·专题综述·

# 儿童型低级别胶质瘤药物化疗及靶向治疗进展

盖菁菁 孔晨晨 赵传 张俊平

【摘要】 儿童型低级别胶质瘤是儿童最常见的中枢神经系统肿瘤，大多数呈非侵袭性，预后较好。手术全切除是重要的预后影响因素，可达到长期生存。然而对于位于脑干、视觉传导通路等脑深部结构的肿瘤，无法手术全切除，药物化疗是临床症状恶化或影像学进展时的首选辅助治疗方法；近年除传统药物化疗外，靶向治疗药物的研发和应用也取得显著进展。本文综述儿童型低级别胶质瘤药物化疗及靶向治疗进展及所面临的挑战，以指导临床实践。

【关键词】 神经胶质瘤； 抗肿瘤联合化疗方案； 血管生成抑制剂； 分子靶向治疗； 儿童； 综述

## Research advances on chemotherapy and targeted therapy of pediatric-type low-grade glioma

GE Jing-jing, KONG Chen-chen, ZHAO Chuan, ZHANG Jun-ping

*Department of Neuro-oncology, Sanbo Brain Hospital, Capital Medical University, Beijing 100093, China*

*Corresponding author: ZHANG Jun-ping (Email: doczhjp@hotmail.com)*

【Abstract】 Pediatric-type low-grade glioma (pLGG) is the most common central nervous system tumor in children, and most pLGG exhibits non-invasive clinical behavior with a good prognosis. Total surgical resection is an important prognostic factor, and patients can achieve long-term survival after total tumor resection. However, tumors in deep location such as brain stem and optic pathway cannot be completely removed by surgery. Chemotherapy is the first choice of adjuvant treatment when the clinical symptoms of pLGG worsen or imaging progress. In recent years, in addition to traditional chemotherapy, the development and application of targeted therapy drugs have also made great progress. This article reviews the research progress and challenges of chemotherapy and targeted therapy of pLGG, in order to provide guidance for clinical practice.

【Key words】 Glioma; Antineoplastic combined chemotherapy protocols; Angiogenesis inhibitors; Molecular targeted therapy; Child; Review

This study was supported by Hygiene and Health Development Scientific Research Fostering Plan of Haidian District of Beijing (No. HP2021-19-50802), and Capital's Funds for Health Improvement and Research (No. 2022-2-8012).

**Conflicts of interest:** none declared

儿童型低级别胶质瘤（pLGG）是儿童最常见的中枢神经系统肿瘤，占30%～40%[1]，大多数呈非侵袭性，较少发生恶性转化（<10%）[2]。手术全切除是最重要的预后影响因素[3]，且术后无需辅助治疗即可达到远期无进展生存[4]，但对于视觉传导通路、脑干等脑深部中线结构或伴随播散的儿童型低级别胶质瘤无法手术全切除，术后常需辅以放化疗[3]。放射治疗的远期不良反应发生率较高，如严重认知功能障碍（30%）、内分泌功能紊乱（26%）、脑血管事件（脑出血和脑梗死，13%）及继发其他肿瘤（22%）等[5]；且有可能增加毛细胞型星形细胞瘤患儿的死亡风险[6]。药物化疗是临床症状恶化或影像学进展时的首选辅助治疗方法[7]，值得注意的是，婴幼儿（≤3岁）肿瘤生长迅速，患儿直接因肿瘤死亡的风险较高，一经确诊即予以药物化疗[8]；>3岁患儿如果

doi：10.3969/j.issn.1672-6731.2024.09.003

基金项目：北京市海淀区卫生健康发展科研培育计划项目（项目编号：HP2021-19-50802）；首都卫生发展科研专项（项目编号：首发2022-2-8012）

作者单位：100093 北京，首都医科大学三博脑科医院神经肿瘤化疗中心

通讯作者：张俊平，Email：doczhjp@hotmail.com

症状不明显，可随访观察，观察期间若出现临床症状或影像学进展，即予以药物化疗。近年随着分子生物学的发展，更多基因突变位点被检出，越来越多的儿童型低级别胶质瘤可以从分子靶向治疗中获益；此外，肿瘤血管生成是肿瘤生长、浸润和转移的必需过程，抗血管生成靶向药物也呈现出一定疗效。本文拟综述儿童型低级别胶质瘤的药物化疗、抗血管生成药物靶向治疗和分子靶向治疗进展，旨在指导临床实践，为未来研究方向提供指引。

一、传统药物化疗

CV方案和TPCV方案是儿童型低级别胶质瘤最常用的一线化疗方案。CV方案为卡铂（CBP）+长春新碱（VCR）；TPCV方案为硫鸟嘌呤（tioguanine）+丙卡巴肼（procarbazine）+洛莫司汀（lomustine）+长春新碱。CV方案和TPCV方案的客观缓解率（ORR）分别为50.5%和52.4%，5年无事件生存率（EFS）为39%和52%，二者疗效相当[9]。但TPCV方案含烷化剂较多，远期继发其他肿瘤的概率较高，不推荐应用于1型神经纤维瘤病（NF1）患儿；此外，TPCV方案片剂较多，幼儿不易服用。由此可见，CV方案和TPCV方案仍对近50%的儿童型低级别胶质瘤患儿无效，故如何优化药物化疗方案以提高疗效是目前主要研究方向之一。一项随机对照临床试验结果显示，CV方案联合依托泊苷与单纯CV方案的客观缓解率分别为41%和46.4%，5年无进展生存率分别为45.3%和46.1%，表明与单纯CV方案相比，CV方案联合依托泊苷并不能提高疗效，且其4级血液学毒性（76%对64%）和3～4级感染（30%对18%）发生率更高[10]。一项单臂Ⅱ期临床试验显示，既往未经药物化疗的儿童型低级别胶质瘤患儿予以长春碱单药治疗后，客观缓解率为25.93%（14/54），5年无进展生存率为53.2%（95%CI：0.413～0.685），基于这一研究结果，加之长春碱价格低廉、药物毒性小，一些国家特别是中低收入国家将其作为一线治疗药物[11]。用于治疗成人型弥漫性低级别胶质瘤的烷化剂替莫唑胺对儿童型低级别胶质瘤的疗效欠佳，不建议作为一线治疗药物；然而对于进展性儿童型低级别胶质瘤，经替莫唑胺治疗后，13.33%（4/30）患儿肿瘤体积缩小＞25%，43.33%（13/30）肿瘤保持稳定，替莫唑胺客观缓解率为13%，疾病控制率为56.7%，提示其可作为儿童型低级别胶质瘤的二线治疗选择[12]。除替莫唑胺外，复发性或进展性儿童型低级别胶质瘤还可再次予以CV方案、贝伐珠单抗、顺铂+依托泊苷、长春碱等。研究显示，37例进展性儿童型低级别胶质瘤患儿经顺铂+依托泊苷治疗后，24例（64.86%）肿瘤体积缩小，疗效维持12个月[13]；16例进展性儿童视路胶质瘤经顺铂+依托泊苷+长春碱联合方案治疗后，4例部分缓解（PR）、5例疾病稳定（SD）、7例疾病进展（PD），客观缓解率为25%，疾病控制率为56.3%[14]；对比分析再次予以CV方案、卡铂单药与长春碱单药对无法手术全切除的进展性儿童型低级别胶质瘤的疗效，3种方案的客观缓解率分别为58.8%、27%和46.4%[15]。

二、抗血管生成药物靶向治疗

重组人血管内皮抑制素是一种多靶点抗血管生成药物，可以抑制血管内皮生长因子（VEGF）、碱性纤维母细胞生长因子（bFGF）、基质金属蛋白酶（MMPs）、整合素、Wnt等信号转导通路。既往研究显示，CV方案联合重组人血管内皮抑制素治疗儿童型低级别胶质瘤可将客观缓解率提高至70%，且起效时间短（中位起效时间仅3个月），有助于尽快缓解肿瘤压迫，改善患儿生活质量[16]。亦有研究在CV方案治疗失败后加用重组人血管内皮抑制素，使肿瘤获得长期缓解[17]。CV方案联合重组人血管内皮抑制素治疗儿童型低级别胶质瘤的前瞻性研究（试验编号：NCT04659421）正在进行中。贝伐珠单抗是一种单一靶向血管内皮生长因子的单克隆抗体，其治疗复发性或进展性儿童型低级别胶质瘤，可诱导肿瘤迅速反应（治疗9周时客观缓解率为86%），有助于缓解急性视力损伤或其他神经功能缺损[18]；但停药后约93%的肿瘤短期内再次进展，停药后中位进展时间仅4个月，且存在蛋白尿、类风湿关节炎、嗜睡等不良反应风险[19]。

三、分子靶向治疗

大多数儿童型低级别胶质瘤存在丝裂原激活蛋白激酶（MAPK）信号转导通路相关基因组改变和MAPK信号依赖性肿瘤进展[20-21]。*BRAF-KIAA1549*融合是最常见的基因变异，发生率约为35%，尤其是毛细胞型星形细胞瘤，有60%～70%的患儿存在*BRAF-KIAA1549*融合。*BRAF* V600E突变也是主要的基因变异，发生率约15%，尤以节细胞胶质瘤和多形性黄色瘤型星形细胞瘤最为常见[22]。存在*BRAF* V600E突变的儿童型低级别胶质瘤患儿总生存期（OS）和无进展生存期（PFS）更短，尤其是*BRAF* V600E突变与细胞周期蛋白依赖性激酶抑制

因子2A(*CDKN2A*)缺失同时发生的患儿[23]。儿童型低级别胶质瘤分子靶向药物的研发和应用在既往数十年取得了显著进展。

1. *BRAF*突变　存在*BRAF*突变的儿童型低级别胶质瘤,可以考虑BRAF抑制剂和(或)MEK抑制剂治疗。达拉非尼(dabrafenib)和维莫非尼(vemurafenib)是第一代强效选择性BRAF抑制剂,有望改善*BRAF*突变患儿预后。有研究纳入32例存在*BRAF* V600E突变的复发性和(或)难治性儿童型低级别胶质瘤患儿,经达拉非尼治疗后,13例(40.62%)部分缓解、1例(3.12%)完全缓解(CR),客观缓解率为44%,1年无进展生存率为85%[24]。在维莫非尼Ⅰ期临床试验中,19例儿童型低级别胶质瘤患儿的客观缓解率为31.6%,最常见的药物不良反应为皮疹,经对症支持治疗后消失且重新开始治疗后并未复发,表明维莫非尼具有良好的抗肿瘤活性且药物毒性可控[25]。司美替尼(selumetinib)和曲美替尼(trametinib)是目前研究最广泛的MEK抑制剂。一项Ⅱ期临床试验(试验编号:NCT01089101)显示,司美替尼对存在*BRAF*突变或融合的毛细胞型星形细胞瘤患儿的客观缓解率分别为29%和39%,提示司美替尼对复发性和(或)难治性儿童型低级别胶质瘤有一定疗效,但约>50%患儿停药后6个月内出现肿瘤进展[26]。曲美替尼治疗进展性儿童型低级别胶质瘤的客观缓解率约为40%,亦有约27%患儿停药后2~4个月出现肿瘤进展,最常见的药物不良反应为发热、皮疹、疲劳和胃肠功能紊乱,治疗期间应警惕眼毒性、心脏毒性和颅内出血等并发症风险[27-28]。联合应用BRAF抑制剂和MEK抑制剂可以提高疗效:一项达拉非尼联合曲美替尼一线治疗存在*BRAF* V600E突变的儿童型低级别胶质瘤的Ⅱ期随机对照临床试验(试验编号:NCT02684058)结果显示,与标准化疗(CV方案)相比较,达拉非尼联合曲美替尼的客观缓解率(47%对11%)和临床获益率(86%对46%)更高,其反应持续时间(23.7个月对6.6个月)和中位无进展生存期(20.1个月对7.4个月)更长久,3~4级不良事件发生率(47%对94%)和因不良反应中断治疗的比例(4%对18%)更低[29]。基于该项研究结果,美国食品与药品管理局(FDA)于2023年3月批准达拉非尼联合曲美替尼用于治疗存在*BRAF* V600E突变的儿童型低级别胶质瘤[30]。此外,既往接受BRAF抑制剂和(或)MEK抑制剂治疗后进展的儿童型低级别胶质瘤患儿,再次应用该方案仍可能有效,约80%患儿可再次获得缓解或延长疾病稳定时间[31]。

2. *BRAF*融合　存在*BRAF*融合的儿童型低级别胶质瘤,可以考虑MEK抑制剂或第二代BRAF抑制剂如托沃拉非尼(tovorafenib)。4例存在*BRAF*融合的儿童型低级别胶质瘤患儿经曲美替尼单药治疗后,3例部分或完全缓解[32];18例存在*BRAF*融合的儿童型低级别胶质瘤患儿经司美替尼单药治疗后,7例部分缓解,客观缓解率为39%(Ⅱ期临床试验,试验编号:NCT01089101)[26]。第一代BRAF抑制剂如达拉非尼、维莫非尼、索拉非尼,无法靶向Raf激酶二聚体,并可能导致下游细胞外信号调节激酶(ERK)信号转导通路异常激活,促进肿瘤加速生长[33],故不适用于*BRAF*融合患儿的治疗;第二代BRAF抑制剂如托沃拉非尼可阻断Raf激酶二聚体并减少下游ERK信号转导通路的异常激活。复发性和(或)难治性存在*BRAF*融合的儿童型低级别胶质瘤经托沃拉非尼治疗后,客观缓解率达50%[34]。目前,托沃拉非尼已被美国食品与药品管理局批准用于复发性和(或)难治性存在*BRAF*突变或融合的儿童型低级别胶质瘤[37]。此类患儿能否选择托沃拉非尼作为一线治疗药物的研究正在进行中[36]。太平洋儿童神经肿瘤联盟(PNOC)开展的一项多中心Ⅱ期临床试验(试验编号:NCT01734512)探讨哺乳动物雷帕霉素靶蛋白(mTOR)抑制剂依维莫司(everolimus)对复发性和(或)进展性儿童型低级别胶质瘤的治疗效果,结果显示,根据儿童神经肿瘤学应答评估(RAPNO)标准,62例患儿中1例完全缓解、3例部分缓解、8例微缓解,客观缓解率为19.4%,6个月无进展生存率为67.4%,中位无进展生存期为11.1个月;与存在常见*BRAF*融合位点的患儿相比,存在罕见和(或)新型*BRAF*融合位点的儿童型低级别胶质瘤患儿的预后更差(中位无进展生存期为6.1个月对16.7个月);而磷脂酰肌醇-3激酶(PI3K)/丝氨酸/苏氨酸激酶(AKT)/mTOR信号转导通路激活和未激活均与临床结局(6个月无进展生存率分别为68.4%和63.3%)无关联性[37]。

3. *mTOR*变异　存在结节性硬化症基因*TSC1/2*变异的室管膜下巨细胞型星形细胞瘤可考虑选择性mTOR抑制剂治疗。有85%~95%的室管膜下巨细胞型星形细胞瘤患儿存在*TSC1/2*基因变异,导致mTOR信号转导通路异常激活。一项Ⅲ期随机对照临床试验显示,与安慰剂相比,mTOR抑制剂依维莫

司治疗室管膜下巨细胞型星形细胞瘤的客观缓解率显著提高(35% 对 0)[38]。基于该项研究结果,美国食品与药品管理局已批准依维莫司用于需干预但不适宜手术切除的结节性硬化症相关室管膜下巨细胞型星形细胞瘤的治疗[39]。

4. *NTRK*融合　存在*TRK*融合的儿童型低级别胶质瘤,可考虑原肌球蛋白受体激酶(TRK)抑制剂如拉罗替尼(larotrectinib)和恩曲替尼(entrectinib)治疗,目前这两种药物已在国内上市。拉罗替尼适用于全年龄段存在*NTRK*融合的实体肿瘤患者,恩曲替尼适用于年龄≥12岁的存在*NTRK*融合的实体肿瘤患儿,治疗过程中均应警惕骨折的风险[40-41]。

5. *FGFR*变异　2023年,美国国家癌症研究所(NCI)与儿童肿瘤协作组(COG)合作开展的儿童MATCH(Molecular Analysis for Therapy Choice)试验(试验编号:NCT03210714)探讨纤维母细胞生长因子受体(FGFR)抑制剂厄达替尼(erdafitinib)在存在*FGFR*变异的胶质瘤患儿中的疗效,初步结果显示,11例儿童型低级别胶质瘤或胶质神经元肿瘤患儿中6例部分缓解或疾病稳定,厄达替尼耐受性良好,主要不良反应为高磷血症和指甲营养不良[42]。但新近一项回顾性研究显示,接受FGFR抑制剂治疗的复发性存在*FGFR*变异的儿童型胶质瘤患儿中,3/7例股骨骨骺滑脱,线性生长速度增快[43]。未来尚待进一步评估FGFR抑制剂的有效性和安全性。此外,*FGFR1*变异还与儿童型低级别胶质瘤的自发性颅内出血存在显著相关性,存在*FGFR1*变异的患儿治疗过程中均发生颅内出血,应警惕[44]。

6. 分子靶向治疗的挑战　尽管儿童型低级别胶质瘤的靶向治疗研究取得显著进展,疗效令人鼓舞,但仍存在一些问题和挑战。首先,早期临床试验欠标准化,纳入标准(如年龄、分子病理学特征、肿瘤播散、临床状态等)、临床终点评估、疗效评价标准等不统一,使得各项研究之间以及各种药物之间不宜对比分析,亟待建立统一的普适性临床试验标准,以使各项研究和各种药物之间具有可比性[8]。其次,儿童型低级别胶质瘤存在耐药、反弹和复发现象,尽管肾素-血管紧张素系统(RAS)/MAPK靶向治疗效果令人鼓舞,但治疗期间仍可能发生肿瘤耐药,也可能因肿瘤复发而终止治疗,或部分患儿停药后3个月内迅速反弹,如何区分上述现象?何时重新启动治疗?尚待更多研究的证实[45]。再次,靶向治疗的最佳持续时间尚不确定,多项临床试验对儿童型低级别胶质瘤进行为期2年的治疗,国际儿童低级别胶质瘤联盟(iPLGGc)临床工作组也推荐将2年作为靶向药物单独治疗时间,但2年的治疗期是经验性治疗,期待未来的药物研究在肿瘤反应、药物毒性和反应持续时间等方面具有可比性[1]。最后,重新启动治疗尚未达成共识[1],对于既往靶向治疗有反应但停药后进展或复发的儿童型低级别胶质瘤患儿,可以考虑同种药物再治疗,但应注意重新启动治疗标准的建立需区分肿瘤反弹与自然进展。

综上所述,对于儿童型低级别胶质瘤,传统药物化疗效果仍有待提高,药物化疗联合抗血管生成药物靶向治疗有望提高疗效,分子靶向治疗发展迅速,疗效令人鼓舞,对于复发性和(或)难治性存在*BRAF*变异、*mTOR*变异或*NTRK*融合的儿童型低级别胶质瘤,可以首选分子靶向治疗,但分子靶向治疗仍存在一些问题和挑战,有待未来更多的研究予以解决。

**利益冲突**　无

## 参　考　文　献

[1] Fangusaro J, Jones DT, Packer RJ, Gutmann DH, Milde T, Witt O, Mueller S, Fisher MJ, Hansford JR, Tabori U, Hargrave D, Bandopadhayay P. Pediatric low-grade glioma: state-of-the-art and ongoing challenges[J]. Neuro Oncol, 2024, 26:25-37.

[2] Broniscer A, Baker SJ, West AN, Fraser MM, Proko E, Kocak M, Dalton J, Zambetti GP, Ellison DW, Kun LE, Gajjar A, Gilbertson RJ, Fuller CE. Clinical and molecular characteristics of malignant transformation of low-grade glioma in children[J]. J Clin Oncol, 2007, 25:682-689.

[3] Margol AS, Yeo KK, Xia C, Onar A, Robison NJ, Freyer DR, Dhall G. A comparative analysis of clinicopathological features and survival among early adolescents/young adults and children with low-grade glioma: a report from the Children's Oncology Group[J]. J Neurooncol, 2018, 140:575-582.

[4] Chen Z, Guo Z, Wang J, Cao D, Xu Y, Dong F, Wan F. Clinical features and outcomes of pediatric intracranial gliomas: results from single center's 226 cases and corroborated with SEER database[J]. Childs Nerv Syst, 2023, 39:593-601.

[5] Williams NL, Rotondo RL, Bradley JA, Pincus DW, Fort JA, Wynn T, Morris CG, Mendenhall NP, Indelicato DJ. Late effects after radiotherapy for childhood low-grade glioma[J]. Am J Clin Oncol, 2018, 41:307-312.

[6] Shi YX, Ma WB, Wang Y. Summary and analysis of clinical features and prognosis in pediatric gliomas based on the SEER database[J]. Zhongguo Xian Dai Shen Jing Ji Bing Za Zhi, 2021, 21:147-155.[石易鑫, 马文斌, 王裕. 基于美国SEER数据库的儿童胶质瘤临床特点和预后分析[J]. 中国现代神经疾病杂志, 2021, 21:147-155.]

[7] de Blank P, Bandopadhayay P, Haas-Kogan D, Fouladi M, Fangusaro J. Management of pediatric low-grade glioma[J]. Curr Opin Pediatr, 2019, 31:21-27.

[8] Mueller S, Fangusaro J, Thomas AO, Jacques TS, Bandopadhayay P, de Blank P, Packer RJ, Fouladi M, van Meeteren AS, Jones D,

Perry A, Nakano Y, Hargrave D, Riedl D, Robison NJ, Partanen M, Fisher MJ, Witt O. Consensus framework for conducting phase Ⅰ/Ⅱ clinical trials for children, adolescents, and young adults with pediatric low-grade glioma: guidelines established by the International Pediatric Low-Grade Glioma Coalition Clinical Trial Working Group[J]. Neuro Oncol, 2024, 26:407-416.

[9] Ater JL, Zhou T, Holmes E, Mazewski CM, Booth TN, Freyer DR, Lazarus KH, Packer RJ, Prados M, Sposto R, Vezina G, Wisoff JH, Pollack IF. Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: a report from the Children's Oncology Group[J]. J Clin Oncol, 2012, 30:2641-2647.

[10] Gnekow AK, Walker DA, Kandels D, Picton S, Giorgio Perilongo, Grill J, Stokland T, Sandstrom PE, Warmuth-Metz M, Pietsch T, Giangaspero F, Schmidt R, Faldum A, Kilmartin D, De Paoli A, De Salvo GL; Low Grade Glioma Consortium and the Participating Centers. A European randomised controlled trial of the addition of etoposide to standard vincristine and carboplatin induction as part of an 18-month treatment programme for childhood (≤16 years) low grade glioma: a final report[J]. Eur J Cancer, 2017, 81:206-225.

[11] Lassaletta A, Scheinemann K, Zelcer SM, Hukin J, Wilson BA, Jabado N, Carret AS, Lafay-Cousin L, Larouche V, Hawkins CE, Pond GR, Poskitt K, Keene D, Johnston DL, Eisenstat DD, Krishnatry R, Mistry M, Arnoldo A, Ramaswamy V, Huang A, Bartels U, Tabori U, Bouffet E. Phase Ⅱ weekly vinblastine for chemotherapy-naïve children with progressive low-grade glioma: a Canadian Pediatric Brain Tumor Consortium study[J]. J Clin Oncol, 2016, 34:3537-3543.

[12] Gururangan S, Fisher MJ, Allen JC, Herndon JE 2nd, Quinn JA, Reardon DA, Vredenburgh JJ, Desjardins A, Phillips PC, Watral MA, Krauser JM, Friedman AH, Friedman HS. Temozolomide in children with progressive low-grade glioma[J]. Neuro Oncol, 2007, 9:161-168.

[13] Massimino M, Spreafico F, Riva D, Biassoni V, Poggi G, Solero C, Gandola L, Genitori L, Modena P, Simonetti F, Potepan P, Casanova M, Meazza C, Clerici CA, Catania S, Sardi I, Giangaspero F. A lower-dose, lower-toxicity cisplatin-etoposide regimen for childhood progressive low-grade glioma[J]. J Neurooncol, 2010, 100:65-71.

[14] Hsu TR, Wong TT, Chang FC, Ho DM, Tang RB, Thien PF, Chang KP. Responsiveness of progressive optic pathway tumors to cisplatin-based chemotherapy in children[J]. Childs Nerv Syst, 2008, 24:1457-1461.

[15] El-Hemaly A, Taha H, Refaat A, Adel F, Elbeltagy M, Arafah O. Efficacy of different salvage regimens in progressive unresectable pediatric low-grade glioma[J]. Oncol Lett, 2022, 24:407.

[16] Ge JJ, Li C, Gao ZM, Xue FJ, Zhang JP. A modified chemotherapy protocol with carboplatin and vincristine for pediatric brain stem low-grade gliomas[J]. Zhonghua Shen Jing Wai Ke Za Zhi, 2017, 33:451-455.[盖菁菁, 李程, 郜志孟, 薛凤君, 张俊平. 卡铂联合长春新碱改良方案治疗儿童脑干低级别胶质瘤[J]. 中华神经外科杂志, 2017, 33:451-455.]

[17] Ge JJ, Li C, Zhang JP. Long-term remission of recurrent brainstem pilocytic astrocytoma with neuraxis dissemination using recombinant human endostatin after failure of vincristine and carboplatin[J]. World Neurosurg, 2018, 110:397-402.

[18] Green K, Panagopoulou P, D'Arco F, O'Hare P, Bowman R, Walters B, Dahl C, Jorgensen M, Patel P, Slater O, Ahmed R, Bailey S, Carceller F, Collins R, Corley E, English M, Howells L, Kamal A, Kilday JJ, Lowis S, Lumb B, Pace E, Picton S, Pizer B, Shafiq A, Uzunova L, Wayman H, Wilson S, Hargrave D, Opocher E. A nationwide evaluation of bevacizumab-based treatments in pediatric low-grade glioma in the UK: safety, efficacy, visual morbidity, and outcomes[J]. Neuro Oncol, 2023, 25:774-785.

[19] Hwang EI, Jakacki RI, Fisher MJ, Kilburn LB, Horn M, Vezina G, Rood BR, Packer RJ. Long-term efficacy and toxicity of bevacizumab-based therapy in children with recurrent low-grade gliomas[J]. Pediatr Blood Cancer, 2013, 60:776-782.

[20] Bale TA, Rosenblum MK. The 2021 WHO Classification of Tumors of the Central Nervous System: an update on pediatric low-grade gliomas and glioneuronal tumors[J]. Brain Pathol, 2022, 32:e13060.

[21] Sun CR, Xu JH, Zhang BY, Xu SS, Dong F, Wei BX, Jiang B, Zhang JM. Interpretation on pediatric-type diffuse gliomas in the 2021 WHO Classification of Tumors of the Central Nervous System (fifth edition)[J]. Zhongguo Xian Dai Shen Jing Ji Bing Za Zhi, 2021, 21:791-803.[孙崇然, 许晶虹, 张布衣, 许素素, 董飞, 卫博星, 蒋飚, 张建民. 2021年世界卫生组织中枢神经系统肿瘤分类(第五版)儿童型弥漫性胶质瘤分类解读[J]. 中国现代神经疾病杂志, 2021, 21:791-803.]

[22] Ryall S, Tabori U, Hawkins C. Pediatric low-grade glioma in the era of molecular diagnostics[J]. Acta Neuropathol Commun, 2020, 8:30.

[23] Lassaletta A, Zapotocky M, Mistry M, Ramaswamy V, Honnorat M, Krishnatry R, Guerreiro Stucklin A, Zhukova N, Arnoldo A, Ryall S, Ling C, McKeown T, Loukides J, Cruz O, de Torres C, Ho CY, Packer RJ, Tatevossian R, Qaddoumi I, Harreld JH, Dalton JD, Mulcahy-Levy J, Foreman N, Karajannis MA, Wang S, Snuderl M, Nageswara Rao A, Giannini C, Kieran M, Ligon KL, Garre ML, Nozza P, Mascelli S, Raso A, Mueller S, Nicolaides T, Silva K, Perbet R, Vasiljevic A, Faure Conter C, Frappaz D, Leary S, Crane C, Chan A, Ng HK, Shi ZF, Mao Y, Finch E, Eisenstat D, Wilson B, Carret AS, Hauser P, Sumerauer D, Krskova L, Larouche V, Fleming A, Zelcer S, Jabado N, Rutka JT, Dirks P, Taylor MD, Chen S, Bartels U, Huang A, Ellison DW, Bouffet E, Hawkins C, Tabori U. Therapeutic and prognostic implications of BRAF V600E in pediatric low-grade gliomas[J]. J Clin Oncol, 2017, 35:2934-2941.

[24] Hargrave DR, Bouffet E, Tabori U, Broniscer A, Cohen KJ, Hansford JR, Geoerger B, Hingorani P, Dunkel IJ, Russo MW, Tseng L, Dasgupta K, Gasal E, Whitlock JA, Kieran MW. Efficacy and safety of dabrafenib in pediatric patients with *BRAF* V600 mutation-positive relapsed or refractory low-grade glioma: results from a phase Ⅰ/Ⅱ a study[J]. Clin Cancer Res, 2019, 25:7303-7311.

[25] Nicolaides T, Nazemi KJ, Crawford J, Kilburn L, Minturn J, Gajjar A, Gauvain K, Leary S, Dhall G, Aboian M, Robinson G, Long-Boyle J, Wang H, Molinaro AM, Mueller S, Prados M. Phase Ⅰ study of vemurafenib in children with recurrent or progressive $BRAF^{V600E}$ mutant brain tumors: Pacific Pediatric Neuro-Oncology Consortium study (PNOC-002)[J]. Oncotarget, 2020, 11:1942-1952.

[26] Fangusaro J, Onar-Thomas A, Young Poussaint T, Wu S, Ligon AH, Lindeman N, Banerjee A, Packer RJ, Kilburn LB, Goldman S, Pollack IF, Qaddoumi I, Jakacki RI, Fisher PG, Dhall G, Baxter P, Kreissman SG, Stewart CF, Jones DTW, Pfister SM, Vezina G, Stern JS, Panigrahy A, Patay Z, Tamrazi B, Jones JY, Haque SS, Enterline DS, Cha S, Fisher MJ, Doyle LA, Smith M, Dunkel IJ, Fouladi M. Selumetinib in paediatric patients with BRAF-aberrant or neurofibromatosis type 1-associated recurrent, refractory, or progressive low-grade glioma: a multicentre, phase 2 trial[J]. Lancet Oncol, 2019, 20:1011-

1022.

[27] Selt F, van Tilburg CM, Bison B, Sievers P, Harting I, Ecker J, Pajtler KW, Sahm F, Bahr A, Simon M, Jones DTW, Well L, Mautner VF, Capper D, Hernáiz Driever P, Gnekow A, Pfister SM, Witt O, Milde T. Response to trametinib treatment in progressive pediatric low-grade glioma patients[J]. J Neurooncol, 2020, 149:499-510.

[28] Manoharan N, Choi J, Chordas C, Zimmerman MA, Scully J, Clymer J, Filbin M, Ullrich NJ, Bandopadhayay P, Chi SN, Yeo KK. Trametinib for the treatment of recurrent/progressive pediatric low-grade glioma[J]. J Neurooncol, 2020, 149:253-262.

[29] Bouffet E, Hansford JR, Garrè ML, Hara J, Plant-Fox A, Aerts I, Locatelli F, van der Lugt J, Papusha L, Sahm F, Tabori U, Cohen KJ, Packer RJ, Witt O, Sandalic L, Bento Pereira da Silva A, Russo M, Hargrave DR. Dabrafenib plus trametinib in pediatric glioma with *BRAF* V600 mutations[J]. N Engl J Med, 2023, 389:1108-1120.

[30] Barbato MI, Nashed J, Bradford D, Ren Y, Khasar S, Miller CP, Zolnik BS, Zhao H, Li Y, Bi Y, Shord SS, Amatya AK, Mishra-Kalyani PS, Scepura B, Al-Matari RA, Pazdur R, Kluetz PG, Donoghue M, Singh H, Drezner N. FDA approval summary: dabrafenib in combination with trametinib for BRAFV600E mutation-positive low-grade glioma[J]. Clin Cancer Res, 2024, 30:263-268.

[31] Fangusaro J, Onar-Thomas A, Wu S, Poussaint TY, Packer R, Kilburn L, Qaddoumi I, Dhall G, Pollack IF, Lenzen A, Partap S, Fouladi M, Dunkel I. LGG-04. A phase Ⅱ re-treatment study of selumetinib for recurrent or progressive pediatric low-grade glioma (pLGG): a Pediatric Brain Tumor Consortium (PBTC) study[J]. Neuro Oncol, 2020, 22(Suppl 3):ⅲ367.

[32] Leclair NK, Lambert W, Roche K, Gillan E, Gell JJ, Lau CC, Wrubel G, Knopf J, Amin S, Anderson M, Martin JE, Bookland MJ, Hersh DS. Early experience with targeted therapy as a first-line adjuvant treatment for pediatric low-grade glioma[J]. Neurosurg Focus, 2022, 53:E15.

[33] Karajannis MA, Legault G, Fisher MJ, Milla SS, Cohen KJ, Wisoff JH, Harter DH, Goldberg JD, Hochman T, Merkelson A, Bloom MC, Sievert AJ, Resnick AC, Dhall G, Jones DT, Korshunov A, Pfister SM, Eberhart CG, Zagzag D, Allen JC. Phase Ⅱ study of sorafenib in children with recurrent or progressive low-grade astrocytomas[J]. Neuro Oncol, 2014, 16:1408-1416.

[34] Kilburn LB, Khuong-Quang DA, Hansford JR, Landi D, van der Lugt J, Leary SES, Driever PH, Bailey S, Perreault S, McCowage G, Waanders AJ, Ziegler DS, Witt O, Baxter PA, Kang HJ, Hassall TE, Han JW, Hargrave D, Franson AT, Yalon Oren M, Toledano H, Larouche V, Kline C, Abdelbaki MS, Jabado N, Gottardo NG, Gerber NU, Whipple NS, Segal D, Chi SN, Oren L, Tan EEK, Mueller S, Cornelio I, McLeod L, Zhao X, Walter A, Da Costa D, Manley P, Blackman SC, Packer RJ, Nysom K. The type Ⅱ RAF inhibitor tovorafenib in relapsed/refractory pediatric low-grade glioma: the phase 2 FIREFLY-1 trial[J]. Nat Med, 2024, 30:207-217.

[35] Dhillon S. Tovorafenib: first approval[J]. Drugs, 2024.[Epub ahead of print]

[36] van Tilburg CM, Kilburn LB, Perreault S, Schmidt R, Azizi AA, Cruz-Martínez O, Zápotocký M, Scheinemann K, Meeteren AYNS, Sehested A, Opocher E, Driever PH, Avula S, Ziegler DS, Capper D, Koch A, Sahm F, Qiu J, Tsao LP, Blackman SC, Manley P, Milde T, Witt R, Jones DTW, Hargrave D, Witt O. LOGGIC/FIREFLY-2: a phase 3, randomized trial of tovorafenib vs. chemotherapy in pediatric and young adult patients with newly diagnosed low-grade glioma harboring an activating RAF alteration[J]. BMC Cancer, 2024, 24:147.

[37] Haas-Kogan DA, Aboian MS, Minturn JE, Leary SES, Abdelbaki MS, Goldman S, Elster JD, Kraya A, Lueder MR, Ramakrishnan D, von Reppert M, Liu KX, Rokita JL, Resnick AC, Solomon DA, Phillips JJ, Prados M, Molinaro AM, Waszak SM, Mueller S. Everolimus for children with recurrent or progressive low-grade glioma: results from the phase Ⅱ PNOC001 trial[J]. J Clin Oncol, 2024, 42:441-451.

[38] Franz DN, Belousova E, Sparagana S, Bebin EM, Frost M, Kuperman R, Witt O, Kohrman MH, Flamini JR, Wu JY, Curatolo P, de Vries PJ, Whittemore VH, Thiele EA, Ford JP, Shah G, Cauwel H, Lebwohl D, Sahmoud T, Jozwiak S. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial[J]. Lancet, 2013, 381:125-132.

[39] Hasskarl J. Everolimus[J]. Recent Results Cancer Res, 2014, 201:373-392.

[40] Yang JCH, Brose MS, Castro G, Kim ES, Lassen UN, Leyvraz S, Pappo A, López-Ríos F, Reeves JA, Fellous M, Penault-Llorca F, Rudzinski ER, Tabatabai G, Vassal G, Drilon A, Trent J. Rationale and design of ON-TRK: a novel prospective non-interventional study in patients with TRK fusion cancer treated with larotrectinib[J]. BMC Cancer, 2022, 22:625.

[41] Pediatric Oncology Committee of China Anti-Cancer Association, Chinese Research Hospital Association. Chinese expert consensus on clinical application of larotrectinib for the treatment of pediatric tumors with TRK fusion[J]. Zhongguo Zhong Liu Lin Chuang, 2023, 50:865-872.[中国抗癌协会小儿肿瘤专业委员会, 中国研究型医院学会儿童肿瘤专业委员会. 拉罗替尼治疗TRK融合儿童肿瘤中国专家共识[J]. 中国肿瘤临床, 2023, 50:865-872.]

[42] Lee A, Chou AJ, Williams PM, Roy-Chowdhuri S, Patton DR, Coffey BD, Reid JM, Jin Piao J, Lauren Saguilig L, Todd Allen Alonzo TA, Berg SL, Jaju A, Fox E, Hawkins DS, Mooney MK, Takebe N, Tricoli JV, Janeway KA, Seibel N, Parsons DW. Erdafitinb in patients with FGFR-altered tumors: results from the NCI-COG Pediatric MATCH trial arm B (APEC1621B)[J]. J Clin Oncol, 2023, 41(16_suppl):10007.

[43] Farouk Sait S, Fischer C, Antal Z, Spatz K, Prince DE, Ibanez K, Behr GG, Dunkel IJ, Karajannis MA. Slipped capital femoral epiphyses: a major on-target adverse event associated with FGFR tyrosine kinase inhibitors in pediatric patients[J]. Pediatr Blood Cancer, 2023, 70:e30410.

[44] Gonzalez-Vega M, M Lebert B, Campion S, Wagner A, Aguilar-Bonilla A, A Smith A. Fibroblast growth factor receptor 1 gene mutation as a potential risk factor for spontaneous intracranial hemorrhage in pediatric low-grade glioma patients[J]. Neurooncol Adv, 2024, 6:vdae074.

[45] O'Hare P, Cooney T, de Blank P, Gutmann DH, Kieran M, Milde T, Fangusaro J, Fisher M, Avula S, Packer R, Fukuoka K, Mankad K, Mueller S, Waanders AJ, Opocher E, Bouffet E, Raabe E, Werle NE, Azizi AA, Robison NJ, Hernáiz Driever P, Russo M, Schouten N, van Tilburg CM, Sehested A, Grill J, Bandopadhayay P, Kilday JP, Witt O, Ashley DM, Ertl-Wagner BB, Tabori U, Hargrave DR; International Pediatric Low-Grade Glioma Coalition. Resistance, rebound, and recurrence regrowth patterns in pediatric low-grade glioma treated by MAPK inhibition: a modified Delphi approach to build international consensus-based definitions[J]. Neuro Oncol, 2024, 26:1357-1366.

（收稿日期：2024-08-14）
（本文编辑：彭一帆）