Clinical and Molecular Features of Disseminated Pediatric Low Grade Glioma - A Systematic Review of Literature

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Abstract

INTRODUCTION

Gliomas account for approximately 46% of all pediatric CNS tumors. There is growing awareness of pediatric low-grade gliomas (PLGG) that disseminate to distant parenchymal or leptomeningeal locations either at the time of initial diagnosis or upon disease surveillance. Disseminated PLGGs (dPLGGs) are associated with a poorer prognosis than non-disseminated PLGGs. To date there is no comprehensive report characterizing the genome profile of dPLGGs and their associated management. This systematic review aims to identify the pattern of genetic alterations and treatment outcomes described for dPLGG.

METHODS

A systematic review of the literature was performed to identify relevant articles. A quality and risk of bias assessment of articles was done using the GRADE framework and ROBINS-I tool, respectively.

RESULTS

Fifty-two studies published from 1994 to 2020 were included in this review with 368 cases reported. There was sporadic reporting of genetic alterations. The most common genetic alteration observed among study subjects was 1p deletion (76%) and *BRAF-KIAA1549* fusion (55%). *BRAF* p.V600E mutation was found in 7% of subjects. A higher proportion of cases demonstrated primary dissemination compared to secondary dissemination (65% vs 25%). First-line chemotherapy consisted primarily of an alkylation-based regimen and vinca alkaloids. Surgical intervention ranged from biopsy alone to surgical resection and CSF diversion, and depended largely upon tumor location and timing of dissemination. Overall, 73% of cases were alive at last follow-up (median, 40.2 months). All studies reviewed either ranked low or moderate for both quality and risk of bias assessments.

CONCLUSION

While 1p deletion and *BRAF-KIAA1549* fusion are the most commonly described molecular alterations in dPLGG, these tumors appear to express heterogeneous molecular and biological characteristics distinct from non-disseminated PLGGs. Additional studies on the molecular and biological features of these tumors are needed to better understand the pathogenesis of dPLGG and to inform the development of additional targeted regimens.

Introduction

Central nervous system (CNS) tumors are the most frequent solid tumors in children, with a prevalence of approximately 5.6 diagnoses per 100,000.¹ Gliomas of the brain and spinal cord are the most frequent subtype, accounting for approximately 45.7% of all pediatric CNS tumors.² Classified as World Health Organization (WHO) grade I or grade II malignancies, pediatric-type low-grade gliomas (PLGG) occur more commonly in early childhood compared to high-grade gliomas which are more common in older children.¹ While adult LGGs have a predilection for the cerebral hemispheres and often undergo a malignant transformation, PLGGs can arise throughout the neuro-axis and are less likely to transform.^{3,4,5,6,7}

The ubiquity of magnetic resonance imaging (MRI) has resulted in an increased detection rate with increased reporting of dissemination of PLGGs throughout the leptomeninges, a phenomenon previously thought to be rare.^{8,9,10,11,12} Dissemination can be present at the time of initial diagnosis with or without an identifiable primary CNS lesion (primary dPLGG) or at the time of disease progression (secondary dPLGG).^{8,9,11,13,14} Recent advances in genetic sequencing and molecular alteration profiling have led to a better understanding of genetic alterations in PLGGs and has also demonstrated fundamental molecular differences between pediatric and adult low grade gliomas. Commonly identified alterations in PLGG include *BRAF* p.V600E, *BRAF* duplication, and *FGFR* alterations.^{5,7,15} While isocitrate dehydrogenase (*IDH* 1/2) mutation is the most common driver in adult low grade glioma, this mutation is rare in PLGG.^{16,17,18} Currently, however there is no comprehensive report collating the molecular landscape of dPLGG.

Management of PLGG typically begins with surgical resection or biopsy, depending upon the location and nature of the disease at diagnosis. When possible, gross total resection of PLGG offers the most favorable predictor of long-term outcome with 10-year survival of greater than 90%.^{10,19,20} When total resection is not possible or safe, the survival rate is predictably lower (50-85%).^{10,14,19,20} Disseminated PLGG demonstrates a variable prognosis as some tumors run an indolent clinical course with prolonged progression free survival while others exhibit a very aggressive behavior.^{10,12,15,21,22} A median survival of 48 months (range, 5-175 months) has been reported in literature.¹² Optimum therapy for dPLGG including the role of expectant management is unknown. In most cases, radiotherapy and alkylating-agent-based chemotherapy is used and the utility of targeted molecular therapies remains investigational.^{5,9,15,22,23}

This systematic review aims to identify the pattern of genetic alterations found in reported cases of dPLGGs, as well as outcomes in relation to adjuvant therapy administered.

Methods

A systematic review of the literature was performed in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) guidelines.²⁴ The search was conducted in OVID Medline and PubMed electronic databases in January 2021 to identify relevant articles published between 1990 and 2020. Medical Subject Headings (MeSH) and non-MeSH terms used included "low grade glioma", "disseminated low grade glioma", "diffuse leptomeningeal glioneuronal tumor", "disseminated leptomeningeal tumor", and "leptomeningeal dissemination". After title and abstract review, the articles were exported and managed using EndNote 20. Searches in the databases were supplemented by manual search to retrieve additional articles identified via reference list review of the initial set of articles. Article inclusion and exclusion were deliberated among two authors (JHC and MCD).

The quality assessment for each article reviewed was conducted using the GRADE framework^{25,26} and risk of bias assessment for cohort studies using ROBINS-I tool respectively.^{27,28} Authors reached a consensus on the critical appraisal of study quality and risk of bias.

Data extracted from articles included author, year of publication, study design, sample size, timing and status of dissemination, molecular characteristics of tumors, surgical and adjuvant therapy, treatment outcome, and follow-up duration. Molecular alterations were reported as a percentage of specimens for which the given alteration was interrogated. Survival data was reported as percentage of patients alive at the time (mean/median in months) of last follow-up.

Results

The database search yielded a total of 708 publications: 339 from OVID Medline and 369 from PubMed. Twelve additional articles identified from examining the reference list of articles were assessed for eligibility. An initial review of identified articles was done based on title and type of article leading to the exclusion of abstract reviews, letters to the editor, conference abstracts, and duplicates. The full text of the remaining articles (N=177) was screened for eligibility. We included only articles that examined disseminated pediatric low grade glioma and/or leptomeningeal glioneuronal tumors among the pediatric population (<19 years). Articles which discussed only the adult population or non-disseminated pediatric low grade glioma, or that were unavailable as English language text were excluded. Articles examining molecular characteristics, surgical and adjuvant therapy, and treatment outcomes were included. To avoid double counting of study subjects, studies conducted by Gnekow *et al*,²⁹ Gajjar *et al*,⁹ and Hukin *et al*,¹¹ were excluded due to their data overlapping with that of von Hornstein *et al*,³⁰ Chamdine *et al*,³¹ and Hukin *et al*,¹² respectively.

Fifty-two full-text manuscripts published from 1994 to 2020 were included in this review (Figure 1). A majority of studies reviewed were case series and reports (73%), followed by retrospective cohort studies (25%) and a single prospective cohort study (2%) (Table 1). Using the GRADE framework, 58% of the reviewed articles were classified as having low quality and 42% with moderate quality. Based on the ROBINS-I tool, 57% of articles assessed had a low risk of bias and 43% had a moderate risk of bias.

Table 1
Reported cases of disseminated PLGG from 1994 to 2020

Author	Year	Study Design	Total Number of Cases	Risk of Bias	Grade
Abongwa et al ⁵⁹	2020	Case Report	3	N/A	Low
Bell et al ⁶⁰	2020	Retrospective Cohort Study	36	Moderate	Low
Chen et al ⁶¹	2020	Case Report	1	N/A	Moderate
Finch et al ⁶²	2020	Case Report	1	N/A	Low
Lakhani et al ⁶³	2020	Case Report	7	N/A	Low
Navarro et al ⁶⁴	2020	Case Report	4	N/A	Moderate
Saez-Alegre et al ⁶⁵	2020	Case Report	1	N/A	Moderate
Ryall et al ⁷	2020	Retrospective Cohort Study	13	Low	Moderate
Tiwari et al ⁶⁶	2020	Case Report	1	N/A	Moderate
Lu et al ⁶⁷	2019	Case Report	1	N/A	Low
Tan et al ⁶⁸	2019	Case Report	1	N/A	Moderate
Tiwari et al ⁶⁹	2019	Case Report	1	N/A	Moderate
Deng et al ⁷⁰	2018	Retrospective Cohort Study	24	Moderate	Low
Guillén et al ⁷¹	2018	Case Report	1	N/A	Low
Nambirajan et al ⁷²	2018	Case Report	1	N/A	Low
Aguilera et al ⁵⁷	2017	Case Report	7	N/A	Moderate
Bavle et al ⁷³	2017	Case Report	1	N/A	Low
Schwetye et al ⁷⁴	2017	Case Report	2	N/A	Low
Sublett et al ⁷⁵	2017	Case Report	1	N/A	Low
Tsang et al ⁷⁶	2017	Retrospective Cohort Study	12	Low	Moderate
Chamdine et al ³¹	2016	Retrospective Cohort Study	38	Moderate	Low
Dodgshun et al ¹⁵	2016	Retrospective Cohort Study	10	Low	Moderate
Gessi et al ⁷⁷	2016	Retrospective Cohort Study	17	Low	Moderate
Cho et al ⁷⁸	2015	Case Report	1	N/A	Low
Lyle et al ⁷⁹	2015	Case Report	1	N/A	Moderate
Preuss et al ⁸⁰	2015	Retrospective Cohort Study	4	Low	Moderate
Rodriguez et al ⁸¹	2015	Retrospective Cohort Study	23	Low	Moderate
Kosker et al ⁸²	2014	Case Report	1	N/A	Low
Legault et al ⁸³	2014	Case Report	1	N/A	Low
Bian et al ⁸⁴	2013	Case Report	6	N/A	Low
Schniederjan et al ⁸⁵	2013	Case Report	9	N/A	Moderate
Rodriguez et al ²²	2012	Retrospective Cohort Study	33	Moderate	Low
Agamanolis et al ⁸⁶	2012	Case Report	3	N/A	Moderate
Moon et al ²¹	2012	Case Report	1	N/A	Low
Demir et al ⁸⁷	2011	Case Report	1	N/A	Moderate
von Hornstein et al ³⁰	2011	Prospective Cohort Study	61	Low	Moderate

Author	Year	Study Design	Total Number of Cases	Risk of Bias	Grade
Shaikh et al ⁸⁸	2011	Case Report	3	N/A	Low
Gardiman et al ⁸⁹	2010	Retrospective Cohort Study	4	Moderate	Low
Rhiew et al ⁹⁰	2010	Case Report	1	N/A	Low
Poliani et al ⁹¹	2009	Case Report	1	N/A	Moderate
Sherman et al ⁹²	2009	Case Report	1	N/A	Moderate
Bourne et al ⁹³	2006	Case Report	1	N/A	Low
Distelmaier et al ⁹⁴	2006	Case Report	1	N/A	Low
Meléndez et al ⁹⁵	2006	Case Report	1	N/A	Low
Milanaccio et al ⁹⁶	2005	Case Report	1	N/A	Low
Tabori et al ⁴³	2005	Retrospective Cohort Study	6	Low	Moderate
Kageji et al ⁵⁶	2003	Case Report	1	N/A	Low
Hukin et al ¹²	2003	Retrospective Cohort Study	13	Moderate	Low
Perilongo et al ²³	2002	Case Report	3	N/A	Low
Jamjoom et al ⁹⁷	1998	Case Report	1	N/A	Low
Morikawa et al ⁹⁸	1997	Case Report	1	N/A	Low
Pollack et al ¹⁰	1994	Case Report	3	N/A	Moderate

Out of the 368 pediatric subjects, 241 had a primarily disseminated disease (Table 2) while 91 were localized LGG on presentation and later found to be secondarily disseminated (Table 2); 36 were unspecified. Average time to secondary dissemination was 21.9 months from original tumor diagnosis. There was sporadic testing and reporting of molecular alterations. Thirty-two studies conducted some genetic analysis of tumors including interrogation for *BRAF* p.V600E, *BRAF-KIAA1549* fusion, *TP53* mutation, *IDH* mutation, 1p deletion, 19q deletion, 1p/19q co-deletion, *FGFR* mutation, and *CDKN2A* deletion. The remaining 20 studies did not report on molecular alterations. Of the studies which did not report on molecular alterations, 50% were published within the last 10 years. Out of 151 tumors (41%) which were interrogated for some genetic alterations (Fig. 2a), 88 tumors (58%) were found to harbor at least one genetic alteration. The most common genetic alteration observed among all study subjects was 1p deletion (76%, n=64/85) and *BRAF-KIAA1549* fusion (55%, n=52/95) (Fig. 2b and Fig. 2c). *BRAF* p.V600E was found in 7% (n=5/72) of subjects tested (Fig. 2d). *IDH* mutation was absent in all 37 cases examined. *FGFR1* and *CDKN2A* analysis was reported by only 2 studies and found to be wild-type in all 10 subjects. Few studies reported genetic alterations specifically for secondarily disseminated tumors. In this group, 3 subjects were tested for *BRAF* p.V600E, with 2 being positive. None of these tumors was analyzed for *CDKN2A* deletion. Only 1 patient with secondary disseminated tumor was tested for 1p deletion and was found positive. All remaining genetic testing among secondarily disseminated tumors was unremarkable (Table 2).

Rates of tumor biopsy and resection varied widely and depended largely upon location of tumor and timing of dissemination. For cases with primary tumor dissemination who received surgical intervention, 72% had biopsy and 28% underwent resection of primary tumor focus. Among the cohort with secondary tumor dissemination, 35% had undergone biopsy and 65% received an upfront tumor resection (prior to dissemination). One-hundred and two out of 368 (28%) patients required CSF diversion via shunt or ventriculostomy. Adjuvant therapy was reported for 250 cases. Two hundred and eight cases (83%) received chemotherapy and 66 cases (26%) received radiation therapy. First-line chemotherapy consisted primarily of an alkylation-based regimen and vinca alkaloids, with 98 cases (47%) receiving vincristine and carboplatin as first line chemotherapy. More heterogeneous second-line regimens were reported (Table 3). Three cases (1.4%) received targeted therapies: *BRAF* or *MEK* 1/2 inhibitors. Among those who received radiation therapy, 71% received craniospinal radiation and 29% received focal radiation.

Table 2
Molecular characteristics of primary and secondary dPLGG

Author	Tumor Type	Average Time to Dissemination (months)	Overall Number of Cases	Molecular Characteristics							Follow-up period mean/median (months)	% alive at follow-up
				BRAF V600E mutation	BRAF KIAA Fusion	P53 mutation	IDH mutation	1p deletion	19q deletion	1p/19q co-deletion		
Primary dPLGG												
Chen et al, 2020 ⁶¹	DLGNT	-	1	/	/	0/1	/	/	/	/	16/16	0
*Bell et al, 2020 ⁶⁰	DLGG	-	36	1/10	5/10	/	/	/	/	/	-/72	75
Finch et al, 2020 ⁶²	Disseminated Pleomorphic Xanthroastrocytoma	-	1	1/1	/	/	/	/	/	/	30/30	100
Lakhani et al, 2020 ⁶³	DLGNT	-	7	/	2/7	/	/	2/7	0/7	0/7	-/-	-
Navarro et al, 2020 ⁶⁴	DLGNT	-	1	0/1	/	/	/	/	/	/	4/4	100
Saez-Alegre et al, 2020 ⁶⁵	DLGNT	-	1	0/1	/	/	0/1	1/1	0/1	0/1	5/5	100
Tan et al, 2019 ⁶⁸	DLGNT	-	1	0/1	1/1	1/1	0/1	1/1	0/1	0/1	-/-	100
Tiwari et al, 2019 ⁶⁹	DLGNT	-	1	/	1/1	/	0/1	1/1	1/1	1/1	18/18	100
Deng et al, 2018 ⁷⁰	DLGNT	-	24	0/6	17/24	/	0/9	24/24	8/24	8/24	-/-	80
Guillén et al, 2018 ⁷¹	DLGNT	-	1	0/1	0/1	/	0/1	0/1	/	/	7/7	50
Nambirajan et al, 2018 ⁷²	DLGNT	-	1	0/1	/	0/1	0/1	1/1	1/1	1/1	5/5	0
Aguilera et al, 2017 ⁵⁷	DLGNT	-	7	0/7	/	/	0/7	/	/	/	-/-	100
Schwetye et al, 2017 ⁷⁴	DLGNT	-	2	0/1	0/2	/	0/1	1/2	0/2	0/2	30/30	50
Tsang et al, 2017 ⁷⁶	DLGG	-	9	0/9	1/9	/	/	/	/	/	89/62.4	67
Dodgshun et al, 2016 ¹⁵	DLGNT	-	9	0/4	4/6	/	/	/	/	/	31/24	78
*Gessi et al, 2016 ⁷⁷	DLGG	-	17	1/17	9/15	/	/	/	/	/	127.4/147	65
Cho et al, 2015 ⁷⁸	DLGNT	-	1	/	/	/	0/1	/	/	/	23/23	100
Lyle et al, 2015 ⁷⁹	DLGNT	-	1	/	/	0/1	0/1	/	/	/	24/24	100
Preuss et al, 2015 ⁸⁰	DLGNT	-	4	/	/	/	0/4	0/3	0/3	0/3	54/50	75

Studies with no molecular analysis were not included in this table.

/ indicates unable to perform

*Timing of dissemination was not specified

Author	Tumor Type	Average Time to Dissemination (months)	Overall Number of Cases	Molecular Characteristics							Follow-up period mean/median (months)	% alive at follow-up
				BRAF V600E mutation	BRAF KIAA Fusion	P53 mutation	IDH mutation	1p deletion	19q deletion	1p/19q co-deletion		
Rodriguez et al, 2015 ⁸¹	DLGNT	-	23	0/9	12/16	/	/	10/17	3/17	3/17	-/-	100
Legault et al, 2014 ⁸³	DLGG	-	1	0/1	0/1	/	/	/	/	/	19/19	100
Schniederjan et al, 2013 ⁸⁵	DLGNT	-	9	/	/	/	0/8	6/8	2/8	1/8	137/137	100
Rodriguez et al, 2012 ²²	DLGNT	-	33	/	/	/	0/10	11/15	3/15	3/15	-/5	76
Agamanolis et al, 2012 ⁸⁶	DLGG	-	3	/	/	/	/	2/3	0/3	0/3	36/36	66
Demir et al, 2011 ⁸⁷	DLGG	-	1	/	/	0/1	/	/	/	/	19/19	100
Gardiman et al, 2010 ⁸⁹	DLGNT	-	4	/	/	/	/	1/1	0/1	0/1	47/48	75
Rhiew et al, 2010 ⁹⁰	DLGNT	-	1	/	/	/	/	1/1	1/1	1/1	16/16	100
Bourne et al, 2006 ⁹³	DLGNT	-	1	/	/	/	/	1/1	0/1	0/1	-/-	100
Perilongo et al, 2002 ²³	DLGG	-	2	/	/	0/2	/	/	/	/	47/24	50
Secondary dPLGG												
Lu et al, 2019 ⁶⁷	DLGNT	24	1	0/1	0/1	0/1	0/1	1/1	0/1	0/1	3/3	0
Bavle et al, 2017 ⁷³	DLGG	28	1	1/1	0/1	/	/	/	/	/	70/70	0
Dodgshun et al, 2016 ¹⁵	DLGNT	-	1	1/1	/	/	/	/	/	/	31/24	100
Poliani et al, 2009 ⁹¹	DLGNT	14	1	/	/	0/1	/	/	/	/	30/30	0
Perilongo et al, 2002 ²³	DLGG	3	1	/	/	0/1	/	/	/	/	47/24	0
Studies with no molecular analysis were not included in this table.												
/ indicates unable to perform												
*Timing of dissemination was not specified												

Table 3
Treatment regimen for reported cases of disseminated PLGG

Author	Chemotherapy		Radiotherapy			Surgery		
	1st line	2nd Line	Craniospinal	Cranial	Spinal	Biopsy Only	Resection	CSF Diversion
Abongwa et al, 2020 ⁵⁹	VCR, CBDCA, TMZ	VCR, VBL, CBDCA, CTX, TMZ, CPT-11,	0/3	0/3	1/3	3/3	0/3	2/3
Bell et al, 2020 ⁶⁰	VCR, CBDCA, TMZ		3/36	4/36	0/36	2/36	14/36	2/36
Chen et al, 2020 ⁶¹	TMZ	-	0/1	0/1	0/1	0/1	0/1	1/1
Finch et al, 2020 ⁶²	VCR, CBDCA	PLX4032	0/1	0/1	0/1	0/1	1/1	0/1
Lakhani et al, 2020 ⁶³	-	-	0/1	0/1	0/1	7/7	0/7	0/7
Navarro et al, 2020 ⁶⁴	-	-	1/1	0/1	0/1	1/1	0/1	0/1
Saez-Alegre et al	VCR	-	0/1	0/1	0/1	1/1	0/1	1/1
Tiwari et al, 2020 ⁶⁶	VCR, CBDCA	-	0/1	0/1	0/1	0/1	1/1	0/1
Lu et al, 2019 ⁶⁷	-	-	0/1	0/1	0/1	0/1	1/1	0/1
Tan et al, 2019 ⁶⁸	VCR, CBDCA		0/1	0/1	0/1	1/1	0/1	1/1
Tiwari et al, 2019 ⁶⁹	-	-	0/1	0/1	0/1	0/1	1/1	0/1
Guillén et al, 2018 ⁷¹	VCR, CBDCA	VBL	0/1	0/1	0/1	1/1	0/1	0/1
Nambirajan et al, 2018 ⁷²	-	-	0/1	0/1	0/1	0/1	0/1	0/1
Aguilera et al, 2017 ⁵⁷	VCR, CBDCA, CDDP, EPEG, CTX, TMZ	VCR, CBDCA, VBL	1/7	0/7	0/7	7/7	0/7	0/7
Bavle et al, 2017 ⁷³	VCR, CBDCA	VCR, CBDCA, VBL, TMZ, CPT-11, rhuMAB-VEGF, GSK2118436B	0/1	0/1	0/1	1/1	0/1	0/1
Rodriguez et al, 2015 ⁸¹	+	+	7/33	0/1	0/1	33/33	0/33	0/33
Schwetye et al, 2017 ⁷⁴	VCR, CBDCA, CTX, TMZ, rhuMAB-VEGF	CBDCA, CDDP, CTX, TMZ, CPT-11 rhuMAB-VEGF,	1/2	0/2	0/2	2/2	0/2	2/2
Sublett et al, 2017 ⁷⁵	VCR, CBDCA, CTX	CDDP, TMZ, CPT-11	1/1	0/1	0/1	1/1	0/1	1/1
Tsang et al, 2017 ⁷⁶	VCR, CBDCA, VBL,	TOPO, TAM, TMZ, 4-DMDR, TPC, Lenalinomide	12/12	12/12	11/12	4/12	8/12	1/12
Chamdine et al, 2016 ³¹	VCR, CBDCA, CDDP, CTX, TMZ, 6-TG, PCB, CCNU	-	5/38	2/38	0/38	21/38	17/38	0/12
Dodgshun et al, 2016 ¹⁵	VCR, CBDCA, VBL, CDDP	CBDCA, TMZ, rhuMAB-VEGF, CPT-11, TPCV	1/10	0/10	1/10	10/10	0/10	3/10

+ Specific therapy not reported.

VCR, Vincristine; VBL, Vinblastine; CBDCA, Carboplatin; CDDP, Cisplatin; EPEG, Etoposide; CTX, Cyclophosphamide; TMZ, Temozolomide; CPT-11, Irinotecan; TESPA, Thiotepa; rhuMAB-VEGF, Bevacizumab; PLX4032, Vemurafenib; BAY 54-9085, Sorafenib; GSK2118436B, Dabrafenib; 6-TG, thioguanine; PCB, procarbazine; TPCV, thioguanine, procarbazine, lomustine, vincristine; CCNU, Lomustine; 4-DMDR, Idarubicin; MCNU, Ranimustine; TOPO, Topotecan; TAM, Tamoxifen; 5-FU, 5-fluorouracil

Author	Chemotherapy		Radiotherapy			Surgery		
	1st line	2nd Line	Craniospinal	Cranial	Spinal	Biopsy Only	Resection	CSF Diversion
Cho et al, 2015 ⁷⁸	+	+	+	+	+	1/1	0/1	1/1
Lyle et al, 2015 ⁷⁹	TMZ	-	1/1	0/1	0/1	1/1	0/1	1/1
Preuss et al, 2015 ⁸⁰	VCR, CBDCA, EPEG, CTX,	-	1/4	0/4	0/4	4/4	0/4	3/4
Kosker et al, 2014 ⁸²	VCR, CBDCA, EPEG	-	0/1	0/1	0/1	1/1	0/1	1/1
Legault et al, 2014 ⁸³	VCR, CBDCA	6-TG, PCB, CCNU rhuMAb-VEGF, CPT-11, BAY 54-9085	0/1	0/1	0/1	0/1	1/1	1/1
Bian et al, 2013 ⁸⁴	VCR, CBDCA, TMZ	-	4/6	1/6	1/6	0/6	6/6	2/6
Schniederjan et al, 2013 ⁸⁵	VCR, CBDCA, VBL, TMZ	-	2/9	0/9	0/9	9/9	0/9	0/9
Agamanolis et al, 2012 ⁸⁶	VCR, CBDCA, CDDP CTX	TMZ	1/3	0/3	0/3	2/3	1/3	1/3
Moon et al, 2012 ²¹	VCR, CBDCA	-	0/1	1/1	1/1	1/1	0/1	0/1
Demir et al, 2011 ⁸⁷	CDDP, EPEG	TMZ	1/1	1/1	0/1	0/1	1/1	1/1
von Hornstein et al, 2011 ³⁰	VCR, CBDCA	CDDP, CTX	0/61	4/61	0/61	29/61	30/61	57/61
Hukin et al, 2003	VCR, CBDCA, CTX, CDDP, EPEG	VCR, CBDCA	3/13	0/13	0/13	5/13	6/13	5/13
Shaikh et al, 2011 ⁸⁸	VCR, CBDCA, TMZ	VBL	0/3	1/3	0/3	0/3	0/3	2/3
Gardiman et al, 2010 ⁸⁹	TMZ	-	0/4	0/4	1/4	3/4	1/4	2/4
Rhiew et al, 2010 ⁹⁰	VCR, CBDCA, TMZ	-	0/1	0/1	0/1	1/1	0/1	0/1
Poliani et al, 2009 ⁹¹	-	-	0/1	0/1	0/1	0/1	1/1	1/1
Sherman et al, 2009 ⁹²	TMZ	VBL	0/1	0/1	0/1	1/1	0/1	1/1
Bourne et al, 2006 ⁹³	VCR, CBDCA, TMZ, CTX, EPEG	-	-	-	-	-	-	-
Distelmaier et al, 2006 ⁹⁴	VCR, CBDCA, EPEG	-	0/1	0/1	0/1	1/1	0/1	0/1
Meléndez et al, 2006 ⁹⁵	VCR, CBDCA	VCR, CBDCA, CDDP, EPEG	0/1	0/1	0/1	0/1	1/1	0/1
Milanaccio et al, 2005 ⁹⁶	VCR, CBDCA	VCR, CBDCA, CDDP, CTX	0/1	0/1	0/1	0/1	1/1	1/1

+ Specific therapy not reported.

VCR, Vincristine; VBL, Vinblastine; CBDCA, Carboplatin; CDDP, Cisplatin; EPEG, Etoposide; CTX, Cyclophosphamide; TMZ, Temozolomide; CPT-11, Irinotecan; TESPA, Thiotepa; rhuMAb-VEGF, Bevacizumab; PLX4032, Vemurafenib; BAY 54-9085, Sorafenib; GSK2118436B, Dabrafenib; 6-TG, thioguanine; PCB, procarbazine; TPCV, thioguanine, procarbazine, lomustine, vincristine; CCNU, Lomustine; 4-DMDR, Idarubicin; MCNU, Ranimustine; TOPO, Topotecan; TAM, Tamoxifen; 5-FU, 5-fluorouracil

Author	Chemotherapy		Radiotherapy			Surgery		
	1st line	2nd Line	Craniospinal	Cranial	Spinal	Biopsy Only	Resection	CSF Diversion
Kageji et al, 2003 ⁵⁶	CBDCA, EPEG, CTX, MCNU	-	0/1	0/1	0/1	0/1	1/1	0/1
Perilongo et al, 2002 ²³	VCR, CBDCA, TMZ	-	1/3	0/3	0/3	2/3	1/3	2/3
Jamjoom et al, 1998 ⁹⁷	-	-	0/1	1/1	0/1	1/1	0/1	1/2
Morikawa et al, 1997 ⁹⁸	-	-	0/1	0/1	0/1	0/1	1/1	1/1
Pollack et al, 1994 ¹⁰	VCR, CBDCA, PCB CCNU	EPEG, 5-FU	1/3	2/3	0/3	0/3	3/3	3/3
+ Specific therapy not reported.								
VCR, Vincristine; VBL, Vinblastine; CBDCA, Carboplatin; CDDP, Cisplatin; EPEG, Etoposide; CTX, Cyclophosphamide; TMZ, Temozolomide; CPT-11, Irinotecan; TESPA, Thiotepa; rhuMAb-VEGF, Bevacizumab; PLX4032, Vemurafenib; BAY 54-9085, Sorafenib; GSK2118436B, Dabrafenib; 6-TG, thioguanine; PCB, procarbazine; TPCV, thioguanine, procarbazine, lomustine, vincristine; CCNU, Lomustine; 4-DMDR, Idarubicin; MCNU, Ranimustine; TOPO, Topotecan; TAM, Tamoxifen; 5-FU, 5-fluorouracil								

Across the entire cohort (primarily and secondarily disseminated disease), the aggregate mean and median follow-up duration was 22.0 and 40.2 months, respectively. Overall, 73% of cases were alive at last follow-up. Seventy-two percent of cases with primarily disseminated tumor and 70% of cases with secondarily disseminated disease were alive at last follow-up. Among cases with secondarily disseminated tumor, 67% of those who had biopsy only and 68% of those who had tumor resection were alive at last follow-up. Forty-four percent of primarily disseminated tumor cases and 31% of secondarily disseminated tumor had no data on treatment outcomes.

Discussion

Despite increasing awareness of dPLGGs, there is limited knowledge on their molecular profile and long-term response to adjuvant therapy. In this systematic review, we report the molecular alterations, treatment offered and the survival experience of 332 children with dPLGGs reported in the literature. Sixty-five percent of cases had primary disseminated disease and 25% had a secondary tumor dissemination at an average time of 21.9 months from solitary tumor diagnosis, with timing of dissemination unknown in 47%. Sixty-two percent of studies reviewed characterized some of the molecular alterations harbored by this subgroup of PLGG.

The most common molecular alterations in dPLGG cases identified in this review were whole arm chromosomal loss of 1p (64/85) and *BRAF-KIAA1549* fusion (52/95). Alterations encountered less frequently were 19q deletion (19/87), 1p/19q co-deletion (18/87) and *BRAF* p.V600E (5/72). This suggests that 1p deletion may have a mechanistic role in glioma leptomeningeal or parenchymal dissemination. Seventy-four percent of cases reviewed were not interrogated for 1p deletion. Further research is needed to ascertain the possible role of 1p deletion in PLGG dissemination. While the frequency of *BRAF-KIAA1549* fusion in non-disseminated PLGGs is high (34 – 73%), 1p deletion, either with or without 19q co-deletion, is uncommon (3 - 15%) and has mainly been described in oligodendrogliomas, occurring with *IDH* mutation.^{7,32,33,34,35} Frequency of *BRAF* p.V600E in PLGG differs by histology.^{36,37,38} A high rate of mutation is found in pleomorphic xanthoastrocytoma (50 – 78%) with moderate rates in gangliogliomas (13 – 49%) and lower rates in pilocytic astrocytoma and other glioma subtypes (0 – 14.3%).^{38,39,40} Fukuoka *et al* have identified a unique *IDH* wild-type oligodendroglioma-like tumors harboring *BRAF* p.V600E with no 1p/19q co-deletion in a small subset of adolescents and young adults.⁴¹ Other alterations including *FGFR* mutation or fusion and deletion of *CDKN2A* are encountered less frequently in PLGGs.^{7,36,37,38}

The biologic features which permit PLGG to disseminate throughout the craniospinal axis remain unclear and the role of specific molecular alterations in this process is unknown. Previous studies have suggested tumor dissemination occurs via the CSF pathway with tumor cells penetrating ependymal lining and interstitial spaces and adhering to leptomeninges at near and distant sites.^{9,10,42} A study conducted by Tabori *et al.* identified an increased rate of epidermal growth factor receptor (*EGFR*) amplification in dPLGGs compared to non-disseminated PLGGs which seem to suggest the possible role of *EGFR* amplification in tumor dissemination.⁴³ The increased *EGFR* amplification promoting tumor growth and the invasive potential of tumor cells may potentially promote tumor dissemination.^{44,45} In other CNS tumor types, some biomarkers have been identified to promote tumor metastasis. Overexpression of *ERBB2* (also known as HER2) leading to activation of the *PI3K/AKT* signaling pathway and *ERK1/2* pathway which results in the up-regulation of *S100A4*, a pro-metastatic gene have been found in metastatic medulloblastoma compared with localized medulloblastoma.^{46,47} *S100A4* has also been found to be up-regulated more often in ependymoma and glioblastoma than in low grade astrocytoma.^{48,49} It is thus possible that *ERBB2* may act in synergy with genetic alterations affecting the RAS/MAPK signaling pathway while also promoting PLGG dissemination via the *PI3K/AKT* and *ERK1/2* pathways. Increased expression of *PDGFR*, a tyrosine kinase has also been found in low grade gliomas.^{50,51} *PDGFR* promotes glioma stem cell migration and invasion through increasing *MMP-2* activity.^{52,53} *PDGFR*-induced *MMP-2* activity in low grade gliomas may contribute to tumor dissemination. While understudied and largely speculative within PLGGs, the drivers of metastasis are known for other CNS tumors. Their possible connection with PLGG dissemination is an intriguing prospect that warrants attention.

Treatment approach for dPLGGs was observed to be similar to that of non-disseminated PLGGs for all treatment modalities. Neurosurgical intervention was largely influenced by the timing of dissemination and the location of primary lesion if identified. The majority (72%) of cases with primary disseminated tumors only had a biopsy done and the remaining 28% had either a gross total resection (GTR) or subtotal resection (STR) of a dominant lesion. As expected, the reverse was observed for cases with secondary disseminated tumors with the majority (65%) of cases having either a GTR or STR and 35% undergoing biopsy alone. A less invasive surgical approach is typically favored in patients with primary dissemination wherein the primary goal is to obtain diagnostic tissue rather than attempt curative excision of lesions. An exception is when a dominant lesion is causing symptoms related to mass effect, edema, or cortical irritation, and surgical resection or debulking facilitates symptom resolution and/or adjuvant therapy initiation. Identifying tumors with dissemination potential would help predict prognosis more accurately and allow improved counselling for patient.

Adjuvant therapy is indicated in almost all cases of dPLGG. The predominant chemotherapeutic agents for first line therapy were vincristine and carboplatin. This treatment combination has been shown to be effective in the management of PLGG.^{5,54,55,56} Second line treatment in cases of disease progression or adverse drug reactions was far more heterogeneous (Table 4). Few children (1.4%) received targeted therapies such as BRAF or MEK 1/2 inhibitors as a second line regimen based on reports from recent studies. Radiotherapy was utilized less frequently, as second or third line therapy for disease progression despite multimodal chemotherapy. The few cases who received radiation as first line therapy were all older children with ages ranging between 3 and 16 years.

The clinical course of dPLGGs tends to be protracted and may require multiple interventions including salvage therapy for disease progression. Compared to non-disseminated PLGG, dPLGG is associated with a worse outcome.^{5,10,11,21,57} Hukin et al reported a 5-year survival rate of 68% and 87% in a cohort of dPLGG and non-disseminated PLGG, respectively.¹¹ Based on the available survival data, 73% of cases reviewed were alive at the last follow-up. Primary disseminated tumors were associated with similar survival rates as secondary disseminated tumors (72% vs. 70%). Survival is likely influenced by the biologic ramifications of molecular alterations specific to each tumor. Tumors expressing *BRAF-KIAA1549* fusion have been observed to have a better survival than BRAF p.V600E (69% vs 52%).^{7,38} Survival for tumors with wild-type BRAF is better than tumors with BRAF p.V600E but not significantly different from tumors with *BRAF-KIAA1549* fusion.^{33,38,58} *CDKN2A* homozygous deletion is also associated with a worse survival outcome especially when the tumor also harbors BRAF p.V600E.^{5,6,32,36,38} From these results, only primary disseminated tumors expressed *BRAF-KIAA1549* fusion, which may play a role in the higher survival seen in this cohort. None of the secondary disseminated tumors interrogated for *BRAF-KIAA1549* fusion were found to be positive, and two out of the 3 cases tested had BRAF p.V600E. None of the secondary disseminated tumors was interrogated for *CDKN2A* deletion. While broad generalizations might be gleaned from a review of the literature, the true relationship between molecular alterations and prognosis in dPLGG demands further study.

There are several limitations to be considered in the interpretation of results presented in this review. The clinical use of variable terminologies to describe this tumor type may have influenced our search results. Beyond including the most common descriptors, we address this by reviewing the reference lists of articles initially identified to find additional articles which may not have been captured by the original search terms. There was a lack of comprehensive reporting on the genomic profile of tumors to draw meaningful conclusions on the pattern of molecular alterations found in all dPLGGs. Finally, many of the included studies were case reports and small case series that carried a measurable risk of bias as determined by the ROBINS-I tool. Based on our GRADE assessment of quality of evidence, all studies reviewed either ranked low or moderate in quality with none ranking high. This underscores the need for clinical trials to specifically include and sub-analyze dPLGG cohorts to better understand the efficacy of PLGG regimen and targeted molecular therapies in the management of this disease.

Conclusion

While 1p deletion and *BRAF-KIAA1549* fusion in dPLGGs have been commonly reported in the literature, these tumors appear to express heterogeneous molecular and biological characteristics distinct from non-disseminated PLGGs. This review suggests that the presence of disseminated disease may not necessarily confer a poor prognosis for all patients as previously noted in earlier reports. There is however lack of comprehensive and quality studies characterizing the molecular makeup of dPLGGs and how treatment approaches including the use of targeted therapy impact survival outcome. Additional studies on the molecular and biological features of these tumors are needed to better understand the pathogenesis of dissemination of PLGG and inform the development of additional targeted regimens to further improve outcomes.

Abbreviations

EGFR - epidermal growth factor receptor

ERBB2 - Erb-B2 Receptor Tyrosine Kinase 2

PI3K/AKT pathway - phosphatidylinositol-3 kinases/protein kinase B pathway

ERK1/2 pathway extracellular signal-regulated kinase

RAS/MAPK signaling pathway - RAS-mitogen-activated protein kinase signaling pathway

PDGFR - platelet-derived growth factor receptor

MMP-2 - matrix metalloproteinase-2

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Authors' contributions:

Michael Dewan responsible for study conception and design. Joseline Haizel-Cobbina, Rut Thakkar, Kelsey Richard and Michael Dewan performed the literature search, data extraction and data analysis. The first draft of the manuscript was written by Joseline Haizel-Cobbina. All authors critically revised the work and approved of the submitted version of the manuscript.

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Figures

Figure 1

PRISMA flow diagram for the literature search to identify disseminated pediatric low grade glioma publications

a)

b)

c)

d)

Figure 2

Pie chart demonstrating percentage of genetic alterations in disseminated pediatric low grade gliomas Fig 2a Percentage of dPLGGs interrogated for genetic alterations Fig 2b Percentage of dPLGGs with 1p deletion Fig 2c Percentage of BRAF-KIAA1549 identified in dPLGGs Fig 2d Percentage of dPLGGs with BRAF p.V600E