Neuro-Oncology Advances

4(1), 1–11, 2022 | https://doi.org/10.1093/noajnl/vdac104 | Advance Access date 25 June 2022

Safety of intra-arterial chemotherapy with or without osmotic blood–brain barrier disruption for the treatment of patients with brain tumors

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Abstract

Background. Intra-arterial administration of chemotherapy with or without osmotic blood–brain barrier disruption enhances delivery of therapeutic agents to brain tumors. The aim of this study is to evaluate the safety of these procedures.

Methods. Retrospectively collected data from a prospective database of consecutive patients with primary and metastatic brain tumors who received intra-arterial chemotherapy without osmotic blood–brain barrier disruption (IA) or intra-arterial chemotherapy with osmotic blood–brain barrier disruption (IA/OBBBD) at Oregon Health and Science University (OHSU) between December 1997 and November 2018 is reported. Chemotherapy-related complications are detailed per Common Terminology Criteria for Adverse Events (CTCAE) guidelines. Procedure-related complications are grouped as major and minor.

Results. 4939 procedures (1102 IA; 3837 IA/OBBBD) were performed on 436 patients with various pathologies (primary central nervous system lymphoma [26.4%], glioblastoma [18.1%], and oligodendroglioma [14.7%]). Major procedure-related complications (IA: 12, 1%; IA/OBBBD: 27, 0.7%; $P = .292$) occurred in 39 procedures including 3 arterial dissections requiring intervention, 21 symptomatic strokes, 3 myocardial infarctions, 6 cervical cord injuries, and 6 deaths within 3 days. Minor procedure-related complications occurred in 330 procedures (IA: 41, 3.7%; IA/OBBBD: 289, 7.5%; $P = .001$). Chemotherapy-related complications with a CTCAE attribution and grade higher than 3 was seen in 359 (82.3%) patients.

Conclusions. We provide safety and tolerability data from the largest cohort of consecutive patients who received IA or IA/OBBBD. Our data demonstrate that IA or IA/OBBBD safely enhance drug delivery to brain tumors and brain around the tumor.

Key Points

- Intra-arterial chemotherapy and osmotic blood–brain barrier disruption are safe.
- Major procedural complications occurred in 12 of 1102 (1%) IA procedures.
- Major procedural complications occurred in 27 of 3837 (0.70%) IA/OBBBD procedures.

Importance of the Study

Intra-arterial delivery of chemotherapy without osmotic blood–brain barrier disruption (IA) or with osmotic blood–brain barrier disruption (IA/OBBBD) has been shown to increase drug concentration in preclinical brain tumor models safely, compared to intravenous delivery. IA/OBBBD has been used to successfully treat chemosensitive brain tumors. We present the largest safety dataset to date from a single institution experience of 436 consecutive patients receiving IA or IA/OBBBD. Overall, we report a low complication rate in both IA and IA/OBBBD therapy. These techniques provide a safe alternative to conventional IV/oral route whilst enhancing drug delivery to tumors and tumor-infiltrated brain.

A major hindrance to treating brain tumors is achieving therapeutic levels of antineoplastic agents within tumor tissue. This is due to several factors including the first pass metabolism of intravenously (IV) delivered drugs prior to circulation through cerebral vasculature and the presence of the blood–brain barrier (BBB).[1,2] Advancements in cerebral catheterization have allowed for intra-arterial administration of chemotherapeutics (IA) directly to the cerebral vasculature, thus obviating the first pass metabolism and associated systemic adverse effects of IV chemotherapy. Several studies have suggested that IA increases the chemotherapy concentration by up to 50% in human[3] and animal studies,[4,5] and further increased up to 90%, when combined with osmotic blood–brain barrier disruption (OBBBD).[6]

The BBB is comprised of endothelial tight junctions, astrocytic end feet processes, and their respective basement membranes that form a selectively permeable barrier that allows precise cerebral homeostasis.[7] In brain tumors, the BBB is often termed the brain–tumor barrier and is known to demonstrate heterogenous drug permeability, contributing to therapeutic failures.[8–11] This impediment to chemotherapeutic penetration can be improved by disruption of the BBB (BBBD). Several strategies have been described for BBBD with variable success, including osmotic (mainly using mannitol), laser interstitial thermal therapy, ionizing radiation, MRI-guided focused ultrasound, and nanoparticle-based therapies.[1,12–15] Additionally, ionizing radiation can transiently enhance delivery of therapeutics,[16,17] but may need to be measured against potential neurotoxicities. On the other hand, laser interstitial thermal therapy and MRI-focused ultrasound techniques disrupt a relatively small brain volume, which limits the ability to treat diffuse brain tumors.

For OBBBD, warm 25% hyperosmolar mannitol is infused intra-arterially, which causes shrinkage of the endothelial cells and altered concentrations of intracellular calcium, leading to changes in the calcium-dependent actin and cadherin interactions thus increasing paracellular solute flux.[10,11] IA and IA/OBBBD have been used at Oregon Health and Science University (OHSU) since 1981 for the treatment of selected brain tumors, with encouraging preliminary reports of efficacy.[13–15,18] While IA/OBBBD may improve progression free survival and outcomes in some chemosensitive tumors,[6,18–23] safety of this approach, especially in those with elevated intracranial pressure and seizure history, remains a major hurdle for clinical translation. In this study, we report a comprehensive retrospective analysis of the complications in 4939 procedures (IA or IA/OBBBD) that were performed in 436 patients.

Methods

Methods of the Study

Procedural and chemotherapy-related complications were retrospectively reviewed from a prospectively maintained database under approval of the OHSU's Institutional Review Board with informed consent obtained prior to initiating the therapy. We report patient demographics, vasospasm, seizure frequency, procedural and chemotherapy-related complications, chemotherapeutics, and degree of disruption (DD). Procedural complications were divided into 2 categories: minor (seizures, groin related, asymptomatic strokes, arterial dissections not requiring intervention, and transient neurological decline [TND]) or major (myocardial infarction [MI], cervical cord injury [CCI], symptomatic stroke, arterial dissection requiring intervention, and death within 3 days). All patients received IA or IA/OBBBD between December 10, 1997 and November 7, 2018 were included.

Evaluation Prior to Treatment

Preprocedural evaluation is similar for both procedures. All cases were discussed in a multispecialty tumor board prior to enrollment. Patients underwent baseline neuropsychological evaluation, electrocardiogram, and port-a-cath placement. Patients underwent neurologic exam and Karnofsky Performance Status (KPS) evaluation, gadolinium-enhanced magnetic resonance imaging (GdMRI) or computerized tomography (CT), chest X-ray, complete blood count with diff., basic metabolic panel or complete metabolic panel, and urinalysis at baseline and prior to each course. Ophthalmologic assessment was also routinely conducted. In addition, patients received carboplatin underwent monthly audiologic assessment.

Patients were admitted to the oncology ward on the eve of the procedure, maintained nil per oral overnight and hydration/alkalinization was initiated for patients receiving high dose methotrexate. Our clinical team consisted of neuro-oncologists, neuro-interventionalist, nurse practitioners, and oncology nurses. GdMRI was

obtained at least 4 hours prior to the procedure to avoid increased seizures previously reported in animal models.[24] GdMRI was performed to rule out increased intracranial pressure and to confirm the vascular territory to be disrupted. Furthermore, imaging was reviewed to confirm open quadrigeminal cistern and basal cisterns, absence of ventriculomegaly in contralateral frontal horn, and absence of uncal herniation prior to procedure.

IA. — Performed under conscious sedation (monitored anesthesia care) once every 4 weeks. Access to the right femoral artery was achieved with a 19-gauge needle and a 5 French diagnostic catheter introduced using Seldinger's technique. The left internal carotid artery (LICA) at C1–2 level, right internal carotid artery (RICA) at C1–2 level, and, depending on anatomy, either the right vertebral artery (RVA) or left vertebral artery (LVA) at C4–5 level were selectively catheterized. Chemotherapy (ie, carboplatin, melphalan, or methotrexate) was given after catheter placement was confirmed. After the procedure, patients were monitored overnight on the general oncology floor with routine postangiography precautions.

IA/OBBBD. — Performed under generalized anesthesia with IV propofol (avoiding other anesthetics is important since they may react with BBB) on 2 consecutive days every 4 weeks for up to 1 year or total of 12 cycles. On day of admission patients were hydrated with D5 1/2NS at 100–150 mL/h for a minimum of 6 hours. Patients were premedicated with an anticonvulsant (commonly levetiracetam) given the risk of increased seizures. Atropine was administered immediately prior to mannitol administration since OBBBD may cause bradycardia due to physiological impacts on the carotid body. Selective arterial catheterization (LICA vs RICA vs RVA vs LVA) was performed depending on the cerebral vascular territory planned to be treated as described above. OBBBD was performed by administering 25% mannitol (warmed to 37°C in a water bath to prevent crystallization) at a rate of 4–10 mL/s (precise flow rate is determined by use of fluoroscopy) for 30 seconds. To evaluate the DD, a nonionic contrast agent (750 mbq of Tc-99-glucoheptonate and 150 mL isovue 300 iopamidal)[16] was administered IV after OBBBD, and a CT was obtained prior to extubation. Previously reported scoring scale was used to document the DD by comparing enhancement in the disrupted to nondisrupted territory.[25] Using this scale, one of 4 grades were assigned: nil, moderate, good, or excellent. Upon completion, patients were transferred to the postanesthesia care unit followed by oncology ward for monitoring of vital signs, neurologic status, and fluid balance. IA/OBBBD was performed again the following day. Two vascular territory (RICA or LICA or vertebral artery) were accessed in total as determined by the neuro-oncology team to maximize delivery. Access of the vertebral artery was generally reserved to second day to minimize theoretical risk of development of brain stem symptoms after first day that may delay second day treatment.

Chemotherapy Regimen

For both IA and IA/OBBBD, in general, 2 chemotherapy regimens were used depending on tumor histology. The first regimen was used for glioma, primitive neuroectodermal tumor (PNET), germ cell tumor, and metastasis and consists of carboplatin (200 mg/m^2 each day, for a total dose of 400 mg/m^2) administered intra-arterially 5 minutes after IA/OBBBD, cyclophosphamide (330 mg/m^2 each day, for a total dose of 660 mg/m^2) administered IV 10 minutes before IA/OBBBD, followed by IV etoposide phosphate (200 mg/m^2 each day, for a total dose of 400 mg/m^2). Carboplatin is known to cause high-frequency hearing loss.[26] The otoprotective effect of administering IV sodium thiosulfate (STS) 2 hours after use of carboplatin and IA/OBBBD was published by our group.[27]

A second regimen was used for primary central nervous system lymphoma (PCNSL) and brain stem glioma. This regimen consisted of methotrexate (2500 mg each day, for a total dose of 5000 mg) administered intra-arterially, and IV cyclophosphamide (500 mg/m^2 each day, for a total dose of 1000 mg/m^2) and IV etoposide phosphate (150 mg/m^2 each day, for a total dose of 300 mg/m^2). In few cases, either dose alterations were made or melphalan was used as a single agent or in combination.

Medical Management

Granulocyte-colony stimulating factor (5 mg/kg) was given on days 3–9 or until the absolute neutrophil count was greater than 1000/mL in both chemotherapy regimens. In addition, patients receiving high dose methotrexate received IV hydration with $NaHCO_3$, titrated to achieve a urine pH > 6.5 and leucovorin rescue was initiated 36 hours following the first dose of methotrexate 80 mg IV followed by 50 mg IV or orally every 6 hours, for a total of 20 doses.

Statistics

Patient and procedure characteristics were summarized using descriptive statistics. The numbers and proportions of events were presented for each complication overall and by procedure type (IA vs IA/OBBBD). Since each patient had multiple procedures, a logistic mixed-effects model was used to compare the occurrence of complication after each procedure between IA vs IA/OBBBD and among types of chemotherapies (for seizures) while accounting for correlation among procedures within the same patient. All analyses were conducted using Stata/SE 16.1 (StataCorp LLP).

Common Terminology Criteria for Adverse Events Guidelines

Common Terminology Criteria for Adverse Events (CTCAE) guidelines were used to report chemotherapy-related complications. Given the long span of the study, both versions 3.0 and 4.0 were used. All versions can be viewed at CTCAE (cancer.gov). In brief, CTCAE guidelines outline severity grades 1–5 (grade 1: mild, grade 2: moderate, grade

3: severe, grade 4: life threatening, grade 5: death) and attribution grades 1–5 (grade 1: unrelated, grade 2: unlikely, grade 3: possible, grade 4: probable, grade 5: definite). In this study, we reported chemotherapy complications with an attribution ≥3, and a severity grade ≥3 based on CTCAE guidelines.

Results

Patient Characteristics and Procedures

4939 procedures were performed (1102 IA and 3837 IA/OBBBD) on 436 patients of whom 56.4% were male (246) with an average age (±SD) of 47.0 ± 20.8 (range: 1–82 years-old) (Table 1). A patient could receive IA followed by IA/OBBBD or vice versa depending on the clinical scenario; 301 patients received at least 1 IA and 253 patients received at least 1 IA/OBBBD. The average number of procedures per patient was 11 (range: 1–57). Various types of brain tumors have been treated including PCNSL (n = 115), glioblastoma (n = 79), oligodendroglioma (n = 64), metastatic tumors (n = 38), and others (Table 1).

For IA, a 3-vessel injection was performed, commonly including the RICA, LICA, and LVA. As such, these vessels were the most frequently treated (depending on clinical scenario and anatomical variations, other vessels were also used) (Table 1). The majority of arterial access sites were the right femoral artery (3006, 60.9%), however these were often alternated for patient comfort. In this series, initial access side was changed to the contralateral side due to scar tissue only in 4 (0.08%) procedures (Table 1). The most common chemotherapy agents used were: carboplatin alone (1306, 26.4%), carboplatin + melphalan (1297, 26.3%), methotrexate + carboplatin (1192, 24.1%), and methotrexate alone (835, 16.9%) (Table 2).

DD and Vasospasm

Vasospasm was seen in 812/6316 arterial catheterizations (7.7%). Vasospasm resolves with injection of warm mannitol and was not related to increase in complications.

Contrast-enhanced CT was performed after the procedure within the first hour, to evaluate the DD. The most common DD in our series was moderate, seen in 1522 (39.6%) procedures, followed by good in 1242 (32.3%), nil in 806 (21%) and excellent in 209 (5.4%) procedures. Assessment was not completed in 59 procedures due to inadequate image quality, unavailability of the imaging, or contrast allergy.

Procedural Complications. — Major and minor postprocedural complications are discussed below and outlined in Table 3. Major complications occurred in 39 procedures (IA: 12, 1.09%; IA/OBBBD: 27, 0.70%) performed on 35 patients. There was no significant difference between IA and IA/OBBBD (P = .292). MI was seen in 3 patients (IA: 1, 0.09%; IA/OBBBD: 2, 0.05%; P = .651), CCI in 6 patients (IA: 1, 0.09%; IA/OBBBD: 5, 0.13%; P = .739), symptomatic stroke in 21 procedures and in 19 patients (IA: 7, 0.63%; IA/OBBBD: 14, 0.36%; P = .228), arterial dissection requiring intervention in 3 patients (IA: 0, 0%; IA/OBBBD: 3, 0.08%;

Table 1. Demographics and Baseline Characteristics

Demographics	Cohort (n = 436)
Age (y)	47.0 ± 1.0 (range: 1–82)
Male	246 (56.4%)
Pathology	
PCNSL	115 (26.38%)
Glioblastoma	79 (18.12%)
Oligodendroglioma, grades II and III	64 (14.68%)
Metastatic brain tumor	38 (8.72%)
SCNSL (secondary CNS lymphoma)	37 (8.49%)
Embryological tumor	37 (8.49%)
Astrocytoma, grades II and III	34 (7.80%)
Pilocytic astrocytoma	10 (2.29%)
Brainstem glioma	6 (1.38%)
Atypical teratoid rhabdoid teratoma	4 (0.92%)
Choroid plexus tumor	3 (0.69%)
Ependymoma	3 (0.69%)
Acute myeloid leukemia	1 (0.23%)
Atypical neurocytoma	1 (0.23%)
Erdheim–Chester disease	1 (0.23%)
Ganglioglioma	1 (0.23%)
Neuroendocrine carcinoma	1 (0.23%)
Plasma cell tumor	1 (0.23%)
Procedures Performed (n = 4939)	
IA	1102 (22.22%)
IA/OBBBD	3837 (77.68%)
Artery catheterized[a]	
RICA	2144 times
LICA	2055 times
LVA	1561 times
RVA	469 times
Left common carotid artery (LCCA)	33 times
Right common carotid artery (RCCA)	16 times
Left external carotid artery (LECA)	22 times
Right external carotid artery (RECA)	16 times
Access site[b]	
Right groin	3006 times
Left groin	1937 times

LICA, left internal carotid artery; LVA, left vertebral artery; PCNSL, primary central nervous system lymphoma; RICA, right internal carotid artery; RVA, right vertebral artery.
[a]Three arteries were catheterized during IA compared to 1 artery at a time in IA/OBBBD.
[b]During 4 procedures 2 access sites were required.

Table 2. Chemotherapy Given and Risk of Seizures per Procedure

	Total	Seizure	Odds Ratio (95% CI)	*P*
Methotrexate alone	835 (16.9%)	81 (9.70%)	Reference	
Carboplatin alone	1306 (26.4%)	24 (1.84%)	0.14 (0.07, 0.29)	.000
Melphalan	150 (3.0%)	2 (1.3%)	0.18 (0.03, 0.98)	.047
Methotrexate + carboplatin	1192 (24.1%)	92 (7.72%)	0.97 (0.56, 1.69)	.919
Methotrexate + melphalan	156 (3.2%)	2 (1.28%)	0.15 (0.03, 0.73)	.018
Carboplatin + melphalan	1297 (26.3%)	5 (0.39%)	0.04 (0.01, 0.12)	.000
Temozolomide	3 (0.06%)	0 (0.00%)	Not defined	

All postprocedural seizures were seen in IA/OBBBD, except for 2, both of which were seen after carboplatin given IA (without OBBBD).

Table 3. Procedure-Related Complications

	Total (*n* = 4939)	IA (*n* = 1102)	IA/OBBBD (*n* = 3837)	Odds Ratio (95% CI)	*P*
Seizure[a]	206 (4.17%)	2 (0.18%)	204 (5.32%)	37.87 (8.25, 173.90)	<.001
Focal motor[b]	229 (4.63%)	4 (0.37%)	225 (5.86%)	Not applicable	
Within 30 min	179 (3.62%)	0 (0.00%)	179 (4.67%)	Not applicable	
Within 24 h	14 (0.28%)	1 (0.09%)	13 (0.34%)	Not applicable	
Within 3 d	16 (0.32%)	3 (0.27%)	13 (0.34%)	Not applicable	
Generalized[b]	38 (0.77%)	0 (0.00%)	38 (0.99%)	Not applicable	
Within 30 min	23 (0.47%)	0 (0.00%)	23 (0.60%)	Not applicable	
Within 24 h	11 (0.22%)	0 (0.00%)	11 (0.29%)	Not applicable	
Within 3 d	4 (0.08%)	0 (0.00%)	4 (0.10%)	Not applicable	
Myocardial infarction	3 (0.06%)	1 (0.09%)	2 (0.05%)	0.57 (0.05, 6.35)	.651
Cervical spine injury	6 (0.12%)	1 (0.09%)	5 (0.13%)	1.44 (0.17, 12.36)	.739
Arterial dissection	13 (0.26%)	0 (0.00%)	13 (0.34%)	Not defined	.086[c]
Requiring intervention	3 (0.06%)	0 (0.00%)	3 (0.08%)	Not defined	1.00[c]
Not requiring intervention	10 (0.20%)	0 (0.00%)	10 (0.26%)	Not defined	.130[c]
Asymptomatic stroke	60 (1.21%)	20 (1.81%)	40 (1.04%)	0.55 (0.30, 1.01)	.054
Symptomatic stroke	21 (0.43%)	7 (0.63%)	14 (0.36%)	0.55 (0.21, 1.45)	.228
Transient neurological decline	53 (1.07%)	11 (1.00%)	42 (1.09%)	1.37 (0.58, 3.25)	.469
Possibly related to seizure	8 (0.16%)	0 (0.00%)	8 (0.21%)	Not defined	.212[c]
Possibly related to metabolic	7 (0.14%)	3 (0.27%)	4 (0.10%)	0.38 (0.09, 1.71)	.209
Possibly related to excellent disruption/swelling	17 (0.34%)	0 (0.00%)	17 (0.44%)	Not defined	.019[c]
Groin complications	16 (0.32%)	10 (0.91%)	6 (0.16%)	0.15 (0.05, 0.46)	.001
Major complication	39 (0.79%)	12 (1.09%)	27 (0.70%)	0.66 (0.31, 1.42)	.292
Minor complication	330 (6.68%)	41 (3.72%)	289 (7.53%)	2.11 (1.37, 3.25)	.001
Total complications	365 (7.39%)	53 (4.81%)	312 (8.13%)	1.72 (1.17, 2.53)	.005

[a]Number of procedures complicated by at least 1 seizure.
[b]Total number of seizures per procedure (number of seizures per 100 procedures).
[c]Based on Fisher's exact test.

P = 1.00). In addition, 6 out of 436 patients (1.38%) died within 3 days (IA: 3, IA/OBBBD: 3).

Minor complications occurred in 330 procedures performed on 132 patients. Among the IA group, 34 patients experienced a minor complication in 41 (3.72%) procedures while 105 patients in the IA/OBBBD group did in 289 (7.53%) procedures (*P* = .001). This higher rate of minor complications can be attributed to seizures. Seizures were seen in 206 procedures (IA: 2, 0.18%; IA/OBBBD: 204, 5.32%; *P* < .001), asymptomatic stroke in 60 procedures (IA: 20, 1.81%;

IA/OBBBD: 40, 1.04%; $P = .054$), groin-related complications in 16 procedures (IA: 10, 0.91%; IA/OBBBD: 6, 0.16%; $P = .001$), arterial dissections not requiring intervention (IA: 0, 0%; IA/OBBBD: 10, 0.26%; $P = .130$), and TND in 53 procedures (IA: 11, 1.00%; IA/OBBBD: 42, 1.09%; $P = .469$).

We have used a similar time frame and criterion as other interventional neuroradiology procedures to define per-procedural deaths. Most of the patients in this study had advanced disease and underwent this therapy as a last resort. For this reason, it was challenging to differentiate between mortality secondary to progression, versus mortality secondary to the therapy. Considering the nature of the procedure, the relevant mortality would be from acute issues such as swelling, acute blood loss secondary to retroperitoneal hemorrhage or a large territory stroke/thromboembolic event. All of these effects would present within 72 hours of the procedure.

There is a difference between procedure number (4939) and selective arterial catheterization number (6316) because during IA, 3-vessel catheterization is performed, and with IA/OBBBD, 1-vessel catheterization is performed. When evaluating for the risk of arterial injury, selective arterial catheterization was taken into consideration.

Seizures.— Across the cohort, 70 (16.1%) patients had a seizure within 3 days after the procedure. A total of 267 seizures were documented in 206 procedures (some patients experienced multiple episodes of seizure after 1 procedure) (Table 3). The majority of seizures were focal motor (229/267, 85.7%) and occurred within 30 minutes of the procedure (179/267, 67%). None of the patients who received IA experienced a generalized seizure while 24 patients experienced 38 generalized seizures after IA/OBBBD; most occurred within 30 minutes (23/38, 60.5%). Of those patients that experienced a generalized seizure, the majority 17/24 (70.8%) had 1 seizure, 3 patients had 2 seizures, 2 patients had 3 seizures, 1 patient had 4 seizures, and 1 patient had 5 seizures, across all treatments.

The most common pathology complicated by seizures was PCNSL, in whom 56 (48.7%) patients experienced seizures, with 34 (60.7%) patients having more than 1 seizure. Other instances of seizures occurred in 1 patient with a grade II oligodendroglioma during 1 procedure, 6 patients across 17 procedures with grade III oligodendroglioma of which one was following IA, 4 patients with grade III astrocytoma of which one was following IA, 1 patient with metastatic breast cancer, 1 patient with a plasma cell tumor, and 1 patient with a germ cell tumor.

Seizures were seen after 204 (5.32%) IA/OBBBD procedure, a much higher occurrence compared to only 2 after 1102 IA procedure (0.18%; odds ratio [OR], 37.87, 95% CI 8.25, 173.90; $P < .001$) (Table 3). Seizures co-occurred with TND in 8 (3.8%) instances, but was not related to other complications. In these cases, the neurological exam returned to baseline within 1 week. The most common chemotherapeutic associated with postprocedural seizures was methotrexate either as monotherapy (81/835 cycles, 9.7%) or combination with carboplatin (92/1192, 7.7%) (Table 2). Likelihood of having a seizure after carboplatin monotherapy (OR, 0.14; 95% CI 0.07, 0.29; $P < .001$) or combination of carboplatin plus melphalan (OR, 0.04; 95% CI 0.01, 0.12; $P < .001$) was significantly lower compared to methotrexate alone.

Access Related (Groin) Complications.— In total, 4943 groin punctures were performed (3006 right, 1937 left). In 4 cases repeated access on the contralateral side was necessary due to scar tissue. The only complication related to access was groin hematoma, which was seen 16 times (0.3%, 12 right, 4 left). These resolved without intervention in 15 patients (93.7%); 1 patient required a blood transfusion. One patient presented to the emergency department with groin pain and associated hematoma, which resolved without intervention. Furthermore, 62.5% (10/16) was seen after IA.

Transient Neurological Decline.— Forty patients experienced TND following 53/4939 (1.07%) procedures. All recovered to baseline within 1 week. TND occurred in 11 (1%) procedures (IA) in 9 patients and 42 (1.09%) procedures (IA/OBBBD) in 31 patients ($P = .469$). While challenging to retrospectively assess the etiology, possibilities are seizures (8/53, 15.09%), metabolic derangement (7/53, 13.21%), and excellent DD and/or intracranial swelling (17/53, 32.08%) procedures.

Asymptomatic Imaging Findings Consistent With Stroke.— GdMRI was obtained monthly, prior to every treatment. Incidental and asymptomatic T2 changes in vascular territories, diffusion-weighted imaging (DWI) changes, and/or contrast enhancement in laminar pattern were observed following 60 of the 4939 procedures (1.21%) (IA $n = 20$ [1.81%], IA/BBBD $n = 40$ [1.04%]; OR, 0.55, 95% CI 0.30, 1.01, $P = .054$). Case example shown in Figure 1G.

Arterial Dissection (Intimal Injury).— Selective arterial catheterization was performed 6316 times (Table 1) and 13 of them (0.21%) were complicated by intimal injury. All injuries occurred during IA/OBBBD (Table 3). Vessels involved were: RICA (1), LICA (6), RVA (2), and LVA (4). Ten out of 13 healed with medical management. The remaining 3 required arterial stenting and healed without permanent deficits; the LICA was the vessel affected in all.

Symptomatic Stroke.— Twenty-one (0.43%) symptomatic strokes of varying sizes occurred, among which 7 (0.63%) occurred after IA and 16 (0.36%) after IA/OBBBD. There were no statistically significant differences between the 2 groups (OR 0.55, 95% CI 0.21, 1.45; $P = .228$). All were managed conservatively and most recovered within 1 month. Case example shown in Figure 1H.

Cervical Cord Injury.— Six patients (0.12%) (1 IA, 5 IA/OBBBD; $P = .739$) experienced CCI. In all occurrences, this complication was seen after injection of a vertebral artery. Symptoms typically started with shoulder and neck pain which progressed to neurologic deficits of varying severity. Details and imaging findings are described in Table 4 and case examples are shown in Figure 1C–F.

Myocardial Infarction.— MI was seen following 3 procedures (0.06%) (1 IA, 2 IA/OBBBD). One patient passed away from ST elevation MI. This patient was scheduled for a

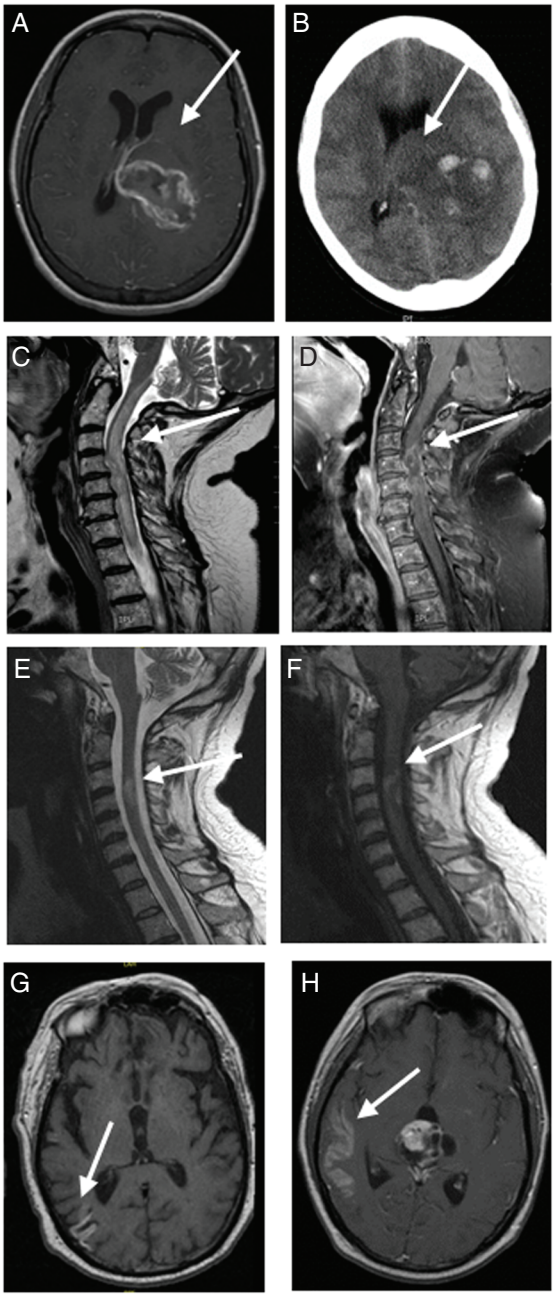

Figure 1. Representative images of rare adverse events. (A and B, case 1) Cerebral edema. 32 y/o female with a large left-sided thalamic grade III astrocytoma experienced neurological decline after first IA treatment. (A) Preprocedural axial T1-weighted post gadolinium MRI shows large tumor and associated edema (B) Postprocedural noncontrast CT head shows worsening edema with midline shift. (C and D, case 2) Cervical cord injury. Case 2. 59 y/o female with PCNSL experienced cervical cord injury after sixth treatment (LVA injection). (C) Sagittal T2-weighted MRI shows cervical stenosis and T2 cervical cord signal. (D) Sagittal T1-weighted MRI shows postcontrast enhancement of the involved region. (E and F) 39 y/o male with grade III oligodendroglioma experienced cervical cord injury after fourth treatment (RVA injection). (E) Sagittal T2-weighted MRI demonstrates a similar cervical cord injury with capacious spinal canal. (F) Sagittal T1-weighted post gadolinium MRI demonstrates contrast enhancement of the involved region. (G and H, cases 3 and 4) Asymptomatic strokes. (G, case 3) Axial T1-weighted post gadolinium MRI demonstrates an asymptomatic imaging change consistent with middle cerebral artery distribution stroke in a 73-year-old with frontal PCNSL. (H, case 4). White arrow points to the left posterior temporal region cortical/laminar enhancement axial T1-weighted post gadolinium MRI shows a symptomatic stroke in a 29-year-old male with atypical choroid plexus papilloma. White arrow points to cortical/laminar enhancement consistent with subacute infarct in the left temporal lobe. CT, computerized tomography; LVA, left vertebral artery; PCNSL, primary central nervous system lymphoma; RVA, right vertebral artery.

carotid stent placement for atherosclerotic disease and the decision was made to treat with IA at the same time. It is hard to assess if the MI is secondary to IA or to carotid artery stenting given the known risk of stenting.[23] The other 2 patients had inconsequential ECG changes.

Death Within 3 Days.— Six patients (1.38%, 6/436) died within 3 days of a procedure (3 IA, 3 IA/OBBBD). The first patient had respiratory distress and possible pulmonary embolism (PE) which was likely the cause of death. The second patient had confirmed PE after the procedure. The third patient had pulmonary edema and heart failure. The cause of death of the fourth and fifth patients remains unclear due to incomplete documentation. The sixth patient had significant brain swelling which caused brain herniation after IA and the family decided to proceed with comfort care Figure 1A and B. This is the only mortality clearly associated with the procedure.

Complications Related to Chemotherapy.— Chemotherapy complications with an attribution ≥3 (possibly, probably, and definitely related to chemotherapy) and a grade ≥3 based on CTCAE guidelines were identified. Across all treatments, 1392 chemotherapy complications occurred, and 359 (82.3%) patients had at least 1 such complication. Among these individuals, each patient had an average (±SD) of 3.9 ± 2.1 complications (range 1–13). As expected, the most common system affected was hematologic, followed by metabolic (Table 5).

Discussion

IA/OBBBD increases drug concentration compared to IA and is associated with improved outcomes in patients with chemosensitive brain tumors.[2,28–30] The data regarding procedural complications of these procedures are limited in the literature. Our data suggest that overall complication rate of IA or IA/OBBBD is similar if not fewer compared to published reports of diagnostic cerebral angiography (DCA), with the exception of rare instances of reversible IA/OBBBD-associated focal seizures. Asymptomatic imaging findings consistent with stroke after DCA has been reported to be ranging between 10% and 20%.[31–36] In our series, this specific complication is 1.2%. This difference may be due to the timing of the GdMRI and difference in

Table 4. Detailed Outline of Patients With CCI Following IA or IA/OBBBD

Diagnosis	Drugs	Procedure	Vessel	Time Course After Discharge	Muscle Strength Discharge/Laterality)	Steroid	STS	Age	Gender
Oligodendroglioma, grade III	Carboplatin	IA/OBBBD	RVA	3 d (progressive)	3/5 right side	+	+	39	M
Astrocytoma, grade IV	Carboplatin	IA/OBBBD	LVA	24 h (progressive)	2/5 left side	+	+	58	M
Astrocytoma, grade III	Carboplatin	IA	RVA	2 d (progressive)	0/5 right side	+	–	51	F
Ependymoma	Carboplatin	IA/OBBBD	LVA	3 d (progressive)	0/5 left side	+	+	13	M
PCNSL—B cell	Carboplatin + MTX	IA/OBBBD	LVA	24 h (progressive)	2/5 left side	+	+	59	F
Oligodendroglioma, grade III	Carboplatin	IA/OBBBD	RVA	3 d (progressive)	4/5 right side	+	+	43	M

CCI, cervical cord injury; IA/BBBD, intra-arterial chemotherapy with osmotic blood–brain barrier disruption; LVA, left vertebral artery; PCNSL, primary central nervous system lymphoma; RVA, right vertebral artery; STS, sodium thiosulfate.

stroke risk factors in our cohort compared to those undergoing DCA. The complications such as arterial dissection (0.2% our series vs 0.4% literature), groin complications (0.3% our series vs 0.4% literature), and TND (1% our series vs 0.4% literature) are also comparable to DCA.

Seizures were one of the most common minor complications. However, the seizures were associated with TND in 8 procedures (3.8%) and all patients who experienced seizures, returned to baseline within 1 week. Other investigators have described the incidence of seizures 6%–13% following OBBBD and often describe this in the context of prior seizure history.[19,21] In our series, only 5.32% of IA/OBBBD procedures were complicated by seizures. It is challenging to determine the influence of IA/OBBBD on seizure activity as this patient population common has history of seizures secondary to brain tumors. Other factors such as missed doses of antiepileptics, drug levels and frequency of seizures, could not be adequately ascertained by retrospective chart review. Future work should focus on protocols to further monitor and reduce this complication.

Asymptomatic imaging findings consistent with stroke (new T2-weighted and/or sDWI changes on MRI) were observed in 60 patients. Although rare, this was the most common complication. It was managed conservatively with no long-term sequelae. This complication is usually not reported in studies evaluating complications of DCA since follow-up GdMRI is not routinely obtained. Our patient population is unique in this perspective because they receive monthly GdMRI, allowing us to capture incidental findings that are consistent with stroke. As expected, patients receiving IA had a higher rate. This was most likely because all 3 vascular territories received treatment with each procedure, which required increased catheter manipulation. The rate of asymptomatic DWI changes following DCA is reported to be 10%–50% in the literature.[32,33,36] This is higher compared to our study. Symptomatic stroke rate was not significantly different comparing IA versus IA/OBBBD ($P = .228$). Careful endovascular technique and use of IV or IA heparin may even decrease this complication further.

Groin-related complications after cerebral angiography are well known and easily managed without causing significant long-term problems. In our series, the groin-related complication rate was very low without difference in laterality. Other known complications of such procedures include arterial injury, pseudoaneurysm, and infections.[34] These rare complications were not seen in our series. Groin-related complications were more common in patients receiving IA compared to IA/OBBBD ($P = .001$). During IA, 3 vascular distributions are treated, which require more manipulation of the catheter at the groin, possibly resulting in more hematomas. Using a femoral access sheath, utilizing micro access kit or adopting radial and distal radial access may decrease this complication further.[31] Arterial injuries were also rare, especially symptomatic or flow-limiting arterial injuries were even more uncommon. With novel catheters and guidewires, this complication is becoming even less common. Majority of the arterial injuries are treated with antiplatelet agents such as aspirin.

One unexpected complication of IA or IA/OBBBD is CCI. CCI presents as a relatively sudden but progressive onset of weakness in extremities within 72 hours of procedure. This has been reported previously by our group,[37] and it was discussed that the pathophysiology is probably multifactorial with vascular streaming and an atypical inflammatory reaction to carboplatin and etoposide. Laminar flow pattern in the anterior spinal artery may have a role in the pathophysiology of the CCI since the injury is centered at the C4–5 level. We have increased the infusion rate of carboplatin, and maintained the catheter placement at C6–7 to further reduce the risk. CCI following DCA has been reported in the context of preexisting cervical canal stenosis (CCS).[38] Unfortunately, since preprocedure cervical MRI is not routinely done in our cohort, it is impossible to establish a causal role. The sudden onset of new symptoms 24–36 hours after the therapy also suggests against preexisting CCS/traumatic injury secondary to hyperextension. The addition of OBBBD is not necessarily the cause of CCI since it occurred after IA in 1 case. Management of CCI is supportive with steroids and aggressive physical therapy. Future work should perhaps include pretreatment evaluation of CCS, which could enhance safety measures.

Table 5. CTCAE Guideline Complications Greater Than or Equal to Attribution 3 and Grade 3

Complication	
Gastrointestinal	34 events/27 patients
Cardiac	12 events/10 patients
Respiratory	19 events/15 patients
Metabolic	175 events/109 patients
Infection/inflammation	130 events/96 patients
Thrombosis	
Pulmonary embolism	9 events/9 patients
Deep vein thrombosis	21 events/21 patients
Not otherwise specified	22 events/22 patients
Eye	7 events/7 patients
Ear	5 events/5 patients
Allergy	9 events/9 patients
Renal	
Hematuria	5 events/5 patients
Renal failure	5 events/7 patients
Neurologic/psychiatric	46 events/32 patients
Endocrine	4 events/4 patients
Blood/bone marrow	
Hemoglobin	95 events/95 patients
Platelets	241 events/241 patients
Neutropenia	249 events/249 patients
Leukopenia	237 events/237 patients
Lymphopenia	49 events/49 patients
Decreased white blood cell (not otherwise specified)	23 events/23 patients
Others (malignancy and osteoporosis)	7 events/7 patients

Another very rare, but severe, complication is mortality secondary to intracranial swelling. This was seen in only 1 case. Swelling after OBBBD is common and monitoring serial neurological examinations and CT for assessment of DD is crucial in management. However, in very rare instances, even cautious application of IA may cause swelling Figure 1A and B. In this cohort, 6 patients died within 3 days of the procedure. One of these was clearly due to swelling, as described above, while the others were due to PE, MI, cardiac or pulmonary failure, or continued progressive disease with rapid clinical decline. If the patient is at high risk for swelling, IA should be considered first. This approach may especially be helpful in large chemosensitive tumors such as PCNSL and embryonal tumors where a rapid reduction in tumor volumes can be expected. Once the risk of increased ICP is mitigated treatment can be switched to IA/OBBBD.

Complications related to chemotherapy in this report may be higher compared to literature because IA or IA/OBBBD was used as second- or third-line therapies. Thus, patients are advanced in their disease process, and have already undergone multiple prior chemotherapies, possibly explaining the high rates of hematologic toxicities.

Ototoxicity related to IA carboplatin has been extensively reported, and was successfully managed with STS.[39] Similarly, our group has also previously reported progressive macular atrophy after IA/OBBBD.[40] This study is limited for this possible complication given limited follow-up. In our experience, these ocular findings rarely reach clinical significance. However, based on these rare preliminary findings, we have incorporated a routine long-term ophthalmology follow-up.

Potential benefits of IA have been shown in a variety of cancers. For example, IA chemotherapy in retinoblastoma is a gold-standard therapy with 60%–80% fewer enucleations.[41] Pulse-focused ultrasound guided BBBD[42] and OBBBD in rodent models both have been shown to increase proinflammatory signaling cascades promoting a sterile inflammatory environment. Early work in immunotherapies demonstrated that checkpoint inhibitors were most effective in inflammatory tumors. As CNS tumors are notoriously immunosupressive,[43] OBBBD may be able to transiently enhance local inflammation, increasing the efficacy of novel immune-modulatory agents such as checkpoint inhibitors in brain tumors. Our improved understanding of OBBBD, along with the addition of modern techniques and tools, may further increase safety and efficacy of this technique in the future. In the era of immune modulating therapies such as checkpoint inhibitors, OBBBD may have future use in synergistically activating an immune response in the brain.[44]

Conclusions

Our large dataset shows the overall safety and tolerability of IA or IA/OBBBD treatments as an option to increase chemotherapeutic delivery to brain tumors and brain around the tumor. Overall, the rate and severity of complications of IA or IA/OBBBD are not different compared to DCA. Severe complications that are persistent and affect the patient long term are uncommon. With the additional safety data outlined in this study, this technique has the potential to be widely applied to neuro-oncology practices. The efficacy of these techniques should be evaluated in future studies. Combining these techniques with novel agents including immunotherapeutics or gene therapy, may unlock new frontiers in our fight against brain tumors.

Keywords

blood–brain barrier | brain tumor | intra-arterial chemotherapy | neuro-oncology

Funding

This work was supported in part by National Institutes of Health grants CA199111, R13CA086959 and CA137488, and a Veterans Administration Merit Review Grant BX003897, the Jonathan D. Lewis Foundation, and by the Walter S. and Lucienne Driskill Foundation, all to E.A.N.

Conflict of interest statement. OHSU and Dr. Neuwelt have a financial interest in technology licensed to Fennec Pharmaceuticals, a company that may have a commercial interest in the results of this research and technology. This potential conflict of interest has been reviewed and managed by OHSU.

Authorship Statement. All authors have read and approved the final version. Implementation of the protocol: K.U., P.A., J.J.L., A.D., R.A.P., J.P.N., D.A.S., S.G., and E.A.N. Analysis and interpretation of the data: K.U., P.A., M.K.M., J.P.T., C.N.K., C.S.N., R.F., and E.A.N. Writing the manuscript: K.U., P.A., M.K.M., J.P.T., C.N.K., C.S.N., A.H., J.J.L., R.F., L.L.M., and E.A.N. Experimental design: E.A.N.

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