·脑胶质瘤·

成人弥漫性中线胶质瘤精准治疗一例

石祥宇 王政 王焕宇 张学斌 杜芳芳 姜炜

【摘要】 **目的** 探索弥漫性中线胶质瘤，*H3* K27M突变型，WHOⅣ级的新型治疗方法。**方法与结果** 女性患者，51岁，病理确诊为弥漫性（左侧额叶、丘脑）中线胶质瘤，*H3* K27M突变型。于手术切除左侧额叶病灶后，经多学科诊疗模式讨论，采取替莫唑胺超早期START化疗方案，治疗3周后头部MRI显示左侧丘脑病灶进展；然后针对颅内病灶行适形调强放射治疗联合依托泊苷（VP-16）节律化疗，根据全外显子组测序提示呈培唑帕尼敏感类型，遂在VP-16节律化疗的基础上联合培唑帕尼序贯治疗。放射治疗后3个月复查MRI提示肿瘤接近完全缓解（神经肿瘤反应评价标准）。**结论** 通过手术切除、放射治疗、药物化疗及靶向治疗的综合治疗策略可以改善弥漫性中线胶质瘤，*H3* K27M突变型患者生存期，但仍需进一步随访观察。

【关键词】 神经胶质瘤； 组蛋白类； 成年人； 精准医学

Precision treatment exploration in a patient with diffuse midline glioma

SHI Xiang-yu[1], WANG Zheng[1], WANG Huan-yu[2], ZHANG Xue-bin[3], DU Fang-fang[1], JIANG Wei[1]
[1]Department of Radiation Oncology, [2]Department of Neurosurgery, [3]Department of Pathology, Tianjin Huanhu Hospital, Tianjin 300350, China
Corresponding author: JIANG Wei (Email: ro7jiang@163.com)

【**Abstract**】 **Objective** To explore new treatment methods for diffuse midline glioma (DMG), *H3* K27M mutant, WHO Ⅳ grade. **Methods** A 51 years old female patient was diagnosed as DMG, *H3* K27M mutant. After resection of the left frontal lobe lesion, we decided to use temozolomide super early chemotherapy treatment named START after multi-disciplinary team (MDT) discussion. After chemotherapy 3 weeks head MRI examination showed the lesion of tumor in the left thalamus had developed. Then conformal intensity-modulated radiotherapy combined with etoposide (VP-16) rhythm chemotherapy was performed for intracranial lesions. The detection of whole exome sequencing (WES) indicated that the patient was sensitive to pazopanib, therefore, treatment of etoposide combined with pazopanib was carried out. **Results** Three months after radiotherapy, the reexamination showed that the tumor nearly achieved complete remission (CR, RANO standard). **Conclusions** The comprehensive treatment strategy of surgery, radiotherapy, chemotherapy and targeted therapy can improve the survival of DMG, *H3* K27M mutant patients, which needs further follow-up observation.

【**Key words**】 Glioma; Histones; Adult; Precision medicine
Conflicts of interest: none declared

2016年世界卫生组织（WHO）中枢神经系统肿瘤分类第四版修订版新增弥漫性中线胶质瘤，*H3* K27M突变型（第27位赖氨酸突变为甲硫氨酸），WHOⅣ级。在新的分类中，以星形胶质细胞分化并伴有组蛋白*H3* K27M基因突变的中线相邻区域、呈浸润性生长的高级别胶质瘤最为常见，好发于儿童，脑干、丘脑或脊髓为其好发部位。目前针对弥漫性中线胶质瘤尚无有效治疗方法，主要局限于传统手术切除肿瘤灶及术后辅助放射治疗，尚未发现手术切除联合药物化疗能够改善患者生存期[1]。近年的研究通过探索发病机制和相关基因突变通路，为发现有效治疗靶点、改善此类患者预后提供了可能[2]。本文报告1例弥漫性中线胶质瘤，*H3* K27M突变型，WHOⅣ级病例经手术最大程度安全切除病灶后，同步施行放射治疗、药物化疗及靶向治疗等

doi:10.3969/j.issn.1672-6731.2019.12.010

作者单位：300350 天津市环湖医院肿瘤放射治疗科（石祥宇、王政、杜芳芳、姜炜），神经外科（王焕宇），病理科（张学斌）
通讯作者：姜炜，Email：ro7jiang@163.com

综合治疗方案的疗效，拟探索此类患者的新型治疗方法。

病例资料

患者 女性，51岁。主因间断性头痛1个月、加重1天，于2018年5月11日入院。患者1个月前无诱因出现间断性头部胀痛，以额顶部最为显著，每日发作3～5次，持续10～30分钟后自行缓解，严重时可伴有恶心呕吐（非喷射状），呕吐物为胃内容物，呕吐后头痛症状略有好转。入院前1周曾于外院行头部CT及MRI检查，提示左侧丘脑、额叶多发结节灶，考虑颅内多发占位性病变，为进一步明确诊断至我院就诊，以“颅内占位性病变”收入院。患者自发病以来，精神、睡眠尚可，大小便如常，体重无明显减轻。既往史、个人史及家族史均无特殊。

诊断与治疗过程 入院后体格检查：体温为36.5 ℃，脉搏89次/min，呼吸为18次/min，血压为123/82 mm Hg（1 mm Hg = 0.133 kPa）。神经系统及实验室检查未发现明显阳性体征或异常指标。头部CT平扫显示颅内多发占位性病灶，分别位于左侧丘脑、额叶，左侧侧脑室额角轻度受压。头部MRI检查显示，左侧额叶、双侧丘脑、右侧大脑脚占位性病变，FLAIR成像呈略高信号，T_1WI呈低信号；增强扫描后左侧额叶和丘脑病灶呈明显强化改变，信号欠均匀，边界尚清晰，其中左侧额叶病灶4.52 cm × 4.16 cm × 4.03 cm（图1）。胸部CT平扫未见明显异常。肝胆胰脾、双肾等器官超声检查未见明显异常。根据上述临床特征及各项辅助检查结果，临床拟诊颅内多发性胶质瘤。入院后2周（2018年5月23日）行左侧额叶病灶探查术并手术切除病灶，术中冰冻病理回报为高级别胶质瘤，进一步肉眼全切左侧额叶病灶。术后24小时CT平扫显示病灶切除范围较为满意。手术切除组织大体标本观察：呈灰白、灰红不规整形组织数块，边界无包膜，与周围正常组织无明显边界，供血血管丰富，约4.02 cm × 3.51 cm × 3.43 cm。HE染色：肿瘤细胞弥漫分布，胞核呈圆形或卵圆形，异型性明显，染色质浓集深染，核分裂象易见，并可见血管内皮细胞增生及小灶性出血、坏死。免疫组织化学染色：显微镜（EnVision二步法 × 400）下可见部分胞核H3K27M表达阳性、H3K27Me表达阴性；Ki-67抗原标记指数为42.5%（WHOⅣ级）。组织病理诊断为弥漫性中线胶质瘤，*H3* K27M突变型。鉴于弥漫性中线胶质瘤，*H3* K27M突变型，WHOⅣ级患者预后不良，为筛选有效的化疗药物，在征得患者及其家属的同意后，进一步行全外显子组测序[WES，领星生物科技（上海）有限公司]，结果显示，*H3F3A*基因p.K28M位点存在突变；*FGFR3*、*PDGFRA*、*KIT*扩增同时伴有*PDGFRA*突变。由于仅切除左侧额叶病灶，而未行双侧丘脑病灶切除，为最大限度地控制肿瘤生长，经多学科诊疗模式（MDT）讨论，决定采取START方案中替莫唑胺超早期药物化疗[75 mg/(m^2·d)口服]方案[3]，患者在治疗期间出现右侧肢体麻木，未予特殊处理，化疗后3周（2018年6月15日）MRI、FLAIR成像平扫（图2a，2b）及T_1WI增强扫描（图2c，2d）均显示，左侧丘脑残留灶体积较治疗前明显增大，考虑左侧丘脑肿瘤进展；随后（2018年6月16日）予以照射剂量为40 Gy（2 Gy/次，共20次）的调强放射治疗（IMRT，图3），并同步行依托泊苷（VP-16）50 mg/d节律药物化疗。当累积照射剂量达40 Gy（2 Gy/次，共20次）后再次行头部MRI检查（2018年7月16日），显示颅内原有病灶控制稳定，左侧丘脑残留灶未再增长。结合既往对此类患者的治疗经验[4]，在40 Gy（2 Gy/次，共20次）的照射剂量基础上，针对左侧丘脑的T_1WI强化区域予以同期推量调强放射治疗（SIB-IMRT）23 Gy（2.30 Gy/次，共10次），同时针对FLAIR成像异常区域以18 Gy（1.80 Gy/次，共10次）进行同期照射，相应剂量分布及剂量体积直方图（DVH）参见图4。

预后与随访 患者放射治疗后1个月（2018年9月4日）进行头部MRI及FLAIR成像检查，可见颅内原有异常高信号范围明显缩小（图5a），增强T_1WI扫描显示左侧丘脑病灶区域异常强化信号缩小、占位效应减轻（图5b）。此时患者一般状况良好，右侧肢体麻木症状基本缓解，KPS评分为100分；继续接受VP-16节律化疗，依据全外显子组测序结果，同时予培唑帕尼（pazopanib）800 mg/d。放射治疗后3个月（2018年11月7日）头部MRI及FLAIR成像显示，颅内原有异常信号范围进一步缩小（图6a），增强T_1WI可见左侧丘脑病灶区域原有异常强化信号几乎消失（图6b）；患者无任何神经系统症状与体征，无需接受激素治疗，根据神经肿瘤反应评价（RANO）标准，考虑肿瘤完全缓解（CR）[5]。

讨 论

2016年WHO中枢神经系统肿瘤分类第四版修

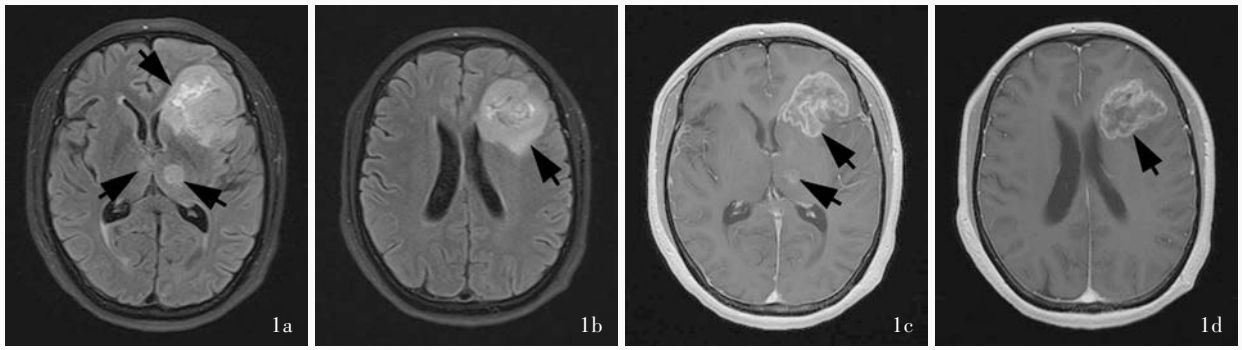


图1 头部MRI检查所见(2018年5月14日) 1a 横断面FLAIR成像显示,双侧丘脑、左侧额叶占位性病变(箭头所示) 1b 横断面FLAIR成像显示左侧额叶占位性病变(箭头所示) 1c 横断面增强T_1WI显示左侧额叶及丘脑病灶呈明显强化改变(箭头所示) 1d 横断面增强T_1WI显示左侧额叶病灶呈明显强化改变(箭头所示)

Figure 1 Head MRI findings on May 14, 2018 Axial FLAIR showed space occupying lesions of bilateral thalamus and left frontal lobe (arrows indicate, Panel 1a). Axial FLAIR showed occupying lesions in left frontal lobe (arrow indicates, Panel 1b). Axial enhanced T_1WI showed the lesions of left frontal lobe and thalamus obvious enhancement changes (arrows indicate, Panel 1c). Axial enhanced T_1WI showed the lesions of left frontal lobe obvious enhancement (arrow indicates, Panel 1d).

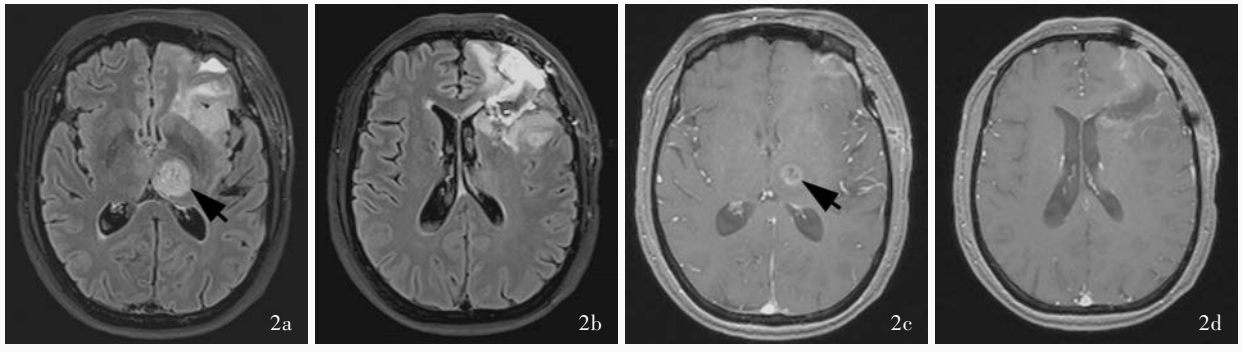
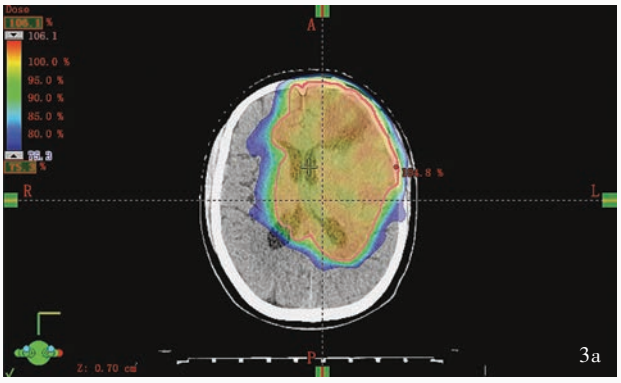


图2 头部MRI检查所见(2018年6月15日) 2a 横断面FLAIR成像显示左侧丘脑肿瘤体积较治疗前明显增大(箭头所示) 2b 横断面FLAIR成像显示左侧额叶病灶切除术后改变 2c 横断面增强T_1WI扫描可见左侧丘脑肿瘤强化范围较治疗前明显增大(箭头所示) 2d 横断面增强T_1WI扫描显示左侧额叶病灶切除术后改变

Figure 2 Head MRI findings on June 15, 2018 Axial FLAIR showed volume of tumor in left thalamus was significantly larger than that before treatment (arrow indicates, Panel 2a). Axial FLAIR showed changes after focus resection in left frontal lobe (Panel 2b). Axial enhanced T_1WI showed the enhancement range of tumor in the left thalamus was significantly larger than that before treatment (arrow indicates, Panel 2c). Axial enhanced T_1WI showed changes after focus resection in the left frontal lobe (Panel 2d).

订版将弥漫性中线胶质瘤,*H3* K27M突变型定义为弥漫性浸润性中线高级别胶质瘤,以星形胶质细胞分化和组蛋白*H3* F3A突变或更少见的*HIST1H3B* K27M突变为主要特征。以脑干、丘脑和脊髓为好发部位,好发于儿童,成人相对少见,患者大多预后不良[6]。Kleinschmidt-DeMasters和Mulcahy Levy[7]认为,伴有*H3* K27M突变的成人弥漫性中线胶质瘤预后与儿童患者相似,总生存期(OS)仅为9.3个月。

本文病例左侧额叶病灶手术切除后经组织病理确诊为弥漫性中线胶质瘤,*H3* K27M突变型。术后患者虽接受START方案替莫唑胺超早期化疗,但右侧肢体麻木症状持续加重,复查MRI提示左侧丘脑病灶出现明显进展。MDT团队就后续手术及辅助放射治疗及药物化疗方案进行讨论:(1)由于左侧丘脑病灶手术切除可能造成严重的神经功能损害,因此暂不考虑外科手术。(2)对于经组织病理确诊的胶质母细胞瘤患者,美国放射治疗肿瘤学组(RTOG)0525指出,相对于标准药物化疗方案对患者生存期的影响,替莫唑胺剂量密度化疗方案并不能使患者进一步获益[8],大多数患者对替莫唑胺START方案-超早期药物化疗无效,而且在本文患者左侧额叶病灶中未发现O^6-甲基鸟嘌呤-DNA甲基转移酶(*MGMT*)启动子区甲基化现象,因此不考虑继续应用替莫唑胺治疗。(3)依据美国国立综合癌症网(NCCN)指南[9]推荐标准,调强放射治疗可最大限度保护靶区周围的正常组织[10];鉴于本文病例既往无放射治疗史,故考虑对其双侧丘脑未行手术切除的病灶,以及左侧额叶手术区域施行调强放射治



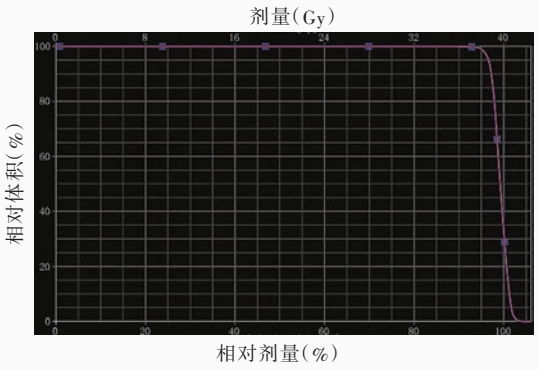
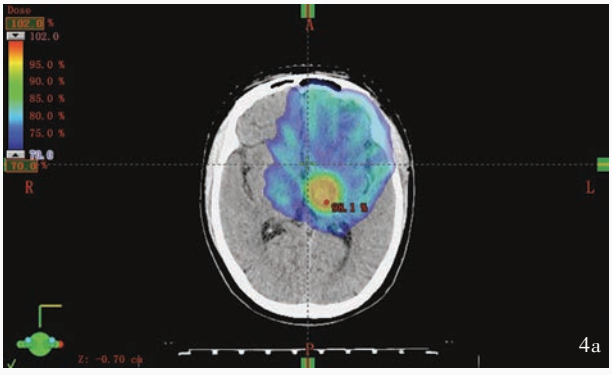


图3 调强放射治疗(总剂量40 Gy,2 Gy/次、共20次) 3a 剂量分布图显示,放疗靶区包括术后残留病灶区域和瘤床周围亚临床病灶(水肿区) 3b 由剂量体积直方图可见,计划靶体积(PTV)要求95%靶体积剂量达40 Gy(2 Gy/次,共20次)处;其最大剂量为<110%

Figure 3 IMRT (total 40 Gy, 2 Gy/time, 20 times) The target volume of radiotherapy includes residual focus area and subclinical focus (edema) around tumor bed (Panel 3a). PTV requires 90% target volume dose of 40 Gy (2 Gy/time, 20 times), and the maximum dose was less than 110% (Panel 3b).



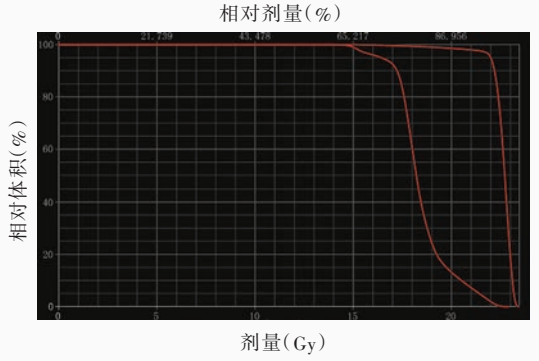
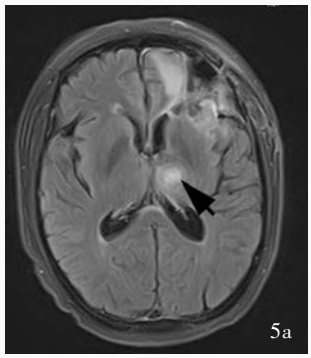
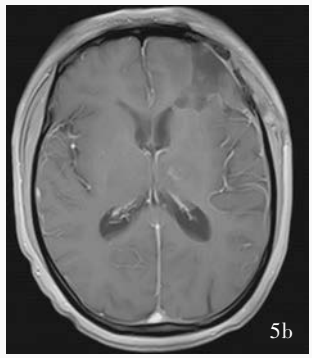
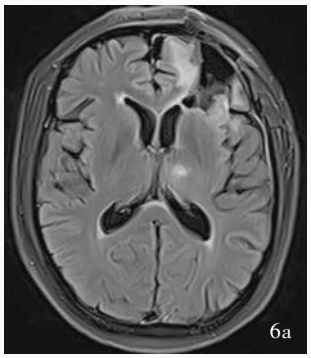


图4 同步推量调强放射治疗(总剂量23 Gy,2.30 Gy/次、共10次) 4a 剂量分布图显示,同步推量放疗靶区包括左侧丘脑强化病灶及FLAIR成像异常区域 4b 剂量体积直方图显示,PTV1体积剂量为23 Gy(2.30 Gy/次,共10次)处、PTV2体积剂量为18 Gy(1.80 Gy/次,共10次)处,均达到靶体积剂量的95%;最大剂量<110%

Figure 4 SIB-IMRT (total 23 Gy, 2.30 Gy/time, 10 times) The target volume of SIB-IMRT included enhanced area of left thalamus and abnormal area of FLAIR imaging (Panel 4a). PTV1 requires 95% target volume dose of 23 Gy (2.30 Gy/time, 10 times) and PTV2 requires 95% target volume dose of 18 Gy (1.80 Gy/time, 10 times). The maximum dose was less than 110% (Panel 4b).







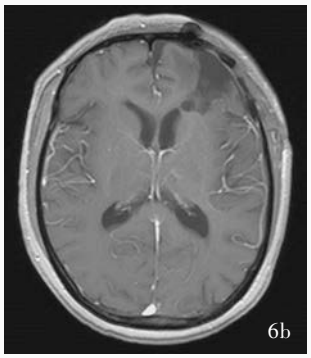


图5 头部MRI检查所见(2018年9月4日) 5a 横断面FLAIR成像显示左侧丘脑异常高信号范围明显缩小(箭头所示) 5b 横断面增强T_1WI显示左侧丘脑异常强化范围明显缩小,占位效应减轻 **图6** 头部MRI检查所见(2018年11月7日) 6a 横断面FLAIR成像显示左侧丘脑异常高信号范围进一步缩小 6b 横断面增强T_1WI显示左侧丘脑病灶区异常强化信号几近消失

Figure 5 Head MRI findings on September 4, 2018 Axial FLAIR showed the range of abnormal high signal of left thalamus was significantly reduced (arrow indicates, Panel 5a). Axial enhanced T_1WI showed the abnormal enhanced signal in the lesion area of left thalamus was significantly reduced, and the space occupying effect was reduced (Panel 5b). **Figure 6** Head MRI findings on November 7, 2018 Axial FLAIR showed the abnormal high signal range of left thalamus was further reduced (Panel 6a). Axial enhanced T_1WI showed the abnormal enhancement signal in the lesion area of the left thalamus almost disappeared (Panel 6b).

疗。(4)节律化疗是针对患者的一种紧密的、规律的、相对低剂量的细胞毒类药物化疗策略,由于节律性化疗抗肿瘤机制不仅可对呈增殖生长的肿瘤细胞产生细胞毒性作用,同时还兼具抗血管生成和免疫增强作用[11-12],因此理论上适用于具备高度血管生成特征的胶质母细胞瘤病例。本文病例颅内肿瘤是呈高度恶性的弥漫性中线胶质瘤,*H3* K27M突变型,组织病理检查显示明显的血管内皮细胞增生及小灶性出血、坏死,因此,在放射治疗期间应同步施行VP-16节律化疗。(5)该例患者左侧额叶病变经全外显子组测序,在明确弥漫性中线胶质瘤,*H3* K27M突变型的诊断的同时,还发现*FGFR3*、*PDGFRA*、*KIT*扩增并伴*PDGFRA*突变。培唑帕尼是一种具有干扰肿瘤细胞存活和生长所需的抗血管生成的新型口服血管生成抑制剂,作为多靶点酪氨酸激酶抑制剂(TKI)药物可覆盖上述所有靶点[13],因此经讨论确定采取多靶点TKI药物培唑帕尼联合治疗方案。

根据上述多学科诊疗讨论结果,经征得患者同意后施行SIB-IMRT适形调强放射治疗联合VP-16节律化疗,以及培唑帕尼靶向治疗的综合方案。目前患者病情稳定,生存期已达17个月。放射治疗后3个月,复查MRI提示肿瘤基本缓解,接近RANO标准中的完全缓解,目前仍定期复查,并探索进一步的治疗。

利益冲突 无

参 考 文 献

[1] Meel MH, Kaspers GJL, Hulleman E. Preclinical therapeutic targets in diffuse midline glioma[J]. Drug Resist Updat, 2019, 44:15-25.

[2] Fleischhack G, Massimino M, Warmuth-Metz M, Khuhlaeva E, Janssen G, Graf N, Rutkowski S, Beilken A, Schmid I, Biassoni V, Gorelishev SK, Kramm C, Reinhard H, Schlegel PG, Kortmann RD, Reuter D, Bach F, Iznaga-Escobar NE, Bode U. Nimotuzumab and radiotherapy for treatment of newly diagnosed diffuse intrinsic pontine glioma (DIPG): a phase Ⅲ clinical study[J]. J Neurooncol, 2019, 143:107-113.

[3] Mao Y, Yao Y, Zhang LW, Lu YC, Chen ZP, Zhang JM, Qi ST, You C, Wang RZ, Yang SY, Zhang X, Wang JS, Chen JX, Yang QY, Shen H, Li ZY, Wang X, Ma WB, Yang XJ, Zhen HN, Zhou LF. Does early postsurgical temo-zolomide plus concomitant radiochemotherapy regimen have any benefit in newly-diagnosed glioblastoma patients: a multi-center, randomized, parallel, open-label, phase Ⅱ clinical trial[J]? Chin Med J (Engl), 2015, 128:2751-2758.

[4] Wang Z, Jiang W, Pang QS, Wang P. Safety analysis of intensity-modulated radiation therapy of glioblastoma with simultaneous integrated boost technique[J]. Zhonghua Fang She Zhong Liu Xue Za Zhi, 2015, 24:431-433.[王政, 姜炜, 庞青松, 王平. 胶质母细胞瘤同期推量IMRT安全性分析[J]. 中华放射肿瘤学杂志, 2015, 24:431-433.]

[5] Chang SM, Wen PY, Vogelbaum MA, Macdonald DR, Bent MJ. Response assessment in neuro-oncology (RANO): more than imaging criteria for malignant glioma. Table 1[J]. Neurooncol Pract, 2015, 2:205-209.

[6] He P, Chen W, Qiu XX, Xi YB, Guan H, Xia J. A rare high-grade glioma with a histone H3 K27M mutation in the hypothalamus of an adult patient[J]. World Neurosurg, 2019, 128:527-531.

[7] Kleinschmidt-DeMasters BK, Mulcahy Levy JM. H3 K27M-mutant gliomas in adults vs. children share similar histological features and adverse prognosis[J]. Clin Neuropathol, 2018, 37:53-63.

[8] Gilbert MR, Wang M, Aldape KD, Stupp R, Hegi ME, Jaeckle KA, Armstrong TS, Wefel JS, Won M, Blumenthal DT, Mahajan A, Schultz CJ, Erridge S, Baumert B, Hopkins KI, Tzuk-Shina T, Brown PD, Chakravarti A, Curran WJ Jr, Mehta MP. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase Ⅲ clinical trial[J]. J Clin Oncol, 2013, 31:4085-4091.

[9] National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Central Nervous System Cancers, Version 2[DB/OL]. 2019[2019-09-16]. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

[10] Amelio D, Lorentini S, Schwarz M, Amichetti M. Intensity-modulated radiation therapy in newly diagnosed glioblastoma: a systematic review on clinical and technical issues[J]. Radiother Oncol, 2010, 97:361-369.

[11] Kerbel RS, Kamen BA. The anti-angiogenic basis of metronomic chemotherapy[J]. Nat Rev Cancer, 2004, 4:423-436.

[12] Lutsiak ME, Semnani RT, De Pascalis R, Kashmiri SV, Schlom J, Sabzevari H. Inhibition of CD4 (+)25+ T regulatory cell function implicated in enhanced immune response by low-dose cyclophosphamide[J]. Blood, 2005, 105:2862-2868.

[13] Hurwitz HI, Dowlati A, Saini S, Savage S, Suttle AB, Gibson DM, Hodge JP, Merkle EM, Pandite L. Phase Ⅰ trial of Pazopanib in patients with advanced cancer[J]. Clin Cancer Res, 2009, 15:4220-4227.

(收稿日期:2019-12-16)