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CLINICAL INVESTIGATION

Nimotuzumab Combined With Chemoradiation Therapy in Newly Diagnosed Pediatric Diffuse Intrinsic Pontine Glioma

Yanwei Liu, MD,[a] Chao Liu, MD,[b] Gang Wang, MD,[c] Rongjie Tao, MD,[d] Jiankun Xu, MD,[e] Liangfang Shen, MD,[b] Heling Wang, MD,[c] Chuanying Zhu, MD,[f] Hui Zhang, MD,[d] Gao Zeng, MD,[g] Jidong Hong, MD,[b] Baoshi Chen, MD,[a] Shujun Wang, MD,[c] Wenlan Bao, MD,[f] Jia Yang, MD,[d] Qingtang Lin, MD,[g] Huan Li, MD,[b] Jing Zhang, MD,[a] Shuai Liu, MD,[a] Wei Zhang, MD,[c] Shuxian Chen, MD,[f] Yongrui Zhao, MD,[e] Jianbing Tang, MD,[b] Zhen Kou, MD,[c] Jun Su, MD,[f] Peng Sun, MD,[g] Longyun Wang, MD,[b] Xiaoyang Sun, MD,[f] Yan Ju, MD,[h] Wenbin Ma, MD,[i] Yu Wang, MD,[i] Xuejiao Shi, MD,[f] Xiaoguang Qiu, MD,[a] and Mawei Jiang, MD[f]

[a]Department of Radiation Oncology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China; [b]Department of Oncology, Xiangya Hospital Central South University, Changsha, China; [c]Department of Radiation Oncology, The Third People's Hospital Of Zhengzhou, Zhengzhou, China; [d]Department of Surgery, Shandong Cancer Hospital & Institute, Jinan, China; [e]Department of Radiation Oncology, Xuan Wu Hospital Capital Medical University, Beijing, China; [f]Department of Radiation Oncology, Xinhua Hospital Affiliated To Shanghai Jiao Tong University School of Medicine, Shanghai, China; [g]Department of Neurosurgery, Xuan Wu Hospital Capital Medical University, Beijing, China; [h]Department of Neurosurgery, West China School of Medicine/West China Hospital of Sichuan University, Chengdu, China; and [i]Department of Neurosurgery, Peking Union Medical College Hospital, Beijing, China

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Purpose: Diffuse intrinsic pontine glioma (DIPG) is a rare and fatal pediatric malignancy of the brainstem with a lack of effective therapeutic options. This study assesses the efficacy and safety of adding nimotuzumab to temozolomide (TMZ) chemoradiation therapy for newly diagnosed pediatric DIPG.

Methods and Materials: We conducted an open-label, single-arm, prospective, multicenter study involving children aged 3-15 years with histologically or radiographically confirmed DIPG from April 3, 2021 to April 13, 2023. Nimotuzumab (150 mg/m^2/wk) was administered concurrently with local radiation therapy (54 Gy/30 f) and TMZ (75 mg/m^2/d) for 6 weeks,

Corresponding authors: Mawei Jiang, MD, E-mail: jiangmawei@xinhuamed.com.cn; and Xiaoguang Qiu, MD, E-mail: qiuxiaoguang@bjtth.org.

Authors responsible for statistical analysis: Yanwei Liu, MD; Email: liuyanwei@bjtth.org and Chao Liu, MD; Email: liuchao854@csu.edu.cn

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Yanwei Liu and Chao Liu contributed equally.

Contributors: X.Q., M.J., Y.L., and C.L.: study concept and design; X.Q., M.J., Y.L, C.L., G.W., R.T., J.X., L.S., H.W., C.Z., H.Z., G.Z., J.H., B.C., S.W., W.B., J.Y. and Q.L.: implementation; Y. L., C.L., H.L., J.Z., S.L., W.Z., S.C., Y.Z., J.T., Z.K., J.S., P.S., L.W., X.S., Y.J., W.M., Y.W., and X.S: acquisition, analysis, and interpretation of data; and all authors: preparation/review of the manuscript.

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Data Sharing Statement: Patient-level data collected as part of this study are not available for analysis by independent researchers. Aggregated data will be provided via publicly accessible databases as required by law. For more information, please contact the corresponding author.

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followed by adjuvant TMZ (150-200 mg/m^2 for 5 consecutive days of a 28-day cycle for 6 cycles) and nimotuzumab (150 mg/m^2 biweekly until to disease progression). The primary endpoint was objective response rate (ORR). The secondary endpoints were overall survival (OS), progression-free survival (PFS), and safety. Adverse events were summarized using descriptive statistics.

Results: Of 48 enrolled patients, with a median age of 7 years (4-14), 28 (58.3%) were histologically confirmed, and 25 (89.3%) had *H3K27M* mutations. With a median follow-up of 26.5 months (95% CI, 14.6-not applicable), the ORR was 37.5%; the median OS and PFS were 10.5 (8.3-11.2) and 7.8 (5.1-8.4) months; and 1-year OS and PFS rates were 33.3% and 26.9%, respectively. Multivariate analysis showed that a partial response and no steroid use were associated with favorable OS. Distant metastasis was observed in 7 patients (14.6%). The most common grade ≥ 3 treatment-related adverse events were leukopenia (27.1%), lymphopenia (27.1%), and neutropenia (25.0%).

Conclusions: Adding nimotuzumab to chemoradiation therapy is feasible, with ORR and survival rates favorably comparable with previous data in pediatric DIPG, despite not meeting the prespecified statistical significance for improved ORR compared with historical data. The overall safety profile was manageable, with no new safety concerns.

Introduction

Diffuse intrinsic pontine glioma (DIPG) is a rare and aggressive brain tumor originating from the pontine region, with an estimated 200-300 new pediatric cases diagnosed annually in the United States.[1] DIPG has a poor prognosis, with a median survival <1 year and a 2-year overall survival (OS) rate of only 5%, making it a leading cause of death among pediatric brain tumors.[2,3] Unlike other gliomas, debulking surgery is generally not recommended for DIPG because of its deep location, infiltrative growth pattern, and diffuse spread. Biopsy followed by radiation therapy remains the cornerstone of treatment, offering improved quality of life and a modest survival benefit.[2] Various studies, predominantly in phases I and II, have explored radiation therapy combined with chemotherapy, targeted therapy, or immunotherapy; however, definitive positive outcomes are inconclusive.[3-5]

The epidermal growth factor receptor (EGFR) is frequently overexpressed and mutated in high-grade gliomas, including DIPG.[6,7] Nimotuzumab, a humanized monoclonal antibody targeting EGFR, inhibits its activation by blocking ligand binding,[8] thereby disrupting downstream signaling pathways such as Ras/Raf/MAPK, PI3K/Akt, and JAK/STAT, which are critical to tumor processes including angiogenesis, invasion, and metastasis.[9,10] In vitro and in vivo experiments demonstrated that nimotuzumab may enhance radiation therapy sensitivity by reducing tumor vasculature and the number of radioresistant cancer stem cells.[11,12] Preclinical studies have suggested synergistic effects between nimotuzumab and temozolomide (TMZ) in reducing proliferation and angiogenesis, and increasing apoptosis in glioma cells.[13] A meta-analysis including 655 patients with advanced nasopharyngeal carcinoma showed the efficacy and safety of nimotuzumab combined with radiation therapy or chemotherapy.[14] Furthermore, nimotuzumab's ability to cross the blood−brain barrier and selectively accumulate in tumor lesions has been confirmed by imaging studies.[15] A phase 2 trial involving 47 pediatric patients with recurrent DIPG indicated that a small subset appeared to benefit from nimotuzumab monotherapy.[16] Therefore, these findings provide the data on the synergistic effect of combining nimotuzumab with radiation therapy and chemotherapy. A pilot phase 2 protocol on nimotuzumab with concomitant radiation and vinorelbine chemotherapy for pediatric DIPG was well tolerated. This protocol combined with reirradiation for locally-relapsing tumors led to OS of 15 months.[17] Nimotuzumab, when administered concomitantly and continued after radiation therapy was well tolerated and demonstrated efficacy comparable with TMZ chemoradiation therapy in pediatric DIPG.[18,19] These data indicate that combining nimotuzumab with concomitant radiation and TMZ chemotherapy may further improve outcomes in pediatric DIPG.

Therefore, we investigated the efficacy and safety of nimotuzumab combined with radiation therapy and TMZ chemotherapy to treat newly diagnosed pediatric DIPG. The cooperative sensitization effects provide a basis for the combination treatment of pediatric DIPG.

Methods and Materials

Patients

Patients who met the following criteria were enrolled: histologically or radiographically diagnosed as new pediatric DIPG according to the diagnostic criteria (2016/2021 World Health Organization Classification)[20]; aged 3-15 years; tumor measurably and diffusely infiltrating the pons, with a tumor diameter over 50% of the pons; Lansky score ≥ 60; and OS predicted to be over 3 months. The main exclusion criteria were recurrent disease, cerebrospinal fluid dissemination or distant metastasis at diagnosis, and a history of antitumor therapy, including debulking surgery (biopsy was permitted), chemoradiation therapy, targeted therapy, or immunotherapy. Patients were allowed to taper corticosteroids at a clinically appropriate pace and discontinue their use, if possible, before the study treatment. Written informed parental consent (and assent for older children) was taken.

Study design and treatment

This single-arm, prospective, multicenter study was conducted at 8 institutions in China. For all enrolled patients, a total dose of 54 Gy/30 fractions was prescribed using the intensity modulated radiation therapy/volumetric modulated arc therapy technique, not exceeding 7 weeks. The gross tumor volume included neuroimaging-based visible tumors indicated by fluid-attenuated inversion-recovery (FLAIR) or T2-weighted sequences. The clinical target volume consisted of a gross tumor volume + 1.0-1.5-cm margin, and the planning target volume consisted of an additional 3.0-mm margin. Starting on day 1 of radiation therapy, TMZ capsules, 75 mg/m^2/d, were orally administered until the end of radiation therapy. During the concurrent chemoradiation therapy period, nimotuzumab (150 mg/m^2) was intravenously administered weekly for 6 weeks. Maintenance nimotuzumab therapy began 1 week after radiation, and maintenance TMZ therapy began 4 weeks after radiation. During maintenance therapy, nimotuzumab, 150 mg/m^2, was administered biweekly consecutively up to 52 weeks or until disease progression. The dose of TMZ at the first cycle was 150 mg/m^2/d for 5 consecutive days, with 23 days of rest (1 treatment course: 28 days). If the adverse event (AE) was ≤grade 2 (except for alopecia, nausea, and vomiting), the absolute neutrophil count was ≥1.5 × 10^9/L, and the platelet count was ≥100 × 10^9/L, the dose was elevated to 200 mg/m^2/d for 5 days with 23 days of rest, that is, 28 days as a course of treatment from the second cycle. A total of 6 TMZ cycles were administered (Fig. E1).

The trial was conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable local laws, following approval from the independent ethics committees of the participating centers.

Assessments

Baseline evaluation was conducted using contrast-enhanced magnetic resonance imaging (MRI) (T1-weighted, T2-weighted, FLAIR, and contrast-enhanced T1-weighted sequences; slice thickness, 3-4 mm) of the whole brain and spine. Efficacy was evaluated using contrast-enhanced brain MRI 4 weeks after completion of radiation therapy, and subsequently every 8 weeks. For patients without spinal metastases at baseline, repeat spinal imaging was only required at the onset of clinically suspicious signs or symptoms. Complete response (CR) was defined as the complete disappearance of all tumors on T2 or FLAIR images. Partial response (PR) was defined by a ≥25% reduction in tumor size by bidimensional measurement from FLAIR or T2 images, maintained for ≥8 weeks, accompanied by a stable or improving neurologic examination based on the Response Assessment in Pediatric Neuro-Oncology criteria.[21] The primary endpoint was objective response rate (ORR). Secondary endpoints were OS, progression-free survival (PFS), and safety. ORR was defined as the proportion of patients who achieved CR or PR, maintained for ≥8 weeks, whereas OS was the time from the start of treatment to death from any cause. PFS was defined as the time from initiating treatment to either disease progression or death from any cause. Patients with spinal metastasis or dissemination were considered to have experienced disease progression. If it was unclear whether the patient had disease progression, treatment was continued for 4 weeks until subsequent assessment. If disease progression was confirmed at this assessment, the date of progression was assigned to the onset of imaging changes.[21]

AEs were evaluated using National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. A serious AE was defined as any treatment-emergent event resulting in death, such as life-threatening events requiring inpatient hospitalization or prolonged existing hospitalization, causing persistent or significant disability/incapacity.

Missing data

For the analysis of PFS, patients were censored for progression when treatment was changed before evidence of progression (at the date of treatment change), at the date of their last MRI if lost to follow-up, or on reaching the cutoff date without progression. For the analysis of OS, patients without a known date of death were censored at the last known date they were documented to be alive.

Statistical analysis

The data collection process for this trial was conducted in strict accordance with the standards outlined in the study protocol. The reporting of study results adheres to the CONSORT (Consolidated Standards of Reporting Trials) guidelines. Descriptive statistics were used to analyze the demographic, baseline, response evaluation, and safety data. Quantitative data are statistically described as mean, median, minimum, and maximum values. The sample size calculation and primary analysis were based on an ORR of 25.6% found in the CNS 2007 04 study.[18] The study initially required an ORR of 45% in 44 patients to ensure 80% power at a 2-sided significance α level of .05 for the primary hypothesis. The full analysis set (FAS) was designed for all patients who received at least 1 dose of nimotuzumab. All enrolled participants who received at least 6 doses of nimotuzumab were included in the per-protocol (PP) population. The features of the different subgroups were compared with the t or χ^2 test. The ORRs are presented as numbers and proportions. Survival differences between the subtypes were evaluated using Kaplan−Meier analysis with the log-rank test. Multivariate Cox regression used the stepwise likelihood ratio method, and all covariates (age, gender, Lansky performance score, symptom duration, MRI enhancement, tumor volume, biopsy status, steroid use, and PR) were entered and analyzed. Restricted mean survival time tests

were conducted for proportional hazard assumptions. The proportion of adverse events is described. Time, severity, expectedness, duration, relationship with drugs, and outcomes of AEs were recorded. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc.).

Results

Patients

Between April 3, 2021 and April 13, 2023, 64 pediatric patients with DIPG were registered at 8 centers in China (Fig. 1). Fifteen patients were deemed ineligible: 4, for not meeting the study criteria; 2, for meeting exclusion criteria; and 9, withdrawal of consent. One patient did not receive treatment because of brainstem hemorrhage. Among the remaining 48 eligible patients (FAS), the diagnosis of DIPG was histologically confirmed in 28 (58.3%) patients, with 25 (89.3%) having the *H3K27M* mutation. Twenty (41.7%) patients were radiologically diagnosed based on the imaging diagnostic evaluation criteria and multidisciplinary central nervous system tumor board consensus.[21] Baseline characteristics were similar among those diagnosed via imaging and biopsy (Table E1). The median age at presentation was 7 years (range, 4-14 years), and the male-to-female ratio was 1:1.3. Patient characteristics are shown in Table 1.

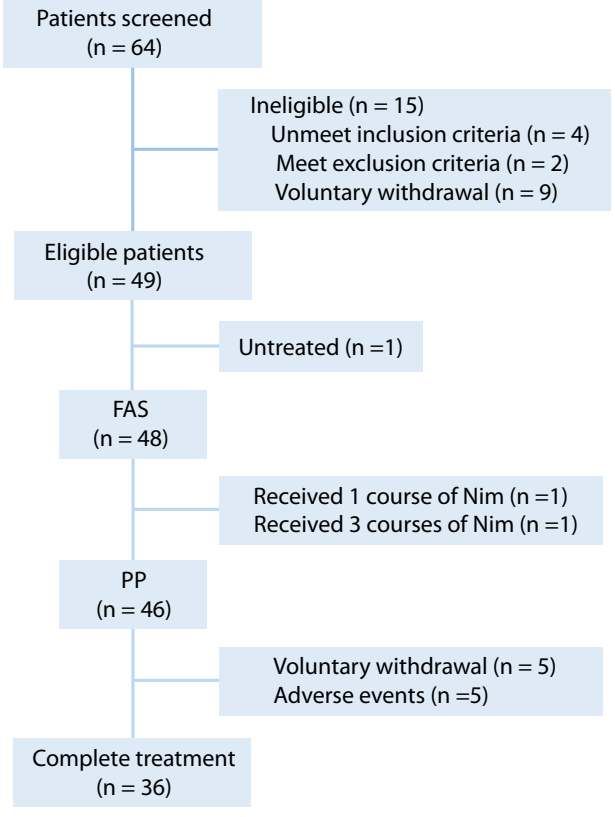

Fig. 1. Flowchart of patients excluded from this study. *Abbreviations:* FAS = full analysis set; Nim = nimotuzumab; PP = per-protocol.

Forty-six patients (95.8%) completed the prescribed concurrent chemoradiation therapy and 6 courses of nimotuzumab therapy (PP), followed by adjuvant maintenance of nimotuzumab and TMZ until tumor progression. The remaining 2 patients (4.2%)completed the prescribed chemoradiation therapy but only received 1 and 3 courses of nimotuzumab and did not receive adjuvant maintenance of nimotuzumab. Five patients (10.4%) completed 52 weeks of nimotuzumab maintenance therapy. Six patients (12.5%) received local reirradiation for tumor progression; the median interval between the initial course of radiation therapy and reirradiation was 8.6 months (range, 6.9-12.4 months); the total dose ranged from 9 to 36 Gy (1.8-2.0 Gy/fraction).

Radiographic outcomes

This study did not meet its primary endpoint as defined in the statistical design. In the FAS of 48 patients, 18 (37.5%) achieved PR; 26 (54.17%) had stable disease; 2 (4.17%) had progressive disease; and 2 (4.17%) were not evaluated because of withdrawal before evaluation (Fig. 2A). The ORR was 37.5%, and the disease control rate (CR + PR + stable disease) was 91.6%. In the PP population of 46 patients, the PR, stable disease, and progressive disease were 18 (39.1%),

Table 1 Patient demographics and disease characteristics

Characteristics	All patients (n = 48)
Age (mean ± SD, y)	7.6 ± 2.67
Gender	
Male	21 (43.8%)
Female	27 (56.3%)
Lansky score	
60	21 (43.8%)
70	18 (37.5%)
80	9 (18.8%)
Mean duration of symptoms (range, mo)	2.04 (0.16-11.1)
Mean tumor volume (range, mm^2)	1972.9 (1248.5-4372.3)
Steroid	
No	39 (81.3%)
Yes	9 (18.8%)
Diagnostic method	
Imaging	20 (41.7%)
Biopsy	28 (58.3%)
***H3K27M* status (n = 28)**	
Negative	3 (10.7%)
Positive	25 (89.3%)
Enhancing lesion	
No	9 (18.8%)
Yes	39 (81.2%)

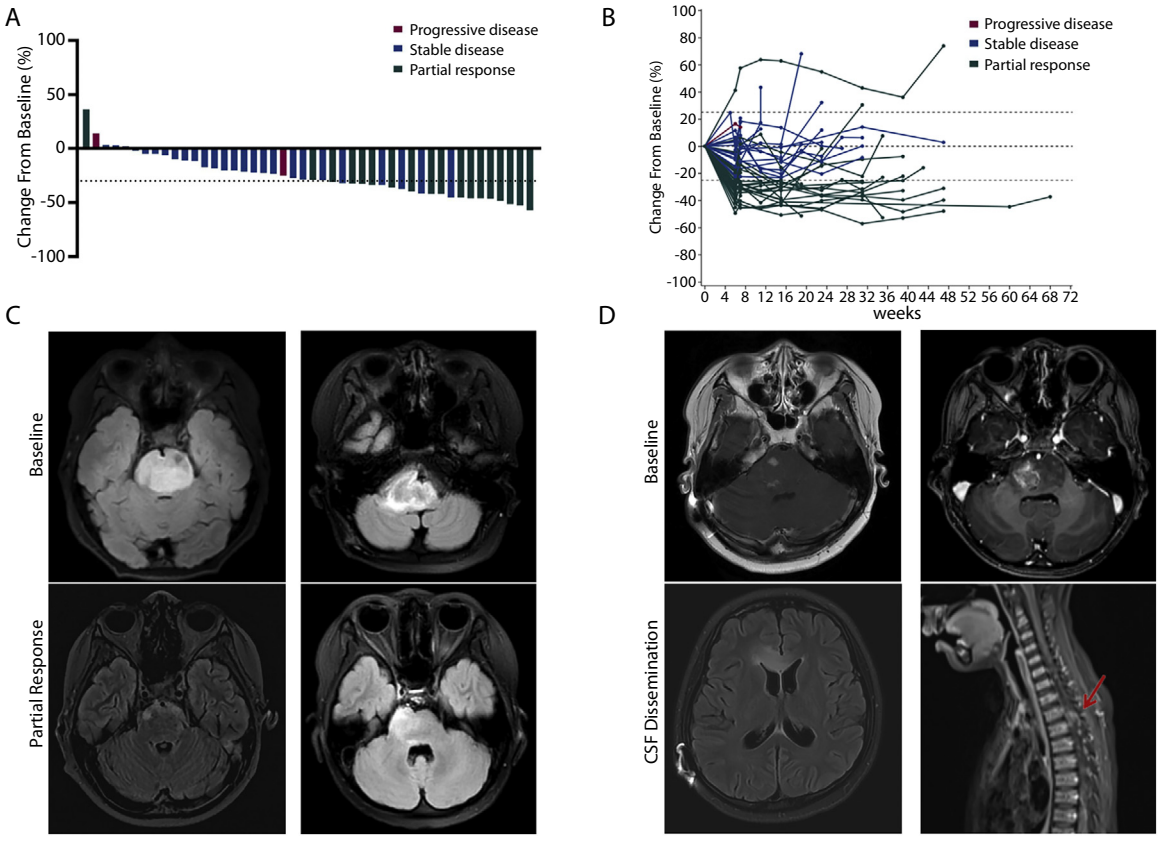

Fig. 2. Radiographic outcomes. Waterfall plot showing the best change from baseline in tumor burden by RAPNO (A); spider plots representing a radiographic response (B). Axial FLAIR images obtained from 2 of the 4 patients with deep tumor reduction (>50%) (C). CSF dissemination images obtained from 2 of the 7 patients with dissemination (D), axial T1 postcontrast images on baseline (the upper), axial FLAIR images demonstrating a metastasis on the corpus callosum (lower left), enhanced MRI spine demonstrating an enhanced leptomeningeal metastasis (arrow) (lower right). *Abbreviations:* FLAIR = fluid-attenuated inversion-recovery; CSF = cerebrospinal fluid; HR = hazard ratio; MRI = magnetic resonance imaging; PR = partial response; RAPNO = Response Assessment in Pediatric Neuro-Oncology.

26 (56.5%), and 2 (4.3%), respectively. The ORR was 39.1%, and the disease control rate was 95.7%. The median time from study entry to PR was 2.1 months (1.3-5.1), and the median duration of radiographic response was 7.7 months (range, 2.9-17.1; n = 7) (Fig. 2B). Among the 18 patients with PR, 4 (22.2%) achieved deep tumor reduction (>50%) (Fig. 2C). The primary local recurrence rate was 72.9%. Seven (14.6%) patients showed distant metastases, of whom 6 had spinal cord involvement and 1 had corpus callosum involvement (Fig. 2D). Among these 7 patients, 3 exhibited progression of the primary pontine lesion, whereas 4 showed stability at the primary site. Enhanced lesions on baseline MRI were observed in all 7 patients (100%), albeit not significantly (Table E2). ORR and survivals showed no significant differences between patients with and without distant metastases.

Survival

The cutoff date of follow-up was May 27, 2024, the median follow-up time was 26.5 months (95% CI, 14.6-NA). In the FAS, the median OS was 10.5 months (95% CI, 8.3-11.2), 1-year OS rate was 33.3% (95% CI, 20.6-46.6%), median PFS was 7.8 (5.1-8.4) months, and 1-year PFS rate was 26.9% (95% CI, 12.3-41.9%) (Fig. 3A). In the PP population of 46 patients, the median OS and PFS were 10.6 and 7.8 months. Multivariate analysis showed that PR (hazard ratio [HR] = 0.39; 95% CI, 0.16-0.88; P = .029) and no steroids use (HR = 3.1; 95% CI, 1.1-8.6; P = .029) were favorable prognostic factors for OS (Fig. 3B). PR (HR = 0.22; 95% CI, 0.08-0.61; P = .004) was also a favorable prognostic factor for PFS (Fig. E2A). Patients with PR have a longer OS (13.2 vs 9.2 months, HR = 0.46; P = .01) and PFS (9.7 vs 5.1 months; HR = 0.29; P < .001) compared with patients without PR (Figs. 3C and E2B). Patients without steroid use exhibited a longer OS (10.8 vs 8.9 months; HR = 2.47; P = .011) and PFS (7.8 vs 5.6 months; HR = 1.71; P = .23) than those with steroid use (Figs. 3D and E2C).

Symptom duration

The functional status of the 48 pediatric patients was assessed using the Lansky score. Two patients could not

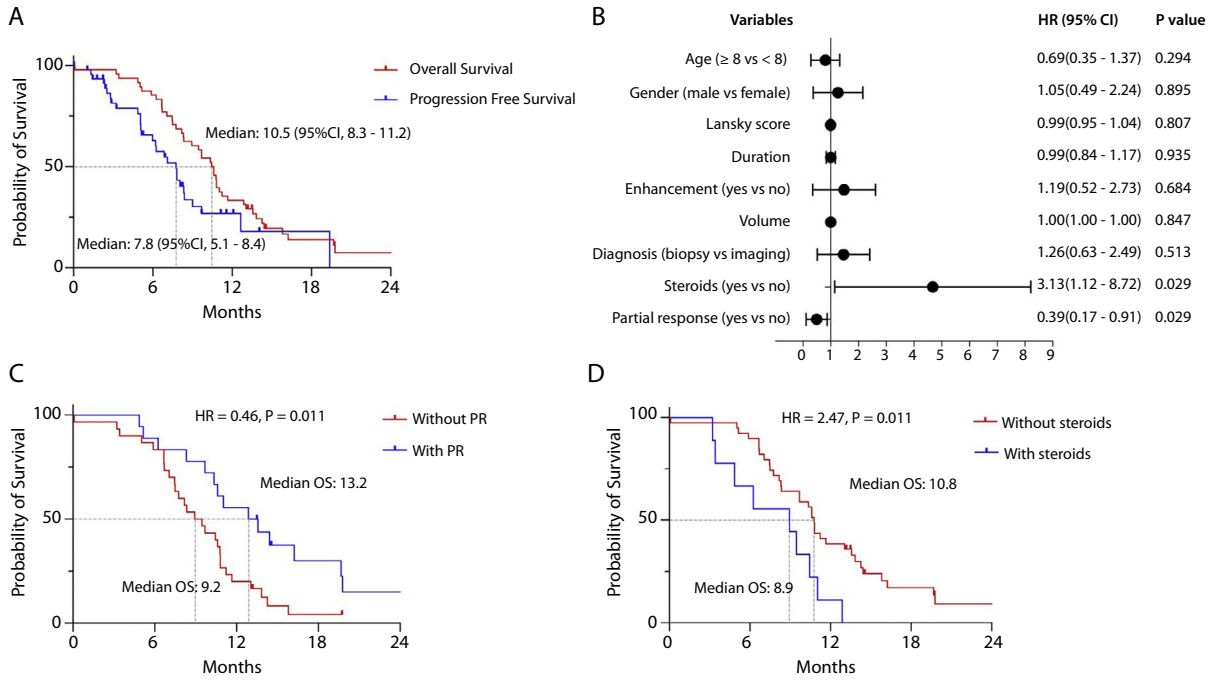

Fig. 3. Survival outcomes. The median OS and PFS (A); forest plot representing the independent prognostic factors for OS (B); patients with PR or without steroids use show a longer OS than those without PR or with steroids use (C and D). *Abbreviations:* HR = hazard ratio; OS = overall survival; PFS = progression-free survival; PR = partial response.

complete the first assessment after radiation therapy because of fatigue, being excluded from further analysis. The remaining 46 patients underwent ≥1 assessment after radiation therapy (Fig. E3). Most patients (43, 93.5%) showed an improved or stable score/status until tumor progression. Improved score/status was observed in 13 (28.2%) patients and was likely to occur between the third (received 30 Gy/15f) and eighth assessments (2 months postradiation therapy). Decline in the state score mostly occurred after the eighth assessment. For patients who received reirradiation, 4 patients experienced symptom relief or stabilization, whereas 2 patients continued to deteriorate following reirradiation.

Toxicity

All pediatric patients received a median of 15.3 (1-29) cycles of nimotuzumab for a median duration of 5.6 (0.2-12.4) months. Treatment-related AEs were reported in all 48 patients (100%) (Table 2), the most common being vomiting (91.7%), leukopenia (72.9%), nausea (47.9%), and fever (43.8%). Treatment-related AEs ≥ grade 3 were leukopenia (27.1%), lymphopenia (27.1%), neutropenia (25%), and thrombocytopenia (8.3%). Twenty-three (47.9%) suspected adverse reactions potentially related to nimotuzumab were reported in 48 patients, with the common ones being leukopenia (22.9%), neutropenia (18.8%), thrombocytopenia (12.5%), vomiting (8.3%), and fever (8.3%). The most common ≥grade 3 AEs were neutropenia (10.4%), leukopenia (8.3%), and thrombocytopenia (6.3%). There was no treatment-related death.

Discussion

The prognosis of pediatric DIPG is dismal, as the median survival is 9-10 months.[16,18,19] Radiation is the only modality effective in reducing tumor burden, ensuring transient symptom control, and providing a 3-4-month survival advantage.[22] Despite the addition of chemotherapy, targeted therapy, or immunotherapy to radiation therapy being tolerable, it did not improve survival for pediatric DIPG.[18,19,23,24] In this study, concomitant therapy with radiation and nimotuzumab and TMZ followed by maintenance therapy with nimotuzumab and TMZ was feasible, with favorably comparable ORR and survival to historical data in pediatric DIPG.[18,19] The overall safety profile was manageable, with no new safety concerns. The results support further investigation of radiation plus chemotherapy and targeted therapy regimen as an alternative strategy in pediatric DIPG treatment.

DIPG is rare, occurring in 10%-15% of all pediatric brain tumors, resulting in very few clinical trials being conducted because of the small number of affected individuals. Patients enrolled in several retrospective or prospective studies on pediatric DIPG were heterogeneous, including other diffuse middle gliomas (DMGs, including the thalamus, spinal cord, medulla, and midbrain) or adults. To our knowledge, DIPG typically results in poorer survival outcomes than other DMGs, of the thalamus, spinal cord, medulla, or

Table 2 Incidence of AEs possibly related to chemoradiation therapy and nimotuzumab

TEAE	Treatment-related AEs	Grade ≥ 3	Nim-related ADRs*	Grade ≥ 3
Total	100% (48/48)	70.8% (34/48)	47.9% (23/48)	16.7% (8/48)
Vomiting	44 (91.67)	1 (2.08)	4 (8.33)	0
Leukopenia	35 (72.92)	13 (27.08)	11 (22.92)	4 (8.33)
Neutropenia	26 (54.17)	12 (25.00)	9 (18.75)	5 (10.42)
Nausea	23 (47.92)	0	3 (6.25)	0
Fever	21 (43.75)	0	4 (8.33)	0
Thrombocytopenia	20 (41.67)	4 (8.33)	6 (12.50)	3 (6.25)
Lymphopenia	16 (33.33)	13 (27.08)	1 (2.08)	0
Anemia	12 (25.00)	2 (4.17)	2 (4.17)	1 (2.08)
Decreased appetite	12 (25.00)	0	1 (2.08)	0
Productive cough	11 (22.92)	0	1 (2.08)	0
Weight decreased	10 (20.83)	2 (4.17)	1 (2.08)	0

Abbreviations: ADR = adverse drug reaction; AE = adverse event; TEAE = treatment-emergent adverse event.
* These adverse effect cannot be excluded as being associated with radiochemotherapy.

midbrain.[25-27] Meanwhile, DIPG patients aged 4-10 years have a worse survival than patients aged <3 or >10 years (9-10 vs 13.6 months).[27] Two prospective clinical studies examining the combination of radiation with TMZ or nimotuzumab in patients aged 3-20 years reported a 1-year OS of 33%-35% in patients with DIPG. The median PFS was 5.5-5.8 months, and the median OS was 9.4-9.5 months, respectively.[18,19] The ORR was significantly different between these 2 studies (25.6% vs 4.8%). A phase 2 study (ACNS0126) obtained a 9.6-month OS following treatment with high-dose chemoradiation therapy (TMZ at a dosage of 90 mg/m^2/d for 42 days; a dose of 59.4 Gy) followed by long-term adjuvant chemotherapy (10 cycles).[28] Recently, immunotherapy with nivolumab and ipilimumab has not demonstrated a survival benefit compared with historical controls.[23] Hypofractionated radiation (39 Gy/13f) and hyperfractionated radiation (twice daily at 1.17Gy/f to a total dose of 70.2 Gy) have also not demonstrated improvements in survival compared with conventional fractionation (54 Gy/30f) in DIPG.[29,30] Reirradiation may offer clinical benefit for some pediatric patients.[31] In our study, 6 patients received reirradiation (9-36 Gy) on tumor progression, and 4 patients experienced symptom relief or disease stabilization. However, because of the lack of high-level evidence, the efficacy of reirradiation remains uncertain. The results of the ONC201 study achieved an ORR of 20% with monotherapy in recurrent DMGs.[26] The findings by Venneti et al[32] support ONC201 as the first monotherapy to improve outcomes in *H3K27M*-mutant DMG. However, one of the key limitations of the ONC201 studies is the heterogeneity of the patient population, which included both recurrent and nonrecurrent cases, spinal, pontine and thalamic DMGs, as well as both pediatric and adult patients.[33] Therefore, the efficacy of ONC201 in pediatric DIPG remains unproven and requires further validation through clinical trials. Unfortunately, the ACTION study (NCT05580562) excluded pediatric DIPG, despite being a prospective, international, multicenter clinical trial designed to evaluate the safety and efficacy of ONCO201 in diffuse gliomas with *H3K27M* mutation. These data suggested that the survival of pediatric DIPG has not improved during the past 2 decades, and effective therapy beyond radiation alone (PFS, 6.0 months and OS, 8.5 months) has not been established.[29] In our cohort, the median PFS and OS were 7.8 and 10.6 months, and the ORR was 37.5%, higher than that following the combination of radiation and nimotuzumab or TMZ (4.8% or 25%, respectively). Although the ORR did not meet the prespecified significance threshold. The comparable ORR and survival outcomes of this strategy relative to historical data support its use as a safe treatment option for pediatric DIPG.

Although pediatric DIPG has the worst prognosis, the OS varies among studies, from 7 to 17.8 months.[27,34,35] Many variables influence the outcomes of pediatric DIPG. Jansen et al[36] analyzed the characteristics of 316 patients with DIPG and found that age ≤3 years, longer symptom duration, and chemotherapy were favorable predictors, whereas ring enhancement on MRI at diagnosis was unfavorable. The survival prediction model developed using the 4 variables was then validated in an external data set of 242 patients.[37] In this study, PR and no steroid use were associated with favorable OS. Yu et al[38] retrospectively reported that PR was related to favorable OS in univariate but not multivariate analysis. Steroids were prescribed to relieve symptoms associated with radiation therapy-induced cerebral edema in patients undergoing treatment. Steroid use during radiation therapy with concurrent TMZ has been reported to correlate with reduced OS and PFS in adult glioblastoma.[39,40] In glioma-bearing mice, pretreatment with dexamethasone reduced survival.[41] Our data showed

that patients treated with steroids exhibited shorter OS (8.9 vs. 10.8 months) than those who did not. However, the Kaplan−Meier curves in Figure 3D exhibit crossover early in the follow-up period but remain separate thereafter. However, restricted mean survival time tests for proportional hazard assumptions showed that these differences did not reach statistical significance, likely because of the limited sample size (Table E3). Therefore, when prescribing steroids in clinical practice, individual patient factors should be carefully considered, and the treatment should be administered with caution.

The diverse range of molecular pathways contributing to DIPG oncogenesis indicates that single-agent therapy is unlikely to provide durable disease control. Biology-guided therapy confirms the proof-of-concept for multiagent therapy in patients with DIPG.[34,42] Recent advances in the molecular understanding of DMG/DIPG with *H3K27M* mutations have led to novel therapeutic approaches. Among them, B7-H3 CAR-T and GD2-targeted CAR-T cell therapy have emerged as promising modalities.[43,44] Gain-of-function mutations and genetic amplification of EGFR are common in *H3K27M*-mutant tumors. Pediatric patients with DIPG frequently harbor an *EGFRvIII* mutation,[45,46] suggesting EGFR alteration as a treatment target. The preliminary efficacy of combined treatment with the vascular endothelial growth factor inhibitor bevacizumab and EGFR inhibitor was observed in pediatric DIPG.[47,48] A phase 3 clinical study showed that the PFS and OS of nimotuzumab were comparable to those achieved with radiation therapy and intensive chemotherapy in pediatric DIPGs.[19] In this study, adding nimotuzumab to radiation therapy and TMZ chemotherapy showed an increasing ORR by 11.9% (37.5% vs 25.6%) compared with radiation therapy combination with TMZ chemotherapy, although not meeting the prespecified significance threshold. Nimotuzumab and TMZ, administered concomitantly and continued after radiation therapy, were well tolerated.

Limitations

First, DIPG biopsy is recommended in clinical trials, as this would allow prospective histomolecular analysis to identify subgroups of patients with longer survival who may benefit from a given therapy. The imaging diagnosis of DIPG met 2 criteria in this study: tumors primarily located in the pons, diffusely infiltrating the pons, and with a tumor diameter of >50% of the pons,[21] and diagnosis confirmed by a multidisciplinary central nervous system tumor board consensus. Although DIPG is an imaging-based diagnosis, because of the difficulty in obtaining materials, the 2021 World Health Organization classification uses histomolecular parameters and radiography to define DIPG, because of the safety and widespread use of biopsy.[20] In clinical trials, the diagnostic method usually includes histomolecular pathology and/or MRI features of DIPG. DIPG is defined as an infiltrative pons glioma with an *H3K27M* mutation, aberrant overexpression of EZH inhibitory protein, or an EGFR mutation. Therefore, detailed pathologic and molecular pathologic examinations are essential for clinical trials to obtain accurate data. Second, it is important to acknowledge that this was a single-arm clinical trial with a relatively small sample size. The sample size possibly result in the failure of many variables to predict prognosis in the subgroup analysis. Thus, further validation in larger, controlled studies is essential. Finally, given that this is a single-arm clinical study involving combination therapy, it may be more appropriate to attribute the AEs observed to the combined regimen, even though radiation therapy, chemotherapy, and nimotuzumab are each associated with distinct toxicity profiles.

Conclusions

This study demonstrated that nimotuzumab combined with TMZ chemoradiation therapy improved ORR by 11.9% compared with TMZ chemoradiation therapy (37.5% vs 25.6%), although the difference was not significant; the OS and PFS were also favorably comparable with previous data (10.5 months vs 9.6 months and 7.8 months vs 5.5 months). Meanwhile, this study demonstrated that multiple agents combined with radiation therapy are well tolerated, which may inform both clinical practice and future trial design.

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