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Designing Next-Generation Local Drug Delivery Vehicles for Glioblastoma Adjuvant Chemotherapy: Lessons from the Clinic

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To date, the clinical outcomes and survival rates for patients with glioblastoma (GB) remain poor. A promising approach to disease-modification involves local delivery of adjuvant chemotherapy into the resection cavity, thus circumventing the restrictions imposed by the blood–brain barrier. The clinical performance of the only FDA-approved local therapy for GB [carmustine (BCNU)-loaded polyanhydride wafers], however, has been disappointing. There is an unmet medical need in the local treatment of GB for drug delivery vehicles that provide sustained local release of small molecules and combination drugs over several months. Herein, key quantitative lessons from the use of local and systemic adjuvant chemotherapy for GB in the clinic are outlined, and it is discussed how these can inform the development of next-generation therapies. Several recent approaches are highlighted, and it is proposed that long-lasting soft materials can capture the value of stiff BCNU-loaded wafers while addressing a number of unmet medical needs. Finally, it is suggested that improved communication between materials scientists, biomedical scientists, and clinicians may facilitate translation of these materials into the clinic and ultimately lead to improved clinical outcomes.

1. Glioblastoma and Clinical Translation

The clinical outcomes and 5-year survival rate for patients with glioblastoma (GB) make it among the most pernicious and challenging diseases to treat. Despite all the resources, time, and talent focused on developing targeted and/or local delivery technologies by the biomaterials community for GB, the clinical performance of the FDA-approved therapy carmustine ((BCNU)-loaded polyanhydride wafers) and clinical trials of other material approaches have been discouraging. As disappointing is the remarkably stagnant clinical translation of next-generation material approaches for GB. Despite encouraging preclinical results from hydrogels and modified wafer formulations loaded with more efficacious chemotherapies, a total of zero have completed even a phase I clinical trial. Other strategies, including convection-enhanced delivery, microsphere formulations, or drug-loaded nanoparticles have seen limited, albeit some, translation into the clinic with mixed results. This lackluster progress can be attributed, in part, to the paucity of communication between material scientists, biomedical scientists, and clinicians. When examining the purported clinical relevance of embedding certain material properties into formulations, it is clear that some widely known truths about the nature of GB progression among clinicians have not reached the biomaterials community.

Furthermore, a closer examination of the lessons from the BCNU wafers and other clinical trials of GB drug delivery materials may enrich and inspire materials scientists to create new systems that satisfy unmet medical needs identified by the clinical community. In tandem, clinicians and biomedical scientists may benefit from a short review highlighting the biocompatibility, safety, longevity, kinetics, tunability, and efficacy of promising new drug delivery materials without inundation by chemical and physical characterizations or discussions.

Another key challenge in treating GB is an incomplete understanding of disease pathophysiology, such as mechanisms driving intrinsic and adaptive GB cell chemoresistance. A combined approach where biomedical scientists and material

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scientists work in parallel and in close communication with clinicians will be key for the timely development of optimal therapeutic options.

2. Principles of Cancer Treatment

Following a landmark phase III trial in 2005, the Stupp protocol was adopted as the standard of care for newly diagnosed GB: maximal safe surgical excision of the tumor mass, followed by radiotherapy and concomitant temozolamide (TMZ), followed by adjuvant TMZ.[1] Despite the added ≈2.5 months survival afforded by the addition of TMZ, the 5-year survival rate[2] remains poor at 5%. A number of factors make GB difficult to treat: 1) the high proliferative and infiltrative capacity, heterogeneity, and intrinsic and acquired chemoresistance of neoplastic cells; 2) the tumor microenvironment; for example, the ability to induce anergic states in surrounding lymphocytes and glial cells, restricting the antitumor immune response; and 3) the brain macroenvironment; namely the surrounding blood–brain barrier and blood–tumor barrier restrict the ability of drugs to reach the brain parenchyma.[3] Despite these unique challenges, the goal of adjuvant oncological therapy (whether local or systemic) remains constant: maximizing cytotoxicity and reducing the risk of recurrence, while minimizing associated toxicity and the emergence of resistance. Indeed, the FDA-approved BCNU wafer technology was developed with these needs in mind. By delivering chemotherapy directly into the tumor cavity, the restrictions imposed by the blood–brain barrier are circumvented, and higher local drug concentrations can be achieved with limited systemic toxicity. However, drawing on general pharmacodynamics principles, are BCNU wafers optimally designed to meet these targets?

Based on in vitro colony-forming inhibition studies, the cytotoxic actions of antitumor agents are, somewhat imprecisely, classified as time-dependent (cell cycle phase-specific agents) or concentration-dependent (cell cycle nonphase-specific agents).[4] This categorization has proved useful when designing clinical dosing regimens for systemically administered agents. In the case of TMZ, peak concentration, rather than prolonged exposure is thought to be more important for treatment efficacy, consistent with its cell cycle nonphase-specific mode of action.[5,6] Accordingly, a dose-dense TMZ schedule (days 1 through 21 of a 28-day cycle) does not improve survival in patients with newly diagnosed GB, compared to standard adjuvant treatment (days 1 through 5 of a 28-day cycle).[6] This logic should hold for BCNU wafers. Given the cell cycle nonphase-specific (and therefore concentration-dependent) mode of action of BCNU, maximal antitumor effect should depend on peak cytotoxic drug level rather than duration of exposure. Accordingly, the FDA-approved wafers achieve high initial dose-delivery of BCNU, which rapidly declines after 5–7 days.[7–10] Critically, however, systemic TMZ is administered repeatedly, as six 5-day 4-week cycles, and not as a single 5-day cycle (effectively equivalent to the BCNU wafers). Indeed, increasing the number of adjuvant TMZ cycles from 6 to 12 improves overall survival by 8.4 months.[11] This therapeutic benefit may be mediated by both increased cytotoxicity, triggered by increased TMZ-mediated DNA alkylation, and minimization of acquired resistance driven by suboptimal drug exposure.[12] This key lesson has been lost with the shift in focus from systemic to locally administered chemotherapy. The antitumor effect of any chemotherapeutic agent, regardless of route of administration, is time-critical: contingent on duration of exposure for time-dependent agents, and repeated high-dose exposure over time for concentration-dependent agents.

Optimizing chemotherapy dosing regimens also depends on the trade-off between increasing drug dose/exposure to enhance antitumor activity and minimizing concomitant toxicity. The extended 12-cycle TMZ regimen may improve survival relative to 6 cycles, but at the expense of increased hematological toxicity.[11] Indeed, the minimum survival threshold at which patients accept chemotherapy closely relates to the severity of its toxic side effects.[13] Reasonably, this principle was not prioritized in the development of the BCNU wafers, given that local delivery of BCNU circumvents the problem of high toxicity associated with systemic administration.[14,15] BCNU wafers seem to be associated with a number of local adverse events (namely cerebral oedema, intracranial infection, and pericavity necrosis), more than those expected from resection alone.[16–19] Side effects peak in the weeks/months following implantation, and can persists for up to 6 months.[17,19,20] Interestingly, this more closely corresponds to the time-scale of polymer degradation than the release kinetics of BCNU, suggesting that these side effects are more closely related to persistence of the wafer within the resection cavity than to early BCNU release.[7–10] In light of this, it is perhaps unsurprising that phase III trials comparing BCNU to placebo wafer have reported similar rates of adverse effects.[21] After FDA-approval of the BCNU wafers, and with treatment extended to patients who were not eligible in the initial clinical trials, mounting concerns were reported through case reports/series, and these may more closely reflect the comparison of wafer to standard resection.[22]

Two chemotherapeutic principles, the importance of sustained/frequent drug exposure and the efficacy versus toxicity trade-off, were perhaps too readily dismissed in the move from systemic to local chemotherapy delivery. Immediately postimplant, BCNU is rapidly released from the wafer, in a "1-cycle" fashion: the wafer delivers the majority of its chemo-payload in under 1 week.[9,10,22] This explains, in part, why the efficacy of BCNU wafers has been modest at best. Subsequently, the empty wafer persists in the resection cavity, heightening adverse effects without concomitant clinical benefit.

Notably, while cyclic dosing may translate into clinical dividends in some patients, lack of a widely efficacious chemotherapeutic agent remains an issue. Namely, patients with unmethylated O^6-Methylguanine-DNA-methyltransferase (MGMT) promoter GMs respond poorly to treatment with DNA alkylating agents such as TMZ[23] and BCNU[24]; among patients with methylated MGMT promoter GMs, the addition of TMZ to radiotherapy confers significant survival benefit (≈6.4 months) which is minimal (≈0.9 months) among patients lacking methylation of the MGMT promoter.[23] Once-susceptible GM cells can also acquire resistance to TMZ following repeated exposure to the drug via mechanisms including upregulation of MGMT levels and down-regulation of DNA mismatch-repair proteins.[25] Overcoming this challenge will require that materials science research advances in

tandem and in close collaboration with drug discovery, which is informed by biomedical scientists and their mechanistic insights into GM pathophysiology.

3. Outcomes and Lessons from the Clinic

While the clinical benefits of BCNU wafers have not greatly ameliorated the tumor burden in GB patients,[26] an abundance of clinical literature using this adjuvant therapy provides key and quantitative lessons for the next generation of local chemotherapy delivery systems. In the development of the underlying material of the wafer technology, a motivational principle was the sustained local delivery of a high chemotherapy concentration within the pharmaceutical window as an adjuvant therapy.[27–30] The distinct time scales of drug release and material longevity in vivo are among the most critical factors involved in developing, optimizing, and evaluating drug delivery technology and have not been given the attention they deserve. Furthermore, a key lesson from the clinic is that the increase to an extended 12-cycle TMZ regimen may provide benefit in reducing tumor burden and prolonging survival (See **Figure 1**).

3.1. Key Lessons

a) Increasing the number of adjuvant systemic TMZ cycles confers a survival benefit, at the cost of heightened side effects.
b) BCNU wafers release the majority of drug payload in the first week, and the side effects of this technology begin after this massive initial bolus release.
c) A higher stiffness matrix does not automatically equate to prolonged release in vivo, and importantly the higher stiffness may exacerbate the negative side effects.

3.2. Critical Materials Challenges and Unmet Medical Needs

a) Local delivery whose time scale for drug release is on par with the time scale for matrix degradation.
b) Materials capable of eluting a prolonged 0th or 1st order release of drug on time scales of months rather than days.
c) Achieving such pharmacokinetic properties with a degradable, soft material.

In summary, BCNU wafers are too stiff[31,32] and remain too long in the body for the therapeutic benefit they provide. Novel methods for local chemotherapy emerging from the biomaterials community should be considered. We hypothesize that improved efficacy and reduced toxicity may depend on, at minimum, providing the same bolus release of chemotherapy from a softer material that biodegrades much faster than the wafer technology. Further benefit, albeit a more technologically challenging solution, may be realized by developing a degradable soft material that remains in the body on the order of 6–12 months while simultaneously eluting chemotherapy with 0th or 1st order release kinetics for the same duration.

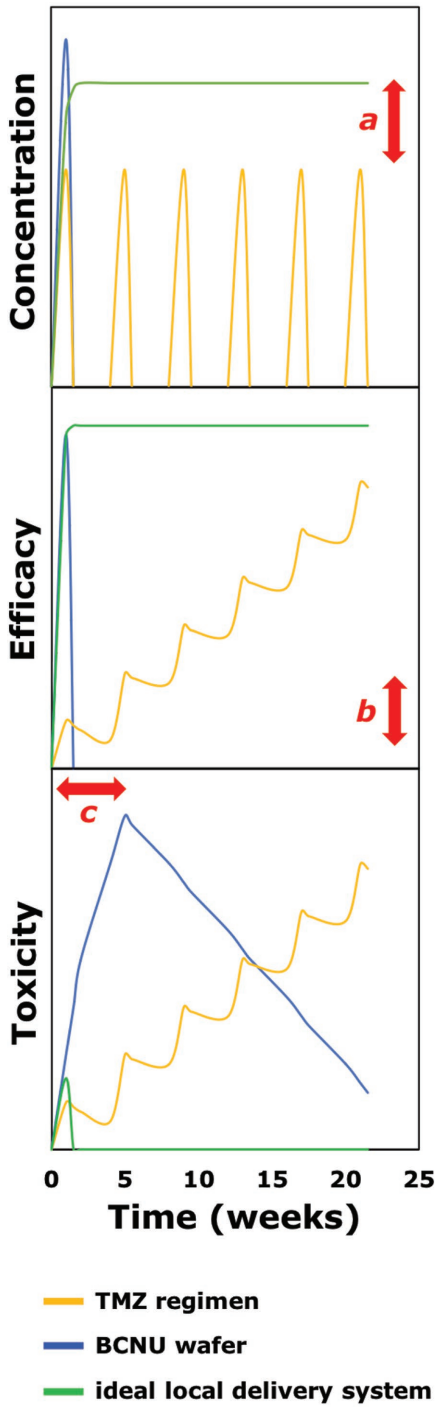

Figure 1. Graphical illustration of concentration, efficacy, and toxicity profiles of an idealized drug delivery system against systemic TMZ adjuvant therapy (Stupp protocol) and stiff FDA-approved BCNU wafers. a) Limitations in systemic toxicity of TMZ are overcome with local delivery. An ideal delivery system will possess a mitigated bolus and 0th or 1st order release kinetics. b) Achievement of a high local concentration of TMZ in local delivery systems sustained over many weeks produces a reduction in tumor burden and increase in efficacy in the idealized local delivery systems. c) BCNU wafers' stiffness mismatch with tissue contribute to toxicity and negative side effects after >80% of drug release. A soft idealized local drug delivery system will have minimal acute toxicity and no negative chronic immune response.

4. Promising Soft Materials for Local Delivery

There is mounting evidence from the biomaterials community that existing hydrogel technology can capture the value of a wafer-type local therapy while mitigating negative side effects, putting them at the forefront of promising local chemotherapy delivery systems in GB. Recent reviews have summarized some of the literature on these local drug delivery hydrogels.[32,33] Certain systems are particularly promising, or have developed proof-of-concept principles that should be adopted with any clinical therapy.

Degradable, soft hydrogels, which are distinct from classic nondegradable materials such as polyHEMA hydrogels, have a number of advantages compared to BCNU wafers. As discussed, wafers elute the vast majority of their chemotherapy payload in 1 week, but the remaining empty wafer may increase the risk of local adverse effects. Critically, hydrogels can be tuned to degrade under different time-scales and are generally biodegraded in under 1 month. Although the kinetics of chemotherapy release may be comparable, hydrogels do not last long enough in the resection cavity (nor are stiff enough) to cause the same adverse effects as wafers. Promising examples of rapidly biodegradable hydrogels include supramolecular or physically assembled hydrogels for parenteral drug delivery applications.[32,34–36] For example, we previously reported physical hydrogels for local GB drug delivery that self-assemble via host–guest interactions.[31,37] These materials release drugs with a bolus, just as the BCNU wafers do, but are biodegradable under timescales of days to weeks. These materials confer an additional advantage over wafers: because their intended use is in less-invasive parenteral drug delivery, materials scientists often embed shear-thinning properties into these supramolecular hydrogels so that they can be nonsurgically implanted in vivo and quickly recover their original stiffness. Stiff BCNU wafers do not possess these shear-thinning and recovery properties. This injectability is advantageous for GB drug delivery because as the material recovers, it fills the gap of the resected tumor with superior epitaxial engagement.[31,32] Preclinical data suggest this improvement in bioavailability affords clear therapeutic benefit,[31] which may mean that shear-thinning soft materials, while retaining the bolus release kinetics of the wafer technology, are more efficacious than their stiff counterparts.

However, if local drug delivery for GB is to move away from this wafer paradigm of 1-cycle benefit, and adopt the more beneficial pharmacokinetic profile from systemic therapy, which includes repeated cycles of TMZ over the course of several months, then the local drug delivery material cannot degrade in under 1 month, as is the case with degradable, physical hydrogels. Furthermore, the local therapy cannot elute most of its payload in under 1 month, as is the case with both physical hydrogels and the BCNU wafers. To avoid the side effects of the wafer, the local drug delivery adjuvant should also be soft with a stiffness on par with that of tissue. This is no easy task: it is highly challenging to develop a physical hydrogel which is biocompatible, biodegradable, injectable, soft, and has an in vivo duration greater than 1 month. This particularly burdensome engineering challenge will require new and creative solutions in chemistry and materials science.

Of course, developing long-lasting, soft, and degradable materials for GB delivery is only useful if the timescale of drug elution is also on the order of 6–12 months. As previously discussed, most supramolecular hydrogels and the FDA-approved wafers possess a bolus release profile. Many approaches have been reported in the literature to mitigate a bolus release, including using capsules or nanoparticles to retard the drug release by introducing an upstream rate-limiting step.[38–40] Ranganath et al. demonstrated the utility of poly(lactic-*co*-glycolic acid) (PLGA) nanocarriers in providing sustained drug release and greater engineering control over the release kinetics for a GB target.[38,39] Rahman et al. explored the utility of an interesting PLGA/PEG microparticle-based paste as a local adjuvant therapy.[41] Such an approach is potentially advantageous in particular for selective tuning of release kinetics for combination therapies, i.e., changing the release rate of one drug (e.g., hydrophobic small molecule) without disturbing the release rate of a second loaded drug (e.g., protein).

Other approaches include exploiting lipid carriers.[42–45] These strategies are promising in providing a scalable method of reducing a bolus release of drugs; in particular, their utility in controlling the release kinetics and improving stability of hydrophobic small molecule drugs[46] is especially useful in anticancer therapy. The delivery of hydrophobic drugs is an important[47] and active area of research, and such lipid carriers are promising both for delivery of these poorly soluble drugs and combination therapies with proteins.

The field has begun to turn to hydrophobic moieties not just for controlled elution of a therapeutically relevant concentration of hydrophobic small molecules, but as a means of overcoming the fundamental mass transfer limitations in controlled drug delivery using a water-based material. Soft materials that serve as alternatives to supramolecular hydrogels include systems such as oleogels.[48] These nonaqueous gels have seen virtually no translation into GB local therapeutics, but a new generation of solvent-free, soft biomaterials for drug delivery are emerging, including supramolecular poly(caprolactone)/poly(ethylene glycol) block polymer systems[36] developed by Tabet and Wang. Hydrophobic solvent-free gels are promising because the absence of bulk solvent may prolong their release kinetics in vivo.

5. Conclusions

In summary, results from the clinic provide useful quantitative lessons and benchmarks to guide the biomaterials community in developing novel local chemotherapy delivery systems. The clinical success of a higher number of adjuvant systemic TMZ cycles should guide the adoption of similar time scales and release kinetics in local drug delivery materials. The stiffness mismatch of BCNU wafers informs the mechanical properties that ideal systems will have.

Many promising soft materials for local drug delivery are in development but have seen little clinical translation. It would be advantageous for physicians to explore such systems utility as adjuvant therapies. These materials are immediately available and have strong potential to both mitigate negative side

effects incurred from BCNU wafers and provide a more efficacious bolus release due to superior epitaxial engagement.

Unmet medical needs remain, and biodegradable soft materials that have extended durations in vivo and elute chemotherapy for similar time scales of many months may very elegantly satisfy these needs. Transdisciplinary communication between clinicians, material scientists, and biomedical scientists is needed for the clinical translation of novel therapies that satisfy such engineering requirements.

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Conflict of Interest

The authors declare no conflict of interest.

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