrant activation of PI3K/AKT (12). One notable example of successful targeting of aberrant signal transduction is demonstrated by the ability of rapamycin to target mTOR activation in a rare glioma, subependymal giant cell astrocytoma (13).

In PNAS, Shankar et al. (14) describe a combined intraoperative method to identify the most common IDH1 mutation, R132H, and treat IDH1 mutant LGG via a delivery approach that bypasses the BBB. Their approach is novel in that they have addressed two fundamental challenges in neurooncology—target identification and therapeutic delivery—in a single intraoperative strategy. Typically, the identification of tumor-specific actionable mutations or of other changes in cell biology occurs over 1 to 2 wk after a tumor specimen is submitted to pathology as sufficient time is required for tissue processing for immunohistochemistry and genomic analyses. This timeline is adequate for conventionally administered adjuvant therapies, which are not given until sufficient time has passed for wound healing. However, when one contemplates the use of a therapeutic directly administered into a brain tumor, or tumor-infiltrated brain surrounding a surgical resection cavity, the demand for rapid evaluation of tumor markers becomes paramount. Results of those analyses need to be available intraoperatively; otherwise, the patient may need to undergo a separate procedure, which can impact risk, patient satisfaction, and the overall cost of treatment. Ideally, the results of therapeutic-specific marker assessment should be available intraoperatively, before the end of the tumor resection procedure.

Shankar et al. (14) demonstrate the feasibility of use of an intraoperative method to assess for IDH1 R132H mutation, and this milestone opens the door to local delivery of a microparticle-based therapeutic during the same surgical procedure. Their qPCR assay satisfies a number of rational requirements for an intraoperative assay. It can be performed without specialized, time-intensive processing of tumor tissue, it provides results in a reasonable timeframe with respect to surgical flow (for this assay, the time to result is less than 30 min in the setting of a surgical procedure that typically lasts from 4 to 6 h), and it appears to have a high sensitivity and specificity. Hence, the assay reasonably can be expected to provide reliable, binary information (mutation present vs. absent) within the usual time window of a brain tumor resection procedure.

This group further demonstrated, in preclinical models, the potential utility of a sustained-release microparticle-based formulation of an NAMPT inhibitor (NAMPTi) that can be deployed intraoperatively upon detection of an IDH mutation. As shown by the authors, systemic administration of a NAMPTi produces only short-duration exposure of the brain to a fraction of the drug's plasma concentration, and repeated dosing produces substantial systemic toxicity. This is an example of where local drug administration could be a better strategy. Local administration has its own challenges, starting with drug formulation. Direct delivery to the brain, even when performed over a period of days, provides a limited time opportunity for drug exposure to tumor cells. Even in the setting of an intact BBB, most unconjugated drugs will eventually diffuse out of the brain. A measure of drug exposure used to describe the pharmacology related to systemically delivered drugs, the area under the curve, takes into account both drug concentration and duration of exposure, and it is well recognized to be predictive of clinical response for many classes of drugs. Another pharmacological approach used for systemically administered therapies is repeated dosing, which can prolong the effective exposure of tumor cells to a therapeutic molecule. At this time, direct brain delivery has a limited window of opportunity for active infusion or application of a therapeutic. There is a time window during surgery when a therapeutic can be applied to the surface of a surgical cavity, or drug infusion catheters can be placed temporarily and used for a period of days perioperatively. There has been limited use of a permanently implanted drug infusion system, but to date that approach has been limited to few sites. The limited window of opportunity for active drug delivery has driven interest in the development of novel formulations which can provide sustained drug exposure, hopefully at therapeutic concentrations. However, even with this approach there is a limited exposure time, as repeated dosing means another surgical procedure and its attendant risks and costs. Hence, appropriate target selection is also of strategic importance. A therapeutic

target that results in temporary growth impairment, but not tumor cell death, is unlikely to translate into a meaningful clinical benefit. In the case of an NAMPTi, in vitro and in vivo studies show substantial depletion of NAD^+ within 24 h of IDH mutant glioma tumor cell exposure, which translates into reduction in tumor volume and survival benefit; these are likely the hallmarks of a therapeutic that has the potential to produce clinical benefit.

The clinical translation of this work will not be straightforward. While there have been multiple clinical trials, and even one approved therapeutic, in the direct brain delivery space, there are many hurdles that have not yet been overcome. Basic principles of drug development, including pharmacokinetics and pharmacodynamics, are underutilized in the setting of neurotherapeutics due to the challenges associated with sampling and monitoring treated tissues. The failure of the first generation of CED clinical trials can be attributed, in part, to a lack of reliable delivery devices and to an inability to monitor and evaluate in real time the extent of drug delivery (15, 16). While these two issues appear to have been addressed successfully with novel catheter designs (17–19) and delivery and monitoring strategies (20, 21), detailed assessment and optimization of drug exposure remain challenging. Neurosurgical oncologists are more actively implementing clinical trials that involve a "phase 0"-like component, in which a therapeutic is delivered to a tumor target via a stereotactically implanted catheter and then the tumor is resected days later, allowing for a detailed evaluation of drug effects in tumor tissue (22). These strategies have recently supported the ongoing development of viral gene therapies in GBM (23, 24) and certainly can be applied to the development of therapeutics for LGG as well.

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