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Blood-brain barrier disruption with low-intensity pulsed ultrasound for the treatment of pediatric brain tumors: a review and perspectives

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Pediatric brain tumors are the most common solid tumor and the first cause of cancer death in childhood, adolescence, and young adulthood. Current treatments are far from optimal in most of these tumors and the prognosis remains dismal for many of them. One of the main causes of the failure of current medical treatments is in part due to the existence of the blood-brain barrier (BBB), which limits drug delivery to tumors. Opening of the BBB with low-intensity pulsed ultrasound (LIPU) has emerged during the last 2 decades as a promising technique for enhancing drug delivery to the brain. In preclinical models, enhanced delivery of a wide range of therapeutic agents, from low-molecular-weight drugs, to antibodies and immune cells, has been observed as well as tumor control and increased survival. This technique has recently entered clinical trials with extracranial and intracranial devices. The safety and feasibility of this technique has furthermore been shown in patients treated monthly for recurrent glioblastoma receiving carboplatin chemotherapy. In this review, the characteristics of the BBB in the most common pediatric brain tumors are reviewed. Then, principles and mechanisms of BBB disruption with ultrasound (US) are summarized and described at the histological and biological levels. Lastly, preclinical studies that have used US-induced BBB opening in tumor models, recent clinical trials, and the potential use of this technology in pediatrics are provided.

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KEYWORDS blood-brain barrier; low-intensity pulsed ultrasound; drug delivery; pediatric; brain tumor

CNS tumors represent the most common solid tumor and the first cause of cancer death in childhood, adolescence, and young adulthood, and their incidence varies from 1 to 5 cases per 100,000 persons.[31] Although there have been significant advances in understanding these tumors, their prognosis remains variable depending on the type of tumor. For example, all children diagnosed with diffuse intrinsic pontine glioma (DIPG) eventually die from their tumor, with a median overall survival (OS) of less than 1 year,[25] and for high-risk medulloblastoma the 5-year OS is less than 50% with standard treatments.[54] Conversely, malignant germ-cell tumors and low-grade gliomas have a 5-year OS above 90%.

The failure of standard treatments is, in part, explained by the low penetration of drugs through the blood-brain barrier (BBB), which protects the brain from the circulating blood flow and restricts approximately 98% of small-molecule drugs (< 0.5 kD) and 100% of large-molecule drugs from crossing the intact BBB.[51] Drug delivery to the brain is restricted by both a mechanical function of the BBB, especially via the tight junctions, and a functional activity through a complex system of endogenous efflux transporters, particularly the ATP-binding cassette (ABC) transporters.

Several strategies have been assessed in order to bypass the BBB and increase drug delivery to brain tumors. High-dose chemotherapy is still used in current clinical protocols but is marked by high systemic toxicity of the

ABBREVIATIONS ABC = ATP-binding cassette; BBB = blood-brain barrier; BBBD = BBB disruption; BCRP = breast cancer resistance protein; DIPG = diffuse intrinsic pontine glioma; GBM = glioblastoma; LIPU = low-intensity pulsed US; NHP = nonhuman primate; NK = natural killer; OS = overall survival; PFS = progression-free survival; pHGG = pediatric high-grade glioma; US = ultrasound.

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drugs.[7] Intraarterial chemotherapy injection consists of locoregional delivery of the drug via the cerebral arteries; a systematic review and meta-analysis has shown that this invasive approach is not superior to intravenous chemotherapy in terms of efficacy and OS.[12] Osmotic disruption of the BBB is performed using hypertonic agents, such as mannitol, injected into a cerebral artery. Although it can increase delivery of drugs into the brain compared to systemic injection alone, the delivery is largely reversed within 10 minutes and not targeted to the tumor, and this technique may induce seizures and increase intracranial pressure. Moreover, osmotic disruption of the BBB in association with carboplatin was inactive in pediatric high-grade and brainstem gliomas.[70] The functional activity of the BBB can also be targeted by inhibition of the drug efflux transporter system. Inhibition of P-glycoprotein with cyclosporin A was evaluated in patients with DIPG in association with etoposide, vincristine, and radiation therapy, but the regimen proved excessively toxic.[23] Convection-enhanced delivery has been largely studied during the last decades, including in patients with DIPG. The first clinical data are encouraging, but volumes of delivery with this invasive technique are still limited.[26] BBB disruption (BBBD) using low-intensity pulsed ultrasound (LIPU) in animals has recently emerged as a promising technique.[29] This technique has been widely assessed in preclinical studies and was first translated to clinical trials in 2014.[9] Encouraging results have since been observed in adult patients treated for recurrent glioblastoma.[30,40]

In this review, the characteristics of the BBB in the most common pediatric brain tumors are reviewed. Then, we focus on ultrasound (US)–induced opening of the BBB to review the principles, mechanisms, and histological and biological effects of BBBD with US; we summarize preclinical studies that have used US-induced BBB opening on tumor models; and we report recent clinical trials that have been initiated.

Methods

A comprehensive review of the literature was performed using a PubMed search and the ClinicalTrials.gov website (https://clinicaltrials.gov) with the following keywords: (blood-brain-barrier, blood-tumor barrier) / (ependymoma, medulloblastoma, glioma, diffuse intrinsic pontine glioma, brain tumor) / (pediatric, children) and (blood-brain barrier, blood-tumor barrier) / ultrasound / (disruption, opening). Relevant articles published in English were selected based on individual merit and included basic science research, human subjects research, clinical trials, and reviews. The reference lists of included articles were searched for additional studies.

The BBB in Pediatric Brain Tumors

Although few studies have focused on specific features of the BBB in pediatric brain tumors, this certainly plays a major role in drug resistance and may explain the discrepancies between some encouraging preclinical in vitro results and failure of treatments once translated into clinical practice.

Diffuse gliomas are very invasive tumors characterized by their capacity to infiltrate the brain parenchyma. In both DIPG and supratentorial malignant gliomas, tumor cells can be mixed with normal brain parenchyma, distant from the primary tumor mass.[24] These tumors generally show little or no contrast enhancement on MRI, indicating an intact BBB. As many as 82.4% and 17.7% of WHO grade III and IV pediatric high-grade gliomas (pHGGs), respectively, do not exhibit enhancement,[68] and contrast enhancement only involves 0%–25% of the tumor volume on average in DIPG.[4] The extent of tumor infiltration compared to the small amount or absence of contrast-enhancement implies that tumor cells can infiltrate brain areas protected by an intact BBB that prevents efficient delivery of systemically administered drugs to tumor cells and the microenvironment. Based on a theoretical model, it was estimated that only 15% of drugs currently administered to patients with DIPG may be likely to spontaneously cross the BBB and reach therapeutic concentration through an intact BBB.[20] Different factors may affect BBB permeability in pHGG, and the microenvironment likely plays an important role. The heterogeneity of BBB permeability was confirmed in a genetic mouse model of pHGG, where it was shown that BBB permeability is 67% higher in cortical pHGG compared to brainstem pHGG. Permeability was not significantly affected by H3.3-K27M mutations, but was significantly correlated with tumor volume.[61] Clinicians hypothesize that the low permeability observed in brainstem gliomas may explain the poor prognosis of these tumors. A similar observation was inferred from a clinical series of DIPGs in which contrast enhancement differed from tumor to tumor, and was more often associated with H3.1-K27M tumors, which have a better prognosis compared to H3.3-K27M tumors.[10] ABC drug efflux transporters are expressed in both brain endothelial cells and glioma cells and transport their substrates from these cells back into the blood circulation, leading to a reduced delivery of many drugs in gliomas.[17] All three major ABC efflux transporters—P-glycoprotein (ABCB1), breast cancer resistance protein (BCRP; ABCG2), and multidrug resistance-associated proteins (ABCC1)—are present in the microvasculature of pHGG, including DIPG.[69] It has been suggested that both P-glycoprotein and BCRP limit the efficacy of dasatinib in a genetic brainstem glioma mouse model.[49]

The permeability of the BBB is very variable as well in medulloblastomas. Signal enhancement after contrast injection varies from 85% to 100% of patients and can be subtle and heterogeneous (see review in Dangouloff-Ros et al.[16]). Group 4 medulloblastomas generally lack or have minimal enhancement[42] and have a poor prognosis; it was also observed that non-Wnt/non–sonic hedgehog tumors with extensive gadolinium enhancement had a worse prognosis in comparison with tumors with no or weak enhancement.[37] However, gadolinium is a small molecule that can pass easily through a damaged BBB. Thus, contrast enhancement may overestimate BBB permeability and give a false appreciation of the ability for drugs to be delivered to a tissue. It has been recently described that Wnt-medulloblastomas, curable tumors even when metastatic, present BBB features that could explain their better prognosis.[53] These tumors have significant hemorrhagic

features compared to other types, both at surgery and in genetic mouse models. In particular, they develop dense aberrant vascular networks and their endothelium exhibits genotype (downregulation of *Cldn5* and *Slc2a1*) and phenotype (fenestrations and disrupted tight junctions) characteristics of peripheral endothelium. These features are driven by Wnt-medulloblastoma paracrine signals and render Wnt tumors BBB porous to systemic chemotherapy. These observations indicate the importance of the BBB in medulloblastoma treatments. Minimal data exist on ependymomas. Although most supra- and infratentorial ependymomas enhance after gadolinium injection,[56] both P-glycoprotein and BCRP are associated with ependymomas vessels, and may participate in transporter-dependent drug efflux in these tumors.[22]

Concept and Mechanisms of US-Induced BBBD

BBBD using LIPU in combination with injection of US resonators (preformed gas microbubbles) has been in preclinical development for more than 20 years.[29] BBBD magnitude varies depending on acoustic parameters (acoustic pressure, frequency, burst length)[11,45] and microbubble size and concentration.[14,47] BBBD is transient and the integrity of the BBB has been shown to be rapidly restored after sonication; it begins to close immediately after disruption and is fully closed in 6–24 hours.[29,57]

When US stimulates systemically administered microbubbles (1–10 μm size), the bubbles expand and contract, resulting in mechanical stretching of the vessel walls in capillaries. This leads to endothelial cell modification with increased transcytosis activity, formation of transendothelial fenestration, and opening of the tight junctions, particularly occludin and claudin-5 proteins.[57,58] Beyond modification of the physical barrier, US and microbubbles may also modify the functional aspect of the BBB. P-glycoprotein expression is inhibited up to 48 hours after sonication, confirming an effect of US on drug efflux mechanisms,[3] without the functional impairment of endothelial cells.[13] These different mechanisms appear progressively in time, and BBBD occurs in two different phases with early/fast leakage, and late/slow leakage.[55] Figure 1 represents mechanisms underlying US-induced BBBD with LIPU.

Preclinical Evaluation of US-Induced BBBD Safety

The safety of BBBD has been assessed through preclinical studies in both small and large animal models. The impact of US and microbubbles in the brain parenchyma depends on US parameters. BBBD has been obtained with acoustic pressures up to 0.5 MPa with few extravasated erythrocytes and very scarce ischemic neurons or apoptotic cells in the sonicated area with a frequency of 690 kHz suitable for transcranial sonication.[28] Few erythrocyte extravasations without ischemic lesions were also observed after sonications in rabbits with acoustic pressures up to 0.6 MPa with a skull-implantable nonfocused 1-MHz US device.[5] A sterile inflammatory response mediated by the NF-κB pathway has been described up to 24 hours after sonication in the rat brain;[36] however, this response is dependent on microbubble dose. Safe sonications without induction of the NF-κB signaling pathway have been performed in the same animal at lower microbubble dosages.[47] Moreover, no microgliosis or astrocytosis has been observed up to 6 months after US-induced BBBD and adeno-associated virus delivery.[60] Repeated BBBDs appear to be as safe as single sessions,[34] and multiple studies have confirmed the feasibility and safety of the technique in nonhuman primates (NHPs) with different US devices. Feasibility of transcranial, cavitation-guided disruption of the BBB in NHPs was first described in the visual cortex with a 500-kHz focused single-element transducer.[41,67] McDannold et al. used a noninvasive multi-array 1024-element device and demonstrated that multiple transcranial BBBDs are safe in deep and superficial targets. Animals repeatedly sonicated in the visual cortex recovered from each session without behavioral deficit or loss in visual acuity, and no signs of brain damage were observed in histological and MRI studies.[43] Finally, a multiparametric study assessing behavioral, neurophysiological, imaging, and histological parameters proved that safe repeated BBBDs are possible with an implantable US device placed into the skull of NHPs in front of eloquent brain areas.[27] BBBD can be observed on MRI as a pressure-dependent contrast enhancement after gadolinium injection in T1-weighted sequences.[29]

US-Induced BBBD and Preclinical Tumor Models

BBBD with LIPU has been shown to enhance the delivery of a wide variety of agents into the brain in preclinical models. Chemotherapeutic drugs used in current neurooncological protocols such as doxorubicin,[65] temozolomide,[6] irinotecan,[6] carboplatin,[19] BCNU,[39] cytarabine,[75] or methotrexate[48] have been delivered in significant amounts after US-induced BBBD. Larger molecular weight molecules, such as monoclonal antibodies (trastuzumab[33]), as well as cells (neuronal stem cells,[8] natural killer [NK] cells[1]) have also been significantly delivered to rodent healthy brain parenchyma and metastases in the brain after BBB permeabilization. Different strategies have been developed to improve local drug/cell delivery and efficacy after US-induced BBBD. These strategies include the use of liposomes,[73] nanoparticles,[63] drug-loaded microbubbles,[21] or magnetic attraction of cells.[59]

BBBD with LIPU was evaluated in preclinical models of metastasis in the brain. Although results were not uniform, a complete disappearance of tumors has been observed in rats treated by trastuzumab associated with US and microbubbles in a breast cancer brain metastasis model (BT-474 HER2-positive human breast ductal carcinoma cells).[52] Growth control was also obtained in an MDA-MB-361 HER2-positive model after weekly treatments of rats with trastuzumab and pertuzumab associated with BBBD. Results were also heterogeneous, and no complete response was observed in this study.[35] The heterogeneity observed in these studies may be due to variations in tumor vasculature or in the US distribution. In the

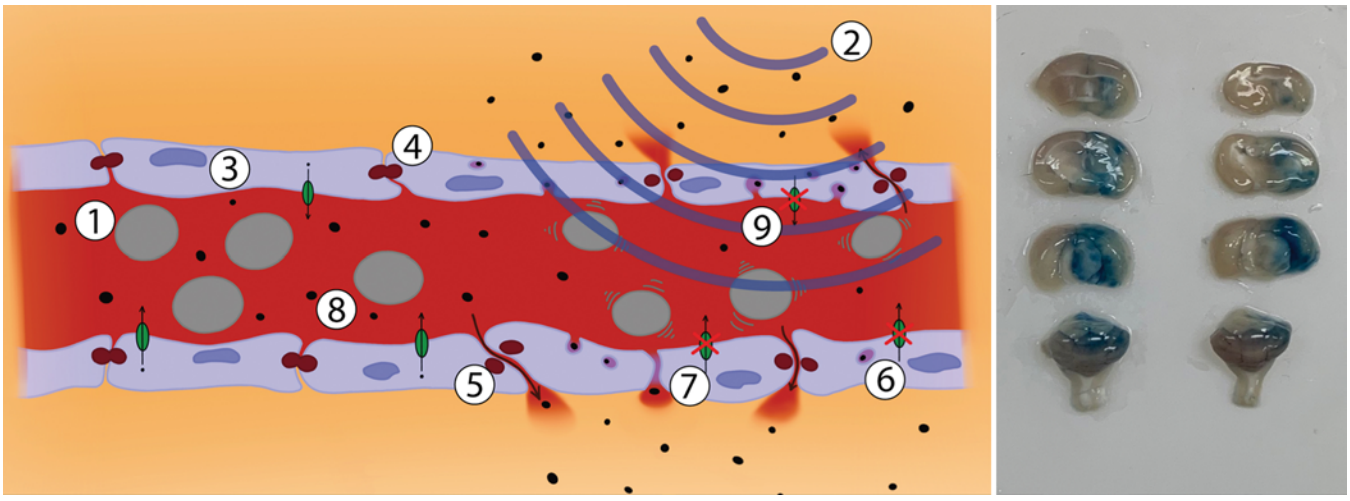

FIG. 1. Mechanisms underlying US-induced BBBD with LIPU. **Left:** Circulation of microbubbles (1) in the US beam (2) creates cavitation. This induces modifications of the endothelial cells (3) and opening of the BBB via different ways. Closed tight junctions (4) are transiently opened, creating intercellular routes (5). Transcellular transport is activated, with formation and movement of vesicles from luminal to abluminal surfaces (6). Vesicles can also merge and form large fenestrations and then form transendothelial channels (7). Drugs (8) can cross the BBB through these intercellular and transcellular ways, and thus be delivered to the brain parenchyma. Inhibition of efflux transporters from sonications may prevent drugs from being transported back into the blood, enhancing accumulation (9). **Right:** Opening of the BBB in a mouse brain with an unfocused US device. Targeted BBB opening appears as blue staining (Evans Blue) in the right hemisphere.

same MDA-MB-361 HER-2 positive model, a reduction in tumor volume and an increase in survival time after applying multiple sonications were observed when HER2-specific NK cells were injected intravenously in association with US.[2]

A large panel of rodent glioma models has also been studied. Tumor control and improved survival was obtained in C6 glioma models treated with BCNU and BCNU-loaded microbubbles,[39,64] in 9L gliosarcoma and glioblastoma (GBM) 8401 models treated with liposomal doxorubicin,[66,74] in a 9L glioma model treated with temozolomide,[71] and in a U87 model treated with bevacizumab.[38] All of these later studies were performed with focused US devices. Recently, significantly increased survival with a trend for tumor growth control was observed in U87 and patient-derived GBM cell-line models in mice treated with carboplatin and BBBD with an unfocused US device.[19]

Clinical Translation of US-Induced BBBD

This emerging technique has recently been translated to the clinic, with either extracranial noninvasive devices or minimally invasive implantable devices (Table 1). In both cases, the skull represents the main obstacle for the application of US in the field of neurooncology, because bone induces distortion and attenuation of the US and causes rapid heating inside the skull.[62] Three external US systems and 1 implantable US system are currently in clinical trials, as reviewed below (Fig. 2). Presently, no children have been included in clinical trials assessing US-induced BBBD.

The ExAblate system, developed by InSightec,[44] was first designed for thermal ablation applications and then extended for use in BBBD. Planning and monitoring of BBBD with this device can be performed using the dual-mode hemispheric array.[15] Several ongoing clinical trials are evaluating the safety and feasibility of BBBD with the ExAblate system in adult patients with high-grade gliomas (www.clinicaltrials.gov nos. NCT03551249, NCT03616860, NCT03712293, NCT02343991), and breast cancer brain metastases (no. NCT03714243). Recently, 5 patients with malignant brain tumors were treated in a phase I, single-arm study[40] (study no. NCT02343991). BBBD was observed at tumor margins, in volumes ranging from 972 to 2430 mm^3. The BBB integrity was confirmed to be restored 20 hours later. The procedure was well tolerated with no new or worsening symptoms during the 24 hours following the sonication, and no significant intracerebral hemorrhage or edema on control MRI. Two patients were previously treated with either oral temozolomide or intravenous doxorubicin, and increased concentrations of temozolomide and, to a lesser extent, doxorubicin were measured in sonicated tissue relative to unsonicated tissue (3.47×10^{-4} ng/mg vs 0.45×10^{-4} ng/mg for temozolomide and 0.22 ng/mg vs 0.15 ng/mg for doxorubicin, respectively). NaviFUS, a Taiwanese biotech company, has designed an external, multichannel hemispheric phased-array US system, the NaviFUS System. The system has been recently assessed in a single-arm dose escalation study in patients with recurrent GBM (study no. NCT03626896). Results have not yet been published. Finally, a single-element, transcranial, focused US system has recently been approved by the FDA for a pilot clinical trial for Alzheimer's disease (Columbia University). The treatment procedure is guided and controlled by neuronavigation and a passive cavitation detection device.[18] To improve the safety of BBBD with extracranial devices, real-time monitoring

TABLE 1. Clinical trials on BBBD with LIPU indexed in https://clinicaltrials.gov in the field of neurooncology

Study Title	PI Location	Status	Condition	US Device	Drug	NCT No.
The use of focused ultrasound and microbubble infusion for altering brain perfusion and the blood brain barrier	Santa Monica, CA, USA	Not yet recruiting	Low-grade glioma of brain	—	—	NCT04063514
Safety and efficacy of transient opening of the blood-brain barrier (BBB) with the SonoCloud-9	Paris, France	Recruiting	Glioblastoma	SonoCloud-9	Carboplatin	NCT03744026
Blood-brain barrier disruption using transcranial MRI-guided focused ultrasound	Toronto, ON, Canada	Active, not recruiting	Brain tumors	ExAblate	Doxorubicin	NCT02343991
Assessment of safety and feasibility of ExAblate blood-brain barrier (BBB) disruption	College Park, MD, USA	Recruiting	High-grade glioma	ExAblate	Temozolomide	NCT03551249
Safety of BBB opening with the SonoCloud	Paris, France	Completed	Glioblastoma	SonoCloud	Carboplatin	NCT02253212
Assessment of safety and feasibility of ExAblate blood-brain barrier (BBB) disruption for treatment of glioma	Toronto, ON, Canada	Recruiting	Glioblastoma	ExAblate	Temozolomide	NCT03616860
Safety and efficacy of SonoCloud device combined with Nivolumab in brain metastases from patients with melanoma	Paris, France	Not yet recruiting	Malignant melanoma brain metastasis	Sonocloud	Nivolumab alone or w/ ipilimumab	NCT04021420
Safety of BBB disruption using NaviFUS system in recurrent glioblastoma multiforme (GBM) patients	Taoyuan City, Taiwan	Completed	Glioblastoma	NaviFUS	—	NCT03626896
Blood brain barrier disruption (BBBD) using MRgFUS in the treatment of Her2-positive breast cancer brain metastases	Toronto, ON, Canada	Not yet recruiting	HER2-positive breast cancer brain metastases	ExAblate	—	NCT03714243
ExAblate blood-brain barrier disruption for glioblastoma in patients undergoing standard chemotherapy	Seoul, Republic of Korea	Recruiting	Glioblastoma	ExAblate	Temozolomide	NCT03712293

NCT = National Clinical Trial; PI = principal investigator.

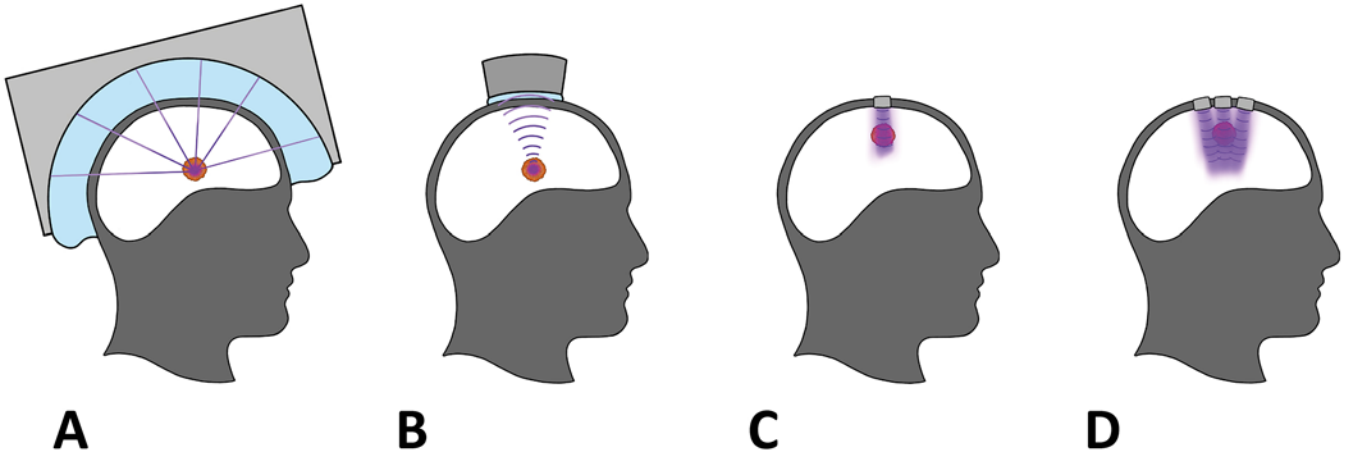

FIG. 2. Schematic representation of US devices developed for clinical application of BBBD with LIPU. **A:** Extracranial hemispheric focused US arrays (ExAblate, NaviFUS). **B:** Extracranial mono-element focused device. **C:** Implantable, unfocused single-emitter US device (SonoCloud-1). **D:** Implantable, unfocused 9-emitter US device (SonoCloud-9).

of acoustic activity (microbubble cavitation) has been developed.[50] This system allows for a stepwise increase of acoustic pressure during the procedure, based on the spectral information received in real-time by an associated hydrophone, thus reducing variability of BBBD for transcranial US devices where the in situ acoustic pressure is unknown.

Another strategy to overcome the bone interface consists of inserting a US device into the skull. The SonoCloud-1 device, developed by CarThera, is an implantable unfocused US device that can be placed in a burr hole and activated using a transcutaneous connection. The first clinical trial using the SonoCloud-1 technology has been performed in adults with recurrent GBM treated with intravenous carboplatin (study no. NCT02253212).[9] Intravenous carboplatin injection was started on average 106 minutes after sonication. The BBBD procedures were well tolerated, without severe adverse events, including when sonicating eloquent brain regions.[30] Both median progression-free survival (PFS) and OS were increased relative to historical data (4.11 vs 2–3 months for PFS and 12.94 vs 6–9 months for OS, respectively), and better tumor control in the sonication field was observed. Another clinical trial is underway to evaluate the safety and feasibility of BBBD using the SonoCloud-1 device in patients with melanoma brain metastases (study no. NCT04021420). The SonoCloud-9 device has been designed to sonicate the tumor and surrounding infiltrative region for patients with GBM. The device, with 9 1-cm–diameter transducers arranged on an implantable grid, is currently being assessed in an international multicenter clinical trial in patients with recurrent GBM (study no. NCT03744026). The SONOKID trial is planned to start in 2020 in Paris (France), and will assess the safety and feasibility of BBBD using the SonoCloud-1 device in association with intravenous carboplatin chemotherapy in recurrent supratentorial malignant primitive tumors (any histological type) in the pediatric population. It will be the first clinical trial on US-induced BBBD in the pediatric population.

Both extracranial and implantable devices have advantages and drawbacks. Extracranial devices are noninvasive, and can focus on deep and variable targets in the brain, but they imply shaving of patients, and long and immobile procedures (2–4 hours); sonication is limited to small brain volumes (1–4 cm^3), with difficulties in targeting superficial lesions. Implantable devices allow for fast procedures (4–15 minutes) and BBBD in larger volumes (4–140 cm^3), but they imply the device has to be implanted during a tumor debulking or biopsy surgical procedure and the targeted volume is fixed in a 1 device/1 volume manner. Thus, clinical use of these devices in the future may be complementary, depending on the particular indication to be treated. Large, superficial, and infiltrative lesions such as extensive high-grade glioma or DIPG may be good targets for implantable devices, while smaller and deep-seated lesions, such as hypothalamic or basal ganglia lesions, may be ideally treated with extracranial devices.

Conclusions and Perspectives in Pediatric Neurooncology

Although there have been significant advances in understanding the biology of pediatric brain tumors, the treatment of these rare neoplasms is still challenging for neurooncologists and neurosurgeons, in part due to limited drug delivery through the BBB. BBBD with LIPU may be a method to overcome this limitation. This technique has many advantages compared to other strategies: 1) non- or minimal invasiveness; 2) local and targeted disruption; 3) possible targeting of both superficial and deep lesions; 4) transient disruption; 5) possible delivery of large molecules or immune cells; and 6) proven safety in preclinical and clinical studies. BBBD with LIPU has recently entered clinical trials in adults, with encouraging results, and clinical trials assessing the feasibility and safety of the technique in the pediatric population are planned to begin in the coming year. It will be the first step toward treatment of pediatric brain tumors with this technique in association with standard drugs, and emerging therapies such as targeted or immune therapies.

Different treatment protocols have been described in preclinical studies, with variable results,[2,75] and both delivery before and after sonication have been assessed in clinical trials.[30,40] The optimal treatment schedule is likely therapy dependent. This implies taking into account the type of treatment (cell, molecule), the pharmacokinetics of the drug (if any) and its route of delivery (oral, intravenous), and the formulation of the treatment (loaded-microbubble, liposome). Thus, each treatment protocol will have to be adapted to the agent delivered.

Moreover, some obstacles specific to the pediatric population will have to be overcome. Skull bone is expected to be similar or have less attenuation to US in children compared with adults, therefore the same transcranial US systems can likely be used. The feasibility of transcranial US ablation of centrally located tumors in pediatric patients performed with the Insightec ExAblate 4000 system is being evaluated (study no. NCT03028246). The thinner skull bone could be compensated for by adjusting the geometry of implantable devices and placing silicon spacers between the bone and the transducer. Anatomical considerations for deep-seated and posterior fossa lesions have to be taken into consideration with implantable devices. The US emitter shape and frequency can be optimized to efficiently cover large and deep tumor areas, and design of the transducer and the connection system will need adjustment for implantation in the posterior fossa due to the orientation of the occipital bone and the cervical muscle insertions. Neuronavigation systems may be needed to accurately insert the devices, especially for those targeting the brainstem. The lengthy procedure needed with extracranial systems can be a limitation in young children. Although constraining, general anesthesia is feasible under certain conditions without interfering with US-mediated disruption, as shown in preclinical studies.[46] The overall transcranial treatment duration can also be reduced with advanced real-time monitoring and rapid electronic beam steering techniques[32] or by designing a single-element US emitter with a relatively large focal size associated with neuronavigation.[72]

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Disclosures

M. Canney and G. Bouchoux are employees of CarThera. A. Carpentier is a paid consultant to CarThera. K. Beccaria was previously an employee of CarThera. A. Carpentier, K. Beccaria, and M. Canney are inventors of intellectual property related to the SonoCloud device that has been licensed to CarThera. A. Carpentier and M. Canney have ownership interest in CarThera.

Author Contributions

Conception and design: Beccaria. Acquisition of data: Beccaria. Analysis and interpretation of data: Beccaria, Canney. Drafting the article: Beccaria. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Beccaria. Study supervision: Beccaria.

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