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Commentary: Current status of intratumoral therapy for glioblastoma

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Glial tumors, particularly high grade glioma and glioblastoma multiforme (GBM), continue to pose a significant challenge to neuro-oncologists and neurosurgeons. Despite vigorous research efforts over the past half-century, survival of GBM after maximal surgery, chemotherapy, and radiation therapy remains poor, reaching a median of 14-16 months after diagnosis[1]. New therapies have shown modest increases in median survival, but the majority of patients in these studies still die within two years after diagnosis[2,3]. Drug delivery to the central nervous system (CNS) poses unique challenges. Availability of drugs to cross the blood-brain-barrier (BBB), or more accurately termed blood-CNS barrier, have limited the number, type, and doses of effective therapies against GBM. Various agents, including chemotherapeutics[4], antiangiogenic drugs[5,6], immunotoxins[7,8], viral vectors and gene therapy[9], among others, have been tried, all with suboptimal results.

Strategies to circumvent the blood-CNS barrier have long been under investigation. Transient osmotic or mechanical disruption of the blood-CNS barrier has been used in order to permit passage of chemotherapeutics into the CNS, though questions regarding lack of specific targeting and safety persist[10]. Localized drug delivery into a postoperative tumor bed also dodges the blood-CNS issue without disruption of normal brain homeostasis, and therefore remains an attractive option for delivery of therapeutics. While ability to cross the blood-CNS barrier has traditionally been critical in designing drugs for use in GBM, the opposite may prove to be most useful for a local delivery strategy. For example, platinum drugs were previously abandoned for treatment of glioma due to their poor passage across the blood-CNS barrier, but are now being re-explored for localized delivery. Adding to the fact that they are not a substrate for principle efflux transporters in the brain, the inability of these agents to cross the blood-CNS barrier may now prove to be an advantage in prolonging the half-life and therapeutic effect of the drug[11-13].

Gliadel wafers, a carmustine-imbedded polyanhydride co-polymer matrix implant, have perhaps been the most successful localized therapy and are FDA approved for newly diagnosed and recurrent glioblastoma, modestly extending overall survival of both groups[14]. Wafer implantation has drawbacks, however, with increased risk of complications such as surgical site breakdown, infection, cerebrospinal fluid leak, brain edema, hydrocephalus, and cyst formation reported in some studies[15], though not all[16,17]. Nonetheless, tumor recurrence is common even after carmustine

wafer use, with median survival times of 16.4 and 9.7 months for newly diagnosed and recurrent GBM, respectively. Histological analysis reveals that most tumor recurrence in high-grade glioma is within 2-3 cm of the tumor margin[18,19], while drug penetration from surface erosion of the wafer is only within millimeters of the implant[20]. Recent efforts in localized drug delivery have therefore focused on increasing local drug penetration to surrounding brain parenchyma. To that effect, much work has been done regarding understanding the brain extracellular matrix/space (ECS).

In addition to size of molecules, diffusion through the ECS is governed by multiple factors, including ECS local geometry, a net fixed negative charge, binding of antigens to receptors, variable degree of dead space, extracellular matrix molecules (hyaluronan), and intratumoral pressure gradients[21]. In order to promote diffusion of chemotherapeutics, nanocarriers such as liposomes and PEGylated nanoparticles have been developed. These surfaces both protect drugs from being prematurely metabolized, as well as provide charge-shielding from the ECS. In fact, studies on rat and human brain have shown that substances of 114 nm were able to diffuse through the ECS when protected from the charge influence of the local environment, as opposed to the previous size of 64 nm when unshielded[22]. Another important consideration when studying drug distribution in the brain parenchyma and interstitial space is the rate and mechanism of drug clearance from the brain. Recently, a novel, ubiquitous pathway in the brain has been described that facilitates exchange of cerebrospinal fluid (CSF), interstitial fluid (ISF), and the clearance of solutes from the interstitium. Designated the "glymphatic system", this pathway consists of a para-arterial CSF influx route, a trans-parenchymal pathway that is dependent upon the astrocytic aquaporin-4 (AQP4) water channel for astroglial water transport, and finally a para-venous ISF clearance route[23]. As understanding of this pathway increases, researchers may be able to better predict the clearance of drug from the interstitial space and therefore tailor dosing of local drug depots. Additionally, knowledge of the glymphatic system and its transport channels may ultimately help to develop novel methods to prolong the half-life of chemotherapeutics and nanocarriers.

Another way to promote local drug penetration through the ECS is by convection instead of relying only on bulk diffusion alone. Indeed, convection-enhanced delivery (CED) of a variety of therapeutics has been a popular topic of drug development and delivery for recurrent glioma in the past decade[24-26]. The CED technique utilizes a catheter that is connected to a pump delivering a pressure head behind the infusion of drug. Studies of CED have shown great promise in terms of penetration of therapy through the ECS[27]. Consequently, CED has become among the most popular vehicles for localized delivery in current time, with 52 studies regarding CED for gliomas published in the past year (pubmed) and 5 ongoing clinical trials of convection enhanced delivery for glioma treatment (clinicaltrials.gov).

Unfortunately, most randomized trials related to CED for glioma have been underwhelming[28]. Perhaps the most notable failure of CED was the PRECISE trial, which did not find any difference in survival when comparing CED of cintredekin besudotox (CB) immunotoxin to gliadel wafers in patients with GBM at first recurrence[29]. A close examination of that study reveals that inconsistent catheter placement, as well as spread of drug into unwanted areas of low resistance, such as subarachnoid space and the ventricles may have reduced the efficacy of CED. With use of currently available image-guidance technology, these issues may be mitigated in future studies. Additionally, novel methods to track CED infusion of drugs may allow real-time feedback of drug distribution. For example, superparamagnetic iron oxide nanoparticles detectable on T2 MRI imaging have recently been incorporated into brain penetrating nanoparticles, providing ability to track therapeutic in the brain for up to one month after administration[30]. Radiolabeled therapeutics are also being used to study the volume of distribution of drug after CED, utilizing interval high-resolution positron emission tomography (PET) scanning to evaluate biologically absorbed doses of radiation in specific anatomical distributions[31]. Still, treatment failure of CED in the PRECISE trial may not be fully explained by suboptimal catheter placement alone. In fact, a retrospective review of catheter placement on patient outcomes in the PRECISE trial showed that overall catheter placement scores did not correlate with local tumor control, progression free survival, or overall survival[32]. The additional issue of infusion backflow also exists in CED, though catheter design has recently been improved with use of multiple ports, backflow-reducing technology, as well as variable injection rates[33-36]. Overall, the pattern of drug dispersal during CED, especially around inhomogeneous peritumoral tissue, has proven to be unpredictable[37], but is steadily improving. Technology development and mathematical modeling may play a future role in determining optimal stereotactic catheter placement, specific to each given tumor and peritumoral environment[38-40]. Aside from the infusion and dispersal issues, CED has an additional disadvantage related to connection of the catheter to an outside system, potentially increasing chance of infection with prolonged or repeated infusions. Additionally, in-hospital monitoring is required during infusion, drastically limiting the effective time that drugs can be administered. Subcutaneous reservoirs of drugs for continuous infusion are being explored, but have yet to be optimized for an intracranial application[25,41].

Despite their poor parenchymal penetration, polymer designs for local delivery offer a great advantage over CED in that a local depot of drug can be placed one time, which then releases slowly over a period of days to weeks[20,42,43]. Recently, efforts to pair CED with the use of nanocarriers, including polymers[44-46], nanoliposomal drug formulations[47-51], metallic nanoparticles[52], liposomally encapsulated radionuclides[53], and nanodiamonds[54], among others, have been explored. With this combination of technologies, CED can effectively deliver nanocarriers to the peritumoral area while the nanocarrier vehicle serves as a "convectible depot" of drug that is released to the local environment over time. The characteristics of polymers as biocompatible depots of drug with controlled, predicable release rate makes them most attractive for this purpose, obviating the need for prolonged infusion times or additional infusions. Furthermore, enhancements to nanopolymer design have allowed for development of smaller carriers, approximately 75 nm in diameter, that are able to penetrate up to sevenfold higher surrounding brain volumes than that of traditional nanopolymer designs of 150-200 nm diameter[55]. Additionally, novel nanopolymer designs can allow for the controlled release of multiple drugs, each with independent release rates to maximize drug synergy[56]. Polymeric nanoparticles have also been successful for use in aiding non-viral gene delivery for GBM treatment, avoiding the pitfalls of viral vector based therapy, and opening a whole new spectrum of therapies for the modality of local drug delivery[57]. Improved kinetics and duration of drug release, increased efficacy, and decreased neurotoxicity is also possible when nanocarrier platforms are utilized for CED[44]. Another advantage of a nanocarrier platform for CED is the ability to incorporate both therapeutic drugs, as well as the diagnostic imaging probe, creating a "theranostic" particle that can be tracked during infusion[58]. A variety of contrast agents can be incorporated for real-time monitoring of infusate distribution, allowing for adjustment of catheter placement or infusion parameters, if necessary[59]. Real-time CED has shown to be safe, highly predictable, and reproducible in animal experiments, and should greatly enhance the characterization of drug distribution in future patient studies[60].

Overall, treatment for high-grade glioma remains suboptimal; however, knowing that current technology allows for robust peritumoral application of therapeutics, local drug delivery options remain attractive for delivering optimal drug volume to tumor cells while avoiding systemic side effects and circumventing the issue of the blood-CNS barrier. As nanomedicine continues to evolve and the process of CED is refined, we may see an explosion of hopeful options that could one day turn this devastating disease into a manageable entity.

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