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CLINICAL STUDY

Children with DIPG and high-grade glioma treated with temozolomide, irinotecan, and bevacizumab: the Seattle Children's Hospital experience

Erin E. Crotty[1,2] · Sarah E. S. Leary[1,2] · J. Russell Geyer[1] · James M. Olson[1,2] · Nathan E. Millard[1] · Aimee A. Sato[3] · Ralph P. Ermoian[4] · Bonnie L. Cole[5,6] · Christina M. Lockwood[7] · Vera A. Paulson[7] · Samuel R. Browd[8] · Richard G. Ellenbogen[8] · Jason S. Hauptman[8] · Amy Lee[8] · Jeffrey G. Ojemann[8] · Nicholas A. Vitanza[1,2]

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Abstract

Introduction Beyond focal radiation, there is no consensus standard therapy for pediatric high-grade glioma (pHGG) and outcomes remain dismal. We describe the largest molecularly-characterized cohort of children with pHGG treated with a 3-drug maintenance regimen of temozolomide, irinotecan, and bevacizumab (TIB) following radiation.

Methods We retrospectively reviewed 36 pediatric patients treated with TIB at Seattle Children's Hospital from 2009 to 2018 and analyzed survival using the Kaplan–Meier method. Molecular profiling was performed by targeted DNA sequencing and toxicities, steroid use, and palliative care utilization were evaluated.

Results Median age at diagnosis was 10.9 years (18 months–18 years). Genetic alterations were detected in 26 genes and aligned with recognized molecular subgroups including *H3 K27M*-mutant (12), *H3F3A* G34-mutant (2), *IDH*-mutant (4), and hypermutator profiles (4). Fifteen patients (42%) completed 12 planned cycles of maintenance. Side effects associated with chemotherapy delays or modifications included thrombocytopenia (28%) and nausea/vomiting (19%), with temozolomide dosing most frequently modified. Median event-free survival (EFS) and overall survival (OS) was 16.2 and 20.1 months, with shorter survival seen in DIPG (9.3 and 13.3 months, respectively). Survival at 1, 2, and 5 years was 80%, 10% and 0% for DIPG and 85%, 38%, and 16% for other pHGG.

Conclusion Our single-center experience demonstrates tolerability of this 3-drug regimen, with prolonged survival in DIPG compared to historical single-agent temozolomide. pHGG survival was comparable to analogous 3-drug regimens and superior to historical agents; however, cure was rare. Children with pHGG remain excellent candidates for the study of novel therapeutics combined with standard therapy.

Keywords Pediatric high-grade glioma · Diffuse intrinsic pontine glioma · Temozolomide · Irinotecan · Bevacizumab

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✉ Nicholas A. Vitanza
Nicholas.Vitanza@seattlechildrens.org

[1] Division of Hematology/Oncology, Department of Pediatrics, Seattle Children's Hospital, University of Washington, 4800 Sand Point Way NE, M/S MB.8.501, PO Box 5371, Seattle, WA 98105, USA

[2] Fred Hutchinson Cancer Research Center, Seattle, WA, USA

[3] Division of Pediatric Neurology, Department of Neurology, University of Washington, Seattle, WA, USA

[4] Department of Radiation Oncology, University of Washington, Seattle, WA, USA

[5] Department of Laboratories, Seattle Children's Hospital, University of Washington, Seattle, WA, USA

[6] Department of Anatomic Pathology, University of Washington School of Medicine, Seattle, WA, USA

[7] Department of Laboratory Medicine, Genetics and Solid Tumor Diagnostics Laboratory, University of Washington and Seattle Children's Hospital, Seattle, WA, USA

[8] Division of Neurosurgery, Department of Neurological Surgery, Seattle Children's Hospital, University of Washington, Seattle, WA, USA

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Introduction

Pediatric high-grade gliomas (pHGG) are aggressive diseases with few long-term survivors [1]. pHGG encompass several malignancies, with anaplastic astrocytoma (AA; WHO Grade III) and glioblastoma (GBM; WHO grade IV) representing the most common histologies. Diffuse intrinsic pontine glioma (DIPG) is a discrete clinical entity arising from the pons included under the umbrella term pHGG, which is universally fatal with a historical median progression-free survival (PFS) of 7 months and median overall survival (OS) of 11.2 months [2]. Recent molecular discoveries have led to a new World Health Organization (WHO) classification, "diffuse midline glioma, H3 K27M-mutant" (DMG), to address the biologic link amongst fatal H3 K27M-mutant glioma of the pons, thalamus, and spinal cord [3]. The historical median 1-year OS for all pHGG is 69% for AA and 59% for GBM with the vast majority succumbing to their disease within 2 years [4]. Resection beyond biopsy is impossible in DIPG and often unattainable in other pHGG where lesions are infiltrative and invade critical structures. Ultimately, conformal radiation is the most impactful modality in prolonging survival and re-irradiation is the most efficacious therapy at recurrence [5–8]. Decades of research have been devoted to exploring cytotoxic agents as neoadjuvant, concurrent, or adjuvant therapies, yielding disappointing results and failing to improve survival [9–16]. While infants under 3 years of age with pHGG are often treated with intensive or prolonged post-operative chemotherapy regimens to delay or obviate radiation, children over 3 years of age are most often treated with focal radiotherapy [17, 18]. Rarely, craniospinal radiation (CSI) is required in the setting of metastatic disease or leptomeningeal dissemination.

In 2009, Seattle Children's Hospital implemented an institutional standard for treating patients with pHGG using a 3-drug maintenance regimen of adjuvant temozolomide (TMZ), irinotecan, and bevacizumab (BEV) following radiotherapy with concurrent TMZ. At the time, no consensus chemotherapy regimen was universally agreed upon and newly released data from the Phase 2 Children's Oncology Group (COG) study ACNS0126 demonstrated that single-agent TMZ during and after radiotherapy failed to improve pHGG survival compared to historical controls. While TMZ toxicity was mild and side effects were tolerable, the OS of 40% and 22% at 1 and 3 years, respectively, did not significantly improve upon a multi-agent chemotherapy regimen per CCG-945 [19–21]. Equipped with ACNS0126 data, we elected to add agents to a TMZ backbone for enhanced cytotoxic benefit and potential synergy. BEV, a monoclonal antibody targeting VEGF, was newly FDA-approved for adult HGG at recurrence, and, while tumor biology undoubtedly differs between adult and pediatric HGG, it was a well-tolerated agent with unconfirmed activity in newly diagnosed pHGG [22, 23]. Additionally, irinotecan demonstrated pre-clinical synergy with TMZ [24]. Ultimately, our institutional standard was informed by contemporary pre-clinical and clinical studies, as well as consideration of feasibility and tolerability in this vulnerable population.

Materials and methods

Patient selection/inclusion

We retrospectively reviewed the medical records of all patients under 21 years of age treated at Seattle Children's Hospital (SCH) between January 2009 and December 2018 with histologically confirmed pHGG (WHO grade III or IV), gliomatosis cerebri (prior to being removed as a distinct clinical entity in 2016), or a radiographic or histopathologic diagnosis of DIPG. Records were reviewed to determine first-line treatment, and data were extracted for patients who received initial therapy per our institutional standard. The collection and use of this retrospective data were approved by the SCH Institutional Review Board (IRB#14449).

Treatment

Standard therapy for pHGG in 2009 included maximal surgical resection (if feasible) followed by focal radiation. All patients reviewed in this cohort additionally received treatment with concurrent oral TMZ (90 mg/m^2/day) during radiotherapy followed by a maintenance regimen of oral TMZ (200 mg/m^2/day) for the first 5 days of the 28-day cycle, intravenous (IV) BEV (10 mg/kg/dose) every 2 weeks, and IV irinotecan (125 mg/m^2/dose) every 2 weeks. This regimen is abbreviated TIB. As our institutional standard of care, TIB was offered as one of several treatment options available at the time of diagnosis and no eligibility criteria were required to be met. Maintenance was given for 12 cycles. Supportive care measures included pre-medications, such as ondansetron for nausea and diphenhydramine to prevent infusion reactions. Oral trimethoprim-sulfamethoxazole (5 mg TMP/kg/day) was given twice weekly for prevention of pneumocystis jiroveci pneumonia (PJP). Corticosteroids were given at the discretion of the treating physician. Blood product transfusions were administered for anemia (hematocrit < 21%) and thrombocytopenia (platelets < 30,000/μL). MRI of the brain and spine with gadolinium contrast was performed at 3-month intervals or earlier for symptoms of possible progression/recurrence. A plain film X-ray of the tibial growth plate was obtained at the start of maintenance,

after 6 cycles, and at the end of therapy to monitor for BEV-associated osteonecrosis.

Molecular data collection

Molecular characterization was performed by UW-OncoPlex™, a targeted next-generation DNA sequencing panel designed to detect single nucleotide variants, small insertions and deletions, copy number alterations, selected gene-fusions, and microsatellite instability [25, 26]. DNA was extracted from formalin-fixed paraffin embedded tissue using the Qiagen GeneRead DNA FFPE Kit (Qiagen, Valencia, CA). Extracted DNA was sheared and sequencing libraries were prepared using KAPA HyperPrep reagents (Roche, Wilmington, MA). Prepared libraries were hybridized to a set of custom probes designed to target panels of genes chosen for their importance in diagnosis, prognosis, and/or treatment (UW-OncoPlex^{TM} versions 4, 5, and 6 targeted exonic and select intronic regions of 199, 262 and 340 genes respectively). Libraries were then sequenced on Illumina NextSeq500 and HiSeq2500 systems (Illumina, San Diego, CA), and sequences were processed through an automated, custom-designed bioinformatics pipeline prior to analysis. For patients with insufficient tumor tissue for DNA extraction, we performed immunohistochemical (IHC) staining for the H3 K27M-mutant protein.

Survival analyses

Statistical endpoints included overall survival (OS), defined as the duration between the date of diagnosis and date of either death from any cause or last follow-up, and event-free survival (EFS), defined as date of diagnosis to date of progression or recurrence. The date of diagnosis was defined as the date of initial biopsy/resection or, in the case of unbiopsied DIPG, the initial MRI. Progression and recurrence were primarily defined radiographically, with confirmation by the SCH multidisciplinary pediatric brain tumor board. Statistical analyses were performed using the Kaplan and Meier method with STATA software version 11. Survival comparisons were performed via log-rank test.

Results

Sixty-one patients with pHGG were treated during the specified timeframe, of whom 36 (10 DIPG and 26 pHGG) received TIB therapy. Patients not treated with TIB elected to enroll on clinical trials (9), receive radiation with or without concurrent temozolomide and without maintenance therapy (13), or declined tumor-directed therapy (3). The cohort of 25 patients treated with alternative regimens were of similar age and gender distribution to our TIB cohort but were primarily composed of patients with DIPG (18) due to clinical trial availability. Among the 26 pHGG patients, pathology included AA (7), GBM (10), glioma NOS WHO III-IV (4), and gliomatosis cerebri (5). The median age at diagnosis was 10.9 years (range 1.5–18.8), with even gender distribution between males (18, 50%) and females (18, 50%). Metastatic disease was present at diagnosis in four (11%) patients, with an additional seven (22%) developing metastatic lesions at progression or recurrence. Tumor resection was performed in 15 patients with a gross total resection (GTR) achieved in 7. Four of these patients required two neurosurgeries to achieve a GTR prior to starting radiation, and one patient underwent a total of three resections. Among DIPG patients, a diagnostic biopsy was obtained in 6/10 (60%).

Focal radiation was delivered in fractionated doses, with a total dose ranging from 50.4 to 60 Gy. CSI ranging from 36 to 39.6 Gy was delivered to four (11%) patients. Notably, three infants under 3 years of age at diagnosis were treated with TIB and upfront radiotherapy. These included patients with DIPG (1), spinal pHGG (1), and localized supratentorial pHGG (1). The latter was a 1-year-old for whom the decision to treat with TIB was determined by a strong family preference based on perceived quality of life and who remains a long-term survivor.

The median duration of maintenance TIB therapy was 271 days, with 15 (42%) patients completing all 12 cycles of maintenance chemotherapy. Therapy was discontinued for progressive disease in 14 (39%), infection in 1 (3%), and patient/family preference in 6 (17%), among whom all 6 patients had some degree of TMZ intolerance. Patient/families opted for a variety of subsequent therapies at disease recurrence/progression as listed in Table 1.

Toxicity

Maintenance therapy was well-tolerated. TMZ was the most commonly modified drug, with 66.7% of patients requiring one or more dosing modifications. Most common adverse effects resulting in drug suspensions included thrombocytopenia (10/36, 28%) and nausea/vomiting (7/36, 19%) (Fig. 1). Transfusions with red blood cells were required in 7/36 (19%) and platelets in 6/36 (17%). Neutropenia was infrequent and did not necessitate granulocyte colony stimulating factor (G-CSF). In one patient, TIB was discontinued due to progressive disease, with imaging showing calcifications concerning for a prior intracranial bleed but without evidence of acute hemorrhage on brain MRI. This patient did not require any interventions. Chemotherapy was administered in an ambulatory infusion center and inpatient hospitalizations during maintenance were uncommon, occurring in ten patients with a median inpatient stay of 8.5 days (range 0–26 days). Reasons for admission included infection

Table 1 Clinical characteristics and treatment

Clinical features	N	(%)	Treatment at diagnosis	N	(%)	Treatment at recurrence/progression	N	(%)
Anatomic location			Extent of resection[b]			DIPG		
Supratentorial	13	(36.1)	DIPG			No tumor-directed therapy	3	(30)
Deep brain	8	(8.3)	Biopsy only	6	(60)	Re-irradiation only	0	(0)
Brainstem	11	(30.6)	No surgical intervention	4	(40)	Chemotherapy + re-irradiation	4	(40)
Spinal cord	4	(11.1)	pHGG			Chemotherapy alone	3	(30)
			Biopsy only	11	(42.3)	pHGG		
Pathology			Subtotal (STR)	8	(30.8)	No tumor-directed therapy	14	(53.8)
DIPG	10	(27.8)	Gross total (GTR)	7	(26.9)	Re-irradiation only	1	(3.8)
Anaplastic astrocytoma	7	(19.4)				Chemotherapy + re-irradiation	1	(3.8)
Glioblastoma	10	(27.8)	Radiation therapy			Chemotherapy + re-irradiation + resection	2	(7.7)
Glioma NOS, WHO III-IV[a]	4	(11.1)	Focal	32	(88.9)	Chemotherapy + stereotactic surgery	1	(3.8)
Gliomatosis cerebri	2	(5.6)	Focal dose range	50.4–60 Gy		(gamma knife)		
WHO grade II histology			CSI	4	(11.1)	Chemotherapy + resection	1	(3.8)
Gliomatosis cerebri	3	(8.3)	CSI dose range	36–39.6 Gy		Chemotherapy alone	6	(23.1)
WHO grade III histology								
			Maintenance TIB			Chemotherapy agents[c]		
Metastases			Median duration (days)	271		Continued TIB	3	(8.3)
Metastatic	4	(11.1)	Range (days)	0–365		Etoposide	9	(25)
Localized or locally	32	(88.9)	> 6 cycles	28	(77.8)	Bevacizumab	7	(19.4)
invasive			< 6 cycles	8	(22.2)	Lomustine	2	(5.6)
						CAR T cells[d]	1	(2.8)
						Nivolumab	1	(2.8)
						Palbociclib[d]	1	(2.8)
						Temozolomide	1	(2.8)
						Trametinib	1	(2.8)

CAR chimeric antigen receptor, *CSI* craniospinal irradiation

[a]Needle biopsies did not provide sufficient material for accurate histologic grading

[b]Extent of resection achieved prior to starting radiation

[c]Some patients received more than one chemotherapy agent

[d]Participants in unpublished clinical trials

(respiratory and skin/soft tissue), malnutrition, feeding intolerance, nausea/vomiting, and ataxia. Two patients required prolonged admissions (43 and 97 days) secondary to complications from poor wound healing that were present prior to maintenance chemotherapy and in each case the initiation of BEV was delayed to facilitate healing.

Supportive care and corticosteroids

Palliative care intervention at SCH is championed as a critical component of a multidimensional supportive care approach. Median time to palliative care referral was 52 days from diagnosis (range 0–713 days), almost always prior to progression/recurrence, with nine patients establishing care prior to the start of TIB maintenance. Our institutional standard emphasizes limited corticosteroids, often exclusively as a bridge from diagnosis to radiotherapy. We found a median of 64 total days of corticosteroid treatment (range 2–602 days), including use at diagnosis, progression/recurrence, and end of life. We found 8/36 (22%) patients were receiving steroids at the initiation of TIB, 1/31 (3%) at the start of maintenance course 6, and 1/16 (7%) at the start of maintenance course 12. Comparatively, DIPG patients showed similar average usage to other pHGG patients, with the longest utilization (602 days) seen in a patient whose prolonged corticosteroid requirement occurred 191 days after completion of TIB and during participation in an immunotherapy trial.

Molecular

SCH pediatric neurosurgical expertise permits DIPG biopsy and, overall, 32 patients (89%) underwent diagnostic biopsy or resection, with one tumor specimen obtained at autopsy. Thirty-one patients (86%) had tumor tissue available for molecular testing, with missing sample procurement ($n = 5$) attributed to insufficient material ($n = 1$),

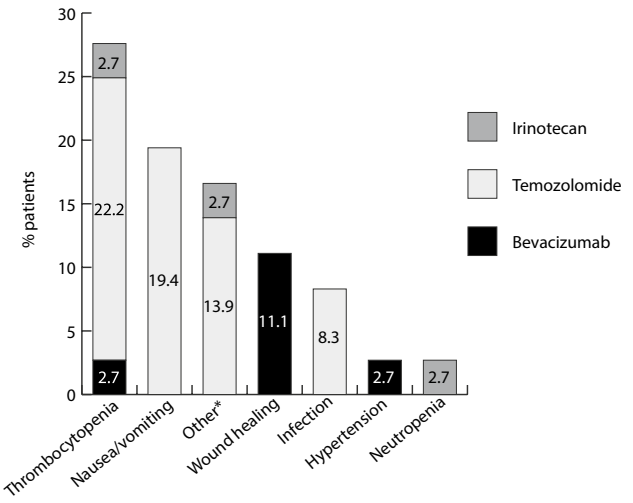

Fig. 1 Toxicity leading to therapy modification. Reported indications for interruptions in dosing of TIB therapy, delineated by suspected agent. *Other includes toxicities not documented or chemotherapy held for patient preference

family declining biopsy and/or autopsy ($n=3$, all DIPG), or neurosurgery and sample storage at another institution ($n=1$). IHC for H3 K27M alterations was performed in 3/5 patients who had insufficient material for DNA extraction but was unable to distinguish between mutations in *H3F3A*, *HIST1H3B*, or *HIST1H3C*.

Recurrent alterations were detected in 26 genes and revealed a heterogenous group of genomic profiles consistent with our current understanding of the molecular diversity of pHGG (Fig. 2). Hypermutant profiles were detected in four patients, among whom two patients had associated germline alterations in *MSH2* or *MSH6*. Recurrent alterations were detected in well-described pHGG tumor suppressor genes, along with pathways involving chromatin or transcriptional remodeling, cell cycle regulation, and receptor tyrosine kinase/RAS/PI3K signaling. *TP53* mutations were the most common overall (18/24 non-hypermutator patients; 75%), followed by alterations in *ATRX* (8/24; 33%), *NF1* (7/24; 29%, germline in 1), *CDKN2A/B* (7/24; 29%), *IDH1 R132H* (4/24; 17%), and *PI3KCA* (5/24; 21%), with gene amplifications in *EGFR* (2/24; 8%), *KIT* (3/24; 13%), *PDGFRA* (3/24; 13%), *MET* (2/24; 8%), and *VEGFR2* (3/24; 13%). As expected, two DIPG tumors with *HIST1H3B* mutations also harbored abberations in *AVCR1*, which encodes ALK2 [27]. Additional details on molecular alterations are listed in Supplemental Fig. 1.

Survival

Median EFS and OS for patients with DIPG was 9.3 and 13.3 months, respectively. This corresponded to a survival 80%, 10%, and 0% at 1, 2, and 5 years. The OS of our DIPG cohort did not appear to be increased solely due to re-irradiation, as when we excluded the four patients who received re-irradiation the OS remained largely unchanged at 13.0 months. In the remaining pHGG cohort, respective median EFS and OS was 16.2 months and 20.1 months, with 85%, 38%, and 16% of patients alive at 1, 2, and 5 years (Fig. 3a, b). *H3 K27M* mutations ($n=12$) correlated with inferior survival when compared to patients without *H3 K27M* alterations (median EFS of 9.9 vs. 20.6 months; $p<0.002$) with 0% survival at 5 years in those with H3 K27M-mutant tumors (Fig. 3c). Greater extent of pHGG resection, as demonstrated by seven patients who achieved a GTR, resulted in a median EFS of 21 months, versus 13.1 months in patients who underwent biopsy or subtotal resection (STR) ($p=0.05$). Excluding patients with DIPG and/or *H3 K27M* mutations from this analysis amplified the survival difference between groups by extent of resection ($p=0.08$), with a median OS of 22.8 months among 14 pHGG patients who achieved biopsy/STR vs. 41.5 months in five patients with a GTR (Fig. 3d). Deaths were attributed to tumor progression in all but one patient, who died from sudden unexplained death due to epilepsy (SUDEP) more than 3 years following completion of GTR, radiation, and TIB therapy for a localized GBM.

Discussion

Our single-center experience demonstrates tolerability of a 3-drug maintenance regimen for children with DIPG and pHGG. Our TIB regimen resulted in comparable survival to other published results of this approach (Table 2), as well as superior survival compared to historical single-agent regimens and nearly all other published treatment strategies. Notably, our DIPG cohort experienced an improved 1-year OS of 80% [95% CI 41–95%] compared to a historical survival of 45.3% using International DIPG Registry (IDIPGR) data or 40% [95% CI 27–53%] with single-agent temozolomide on ACNS0126 [2, 19].

While data from relatively large trials such as HERBY and ACNS0126 has left the standard treatment for pHGG beyond focal radiotherapy unclear and the roles of TMZ and BEV disputed, recent studies support this 3-drug regimen [28–30]. Our cohort of 36 patients over a 10-year follow-up period confirms these findings with a cumulative 79 patient-years treated, along with the insight of molecular and supportive care characterization. In our pHGG cohort, not including DIPG, we found similar outcomes to those

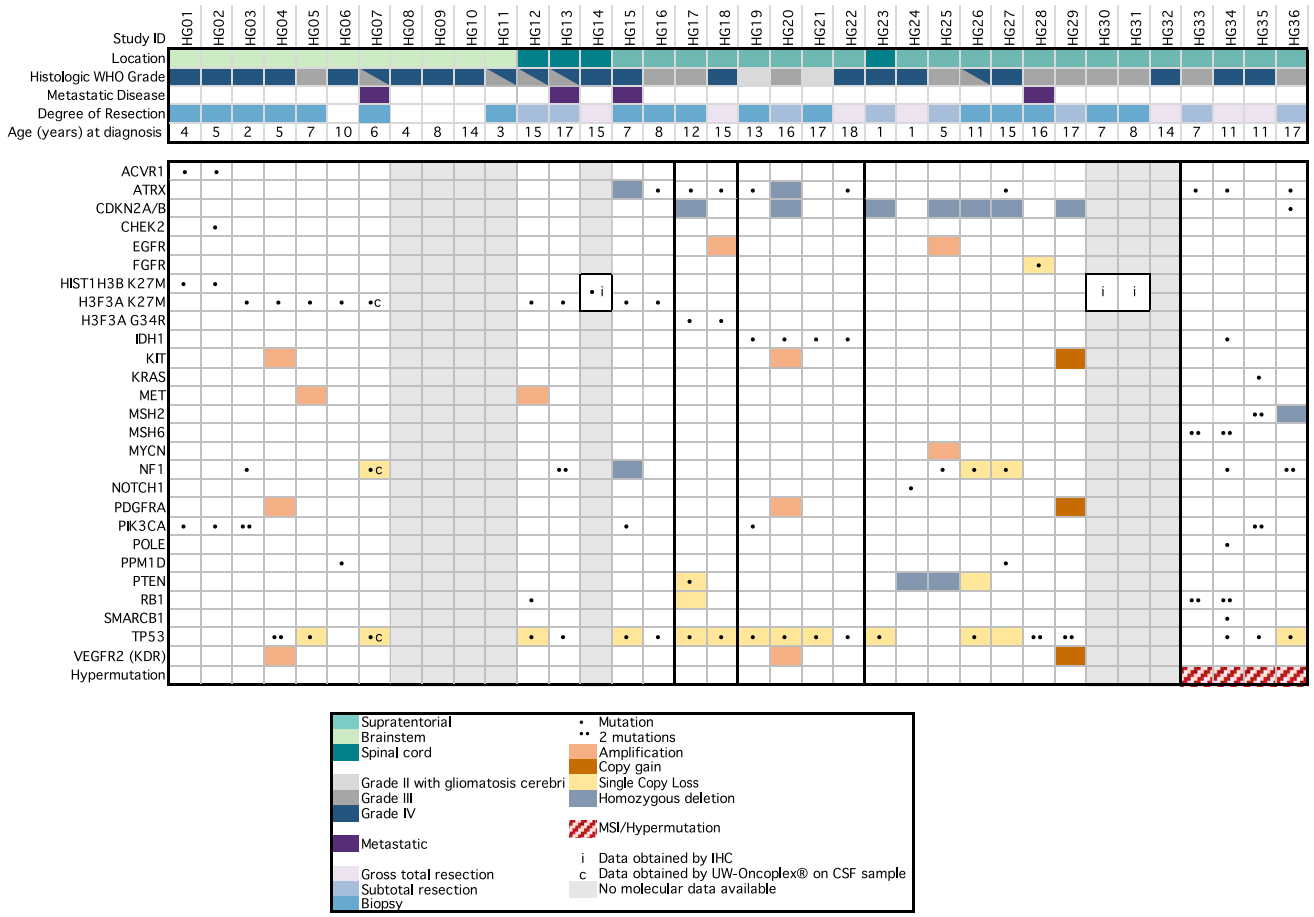

Fig. 2 Molecular characteristics. Genetic alterations were detected in 26 genes by UW-OncoPlex^{TM} or IHC (in the case of one patient) on tumor tissue obtained from 29 patients at diagnosis, recurrence, or autopsy. Clinical features describe status at diagnosis including tumor location, histologic WHO grade, presence of metastatic disease, and patient age. Recurrently mutated genes are grouped and align with recognized molecular subgroups from left-to-right: (1) H3 K27M-mutant, (2) *H3F3A* G34-mutant, (3) *IDH*-mutant, and (4) hypermutation. Hypermutator signatures were identified in four patients with alterations spanning the majority of genes, therefore only select mutations are depicted (right of figure)

reported by Hummel et al., with an improved 1-year OS (85% [95% CI 64–94%]) with this regimen compared to the 2-drug regimen studied in the HERBY trial, which showed a decrement in survival when BEV was added to standard radiotherapy plus TMZ. In that pediatric study, median EFS and OS at 1 year were 8.2 months and 75% [95% CI 61–84], respectively, in the BEV-treated arm [31]. Our results may suggest an important role of irinotecan for mechanistic synergy or, moreover, the added benefit of a multi-agent regimen. However, it is also important to note the inherent limitations and challenges of comparing our retrospective analysis with a randomized controlled trial, which may have narrower eligibility criteria, more uniform patient population, and more detailed collection of adverse events. TIB was offered as an institutional standard of care, therefore patient participation was not randomized and may have been subject to provider and selection bias.

This retrospective review also replicates the well-described survival benefit in pHGG patients who achieve maximal surgical resection or GTR [32]. It is notable that amongst seven patients who achieved a GTR prior to initiating radiation, five underwent multiple surgical resections. In light of this apparent outcome benefit, we advocate for thoughtful, repeat resection upfront with the aim of removing all detectable disease when feasible. However, the authors realize that this observation may also reflect the biologic implications of midline tumors that are more often located in eloquent cortex or brainstem regions and may only be amenable to biopsy. For the larger subgroup of patients who had residual disease following resection, radiographic treatment response was not captured in this study largely due to a lack of universal imaging standards for analysis and evolution in imaging sequences during

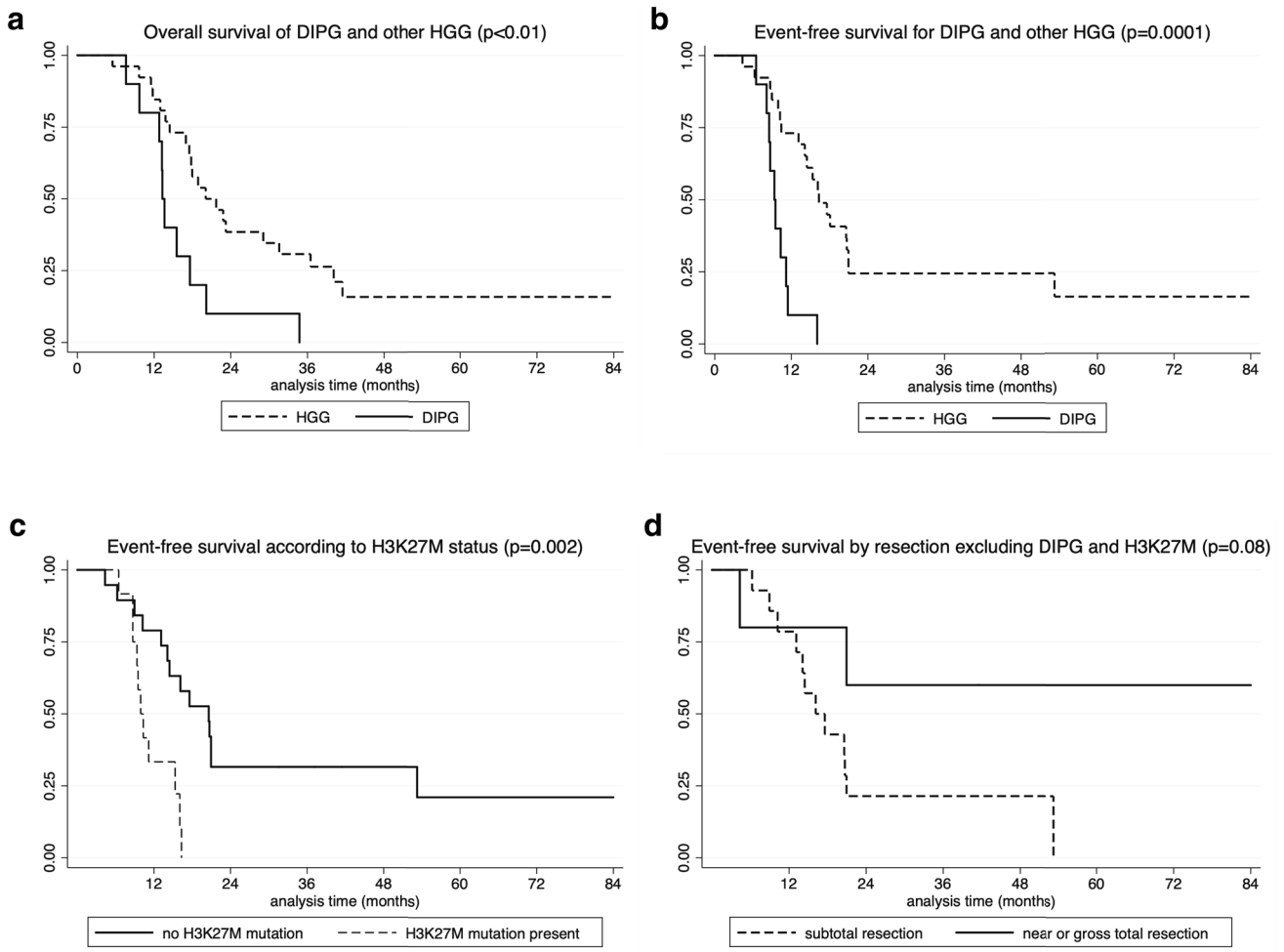

Fig. 3 Survival outcomes. Estimates of overall survival (**a**) and event-free survival (**b**) for patients with DIPG ($n=10$) and other pHGG ($n=26$) treated with a maintenance TIB regimen following radiotherapy with concurrent temozolomide ($p<0.01$ and 0.0001, respectively). **c** EFS for patients with ($n=12$) and without ($n=19$) alterations detected in H3 K27M ($p=0.002$). **d** EFS by extent of resection of pHGG patients who received a GTR ($n=5$) vs. biopsy or STR ($n=14$) prior to radiation ($p=0.08$). **d** Excludes patients with DIPG or H3 K27M mutations, as GTR was largely unachievable due to tumor location

the study timeframe, but would be critical endpoints to evaluate in prospective studies.

This is the largest published cohort of pediatric patients treated with TIB to be molecularly characterized. While our patient numbers are too limited to draw prognostic conclusions, the mutational frequencies identified follow known biological subgroups including adolescent pHGG with *IDH1/ATRX/TP53* mutations, younger DMG patients with H3.3 K27M-mutant tumors, and hypermutator profiles. Our data support clustering of *ATRX, IDH1*, and *TP53* alterations in pHGG, as has been previously described [1, 33], with *IDH1* mutations localizing exclusively to supratentorial tumors. As demonstrated in the post hoc analysis of the HERBY trial, pHGG tumors harboring alterations in the MAPK pathway had improved survival with the addition of BEV [33]. It is possible that our cohort contained a greater proportion of MAPK-altered tumors, conferring a small benefit with this 3-drug regimen. Of note, UW-OncoPlex™ has been updated with additional genetic mutations as they became clinically relevant. Specifically, *ACVR1* alterations were not evaluated on earlier versions, possibly resulting in an underestimation of the true incidence.

The toxicity profile of TIB was similar to published data for single-agent TMZ, irinotecan, or BEV and concurrent delivery was not overly toxic. Concerns about potential negative effects of BEV on vasculature homeostasis were not borne out, nor did we find an increased incidence of metastatic disease at progression/recurrence (7/36, 19%) as compared to reports of non-BEV-containing regimens (4/15, 27%) [34]. TIB was well-tolerated and would be practical to administer in a variety of clinical settings.

Table 2 Historical survival

	Study	Treatment	Year	N	Median EFS (months)	Median OS (months)	1 year EFS (95% CI)	1 year OS (95% CI)
pHGG	Seattle	RT + TMZ TMZ + irinotecan + BEV	2009–2018	26	16.2	20.1	73 (52–86)	85 (64–94)
	Grill et al. HERBY	RT + TMZ + BEV TMZ + BEV	2011–2015	60	8.2 (7.8–12.7)		38 (26–51)	75 (61–84)
		RT + TMZ; TMZ		56	11.8 (7.9–16.4)		48 (35–61)	68 (54–78)
	Hummel et al. Cincinnati/Lurie	RT + TMZ + BEV TMZ + irinotecan + BEV	2009–2013	12	15.2	25.4	92 (77–100)	92 (77–100)
	Cohen et al. ACNS0126	RT + TMZ TMZ	2002–2004	90			38 (27–47)	
DIPG	*Cooney et al.* *DIPG Registry*		*2004–2014*	*372*	*7.0*	*11.2*	*19.2*	*45.3*
	Seattle	*RT + TMZ* *TMZ + irinotecan + BEV*	*2009–2018*	*10*	*9.3*	*13.3*	*10 (1–36)*	*80 (41–95)*
	Hummel et al. *Cincinnati/Lurie*	*RT + TMZ + BEV* *TMZ + irinotecan + BEV*	*2009–2013*	*15*	*8.2*	*10.4*		
	Zaky et al. *CHLA*	*RT + TMZ* *TMZ + irinotecan + BEV*	*2007*	*6*	*10.4 (7.9–12.8)*	*14.6 (11.8–17.4)*		
	Cohen et al. *ACNS0126*	*RT + TMZ; TMZ*	*2004–2005*	*63*	*6.1*	*9.6*	*14 (13–15)*	*40 (38–42)*

Median, overall, and event-free survival on selected clinical studies of comparable regimens in pHGG, sorted by year. DIPG cohorts are highlighted in italics

RT radiation therapy, *RT + TMZ* temozolomide given during radiation, *Cincinnati* Cincinnati Children's Hospital Medical Center, *Lurie* Ann & Robert H. Lurie Children's Hospital of Chicago, *CHLA* Children's Hospital of Los Angeles)

The role of supportive care in DIPG and other pHGG outcomes is an active area of study, which we hope to enhance by our report of early palliative care referral and limited corticosteroids. SCH encourages palliative care referral at diagnosis and is participating in a prospective study evaluating whether early referral improves patient-reported symptom burden and Quality of Life (QOL) amongst a broader cohort of patients [NCT01838564]. Published data on corticosteroid use for symptom management is sparse; however, the myriad of side effects and negative effects on QOL in pediatric patients are well-characterized [35, 36]. Pre-clinical observations also support corticosteroids' detrimental effects on brain tumor treatment due their role in repairing the blood–brain barrier and limiting chemotherapy delivery [37, 38]. Overall, we strongly support the use of supportive care measures that may translate to an improved QOL, especially for these frequently fatal diseases.

While previous reports vary regarding the utility of single-agent TMZ, irinotecan, or BEV, as well as that of TIB, our cohort demonstrates improved 1-year OS in DIPG and comparable survival in other pHGG with this regimen. Nonetheless, cure was rare for pHGG and absent for DIPG. Ultimately, this treatment strategy may best serve as a backbone for additional agents, including molecularly-targeted or immunotherapeutic. Furthermore, a subset of patients searching for potential improvement in QOL or modest survival benefit, who are unable to enroll in early phase studies due to geographic or economic barriers and/or who do not meet study enrollment criteria, could benefit from this regimen.

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Data availability All data generated or analysed during this study are included in this published article [and its supplementary information files].

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This retrospective chart review study involving human participants was in accordance with the ethical standards of our institutional and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Institutional Review Board of Seattle Children's Hospital approved this study (IRB#14449).

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