Therapeutic effect and side effects of Bevacizumab combined with Irinotecan in the treatment of paediatric intracranial tumours: Meta-analysis and Systematic Review

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Abstract
What is known and objective: Bevacizumab (BVZ) is an angiogenesis inhibitor that often works well with chemotherapeutic drugs for the treatment of solid intracranial tumours in children. This meta-analysis discusses the efficacy and side effects of BVZ combined with irinotecan in the treatment of patients (younger than 21 years of age) with recurrent, progressive or refractory intracranial tumours.

Methods: We searched for articles published before 31 October 2018 in PubMed, EMBASE, Cochrane library and Web of Science. We selected relevant literature on the combination of BVZ and irinotecan in the treatment of children with intracranial tumours. Objective response was evaluated by combining partial response (PR), complete response (CR), stable disease (SD) and progressive disease (PD), and survival time was evaluated by combining overall survival (OS) and progression-free survival (PFS); common side effects were also analysed. All data included were obtained from single-arm data, with no control groups.

Results and discussion: A total of 13 studies involving 272 patients were included. We found that out of 41% patients who showed an objective response following the BVZ therapy combined with irinotecan, 28% achieved a PR, 13% achieved a CR, 32% showed a SD, and 43% had a PD; PFS and OS were 6.47 and 11.9 months, respectively; gastrointestinal dysfunction, leukopenia and hypertension were the three most common adverse events, accounting for 36.7%, 33.6% and 22.1%, respectively, whereas musculoskeletal disorders had the lowest occurrence, accounting for 3.9%.

What is new and conclusion: BVZ combined with irinotecan-based chemotherapy had a better response and prolonged survival in the treatment of paediatric intracranial tumours than radiation therapy or chemotherapy. Gastrointestinal dysfunction, leukopenia and hypertension were the toxic side effects with the highest incidence.

Keywords
Bevacizumab, combination therapy, irinotecan, intracranial tumour, paediatric, toxicity, treatment effect
WHAT IS KNOWN AND OBJECTIVE

In the incidence of malignant diseases in children, intracranial tumours rank second only after leukaemia. Although great progress has been made in the treatment of malignant intracranial tumours in children in the fields of surgery, radiotherapy and chemotherapy, a considerable proportion of patients still suffer from intractable, progressive or recurrent diseases, and the therapeutic response is still poor. New methods are needed to treat this disease.1

Angiogenesis is the key and rate-limiting factor in tumour development. Vascular endothelial growth factor (VEGF) plays a key role in this process.2 Vascular endothelial growth factor is a key mediator of angiogenesis and plays an important role in tumour growth, invasion and metastasis. Its overexpression can accelerate the progression and metastasis of intracranial tumours. Because of VEGF overexpression in tumours of the central nervous system,3,4 vascular endothelial growth factor inhibition can inhibit the angiogenesis of intracranial tumours; thus, VEGF has become an effective target for the treatment of solid intracranial tumours. VEGF overexpression is also found in intracranial tumours in children, and VEGF-targeted therapy may be an effective therapeutic approach for the treatment of paediatric intracranial tumours.5 Bevacizumab (BVZ) is an angiogenesis inhibitor that targets VEGF; it specifically binds to VEGF-A and inhibits tumour angiogenesis by blocking the interaction of VEGF with its receptor on the surface of endothelial cells,6 and thus inhibits the growth and metastasis of intracranial tumours. In addition, BVZ can also improve the delivery of cytotoxic chemotherapeutic drugs by altering the tumour vascular system, reducing the elevated tissue pressure in tumours and enhancing the efficacy of chemotherapeutic drugs.7

However, previous studies found that BVZ showed only modest activity when used as a single drug and exhibited better efficacy when used in combination with conventional chemotherapeutic drugs for the treatment of intracranial tumours.8 Although the use of BVZ alone is effective, it is not ideal and requires a combination of drugs. Irinotecan is a topoisomerase-1 inhibitor, a relatively classic chemotherapeutic drug. It can block topoisomerase-1 and inhibit DNA replication and transcription.9 The combination of irinotecan and BVZ has been proven to improve the prognosis of adult patients with high-grade gliomas. Studies have reported encouraging results with an objective response rate as high as 60% and a prolonged median progression-free survival (PFS).10,11 The combination of BVZ and irinotecan for the treatment of relapsed grade III glioma patients showed high response rates with a PFS of 4-7 months and an overall survival (OS) of 7-15 months.12,13 To improve the therapeutic effect on paediatric central nervous system tumours, many studies have tested a variety of new targeted therapies including antiangiogenic drugs. In the treatment of childhood intracranial tumours, BVZ in combination with irinotecan has also been found to efficacious.14 However, data on the safety and efficacy of BVZ in combination with irinotecan in the treatment of patients with intracranial tumours under 21 years of age is limited, and the extent to which this combination can be extended to patients under 21 years of age is uncertain.

Clarifying the efficacy and side effects is of great value in guiding clinicians to use the drugs appropriately. We therefore performed this meta-analysis to evaluate the efficacy and toxicity of this combination therapy regimen in children with intracranial tumours.

METHODS

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.15

Eligibility criteria

Eligible studies had to satisfy the following prespecified PICOS criteria: (a) P: patient under 21 years of age; (b) I: BVZ combined with other drugs; (c) C: None (d) O: partial response (PR), complete response (CR), stable disease (SD) and progressive disease (PD); (e) S: retrospective study. Studies of BVZ monotherapy were not included, and studies of BVZ in combination with other antineoplastic drugs, either one or more drugs, were included. All data are from single-arm data, with no control group.

Search strategy

We searched for articles published before 31 October 2018 in four electronic databases: PubMed, EMBASE, Cochrane library and Web of Science. The search terms used were: ‘BVZ and irinotecan’ or ‘CPT-11’ and ‘child’ or ‘childhood’ or ‘adolescent’ or ‘teenager’ or ‘paediatric’ and ‘medulloblastoma’ or ‘glioblastoma’ or ‘intracranial tumours’ or ‘cns tumours’ or ‘brain tumour’ or ‘brain haemangiomia’ or ‘central nervous system tumour’ or ‘meningioma’ or ‘neuroectoderm tumour’ or ‘granular cell tumour’ or ‘ependymoma’.

If there were duplicate studies, articles published earlier or providing more detailed information were selected. If the review contained raw data, that has also been included in this study.

Study selection

All studies were manually read. The retrieved literature was reviewed, and the eligibility of all potential studies was independently assessed by two reviewers according to the above criteria. The third researcher resolved the differences by screening the literature.

Data extraction

The data of each included study were extracted by the investigator using a predesigned data table and independently reviewed by another investigator to ensure accuracy.
2.5 | Definition of outcomes

The therapeutic effect of BVZ combined with other drugs on paediatric intracranial tumours was evaluated from three perspectives involving six indicators: the first perspective was PFS and OS and the second was objective response; the reported PR, CR, SD and PD were extracted from all studies and combined; the third one was side effects: the side effects extracted from each study were classified and combined, and the incidence of 10 common side effects was analysed.

CR refers to the complete disappearance of all lesions; PR refers to >50% reduction in the largest cross-sectional area of the tumour; PD refers to an increase in tumour size by >25%, emergence of a lesion in a new area, or a new progressive symptom caused by tumour progression; SD refers to tumour shrinkage but not enough to be described as PR (<50%) or a <25% increase in tumour size, but not sufficient to prove that it is PD; Objective tumour response refers to a significant decrease in tumour size, including PR, CR; PFS refers to time to disease progression (95% CI = 0.29. −0.58, P < 0.01); I² = 27%) (Figure 2A), 13% patients achieved CR (95% CI = 0.04. −0.22, P < 0.01; I² = 0%) (Figure 2B) and that combination therapy had a positive anti-tumour activity in children with intracranial tumours. Eleven studies reported the incidence rate of SD in combination therapy. The pooled results were encouraging, and at least 32% of patients achieved SD after combination therapy (95% CI = 0.22-0.42, P < 0.01; I² = 49.5%) (Figure 2C).

Objective response, including PR and CR, implies that treatment is effective to varying degrees. Nine studies reported the incidence rate of PR, and 4 studies reported the incidence rate of CR in BVZ therapy in combination with irinotecan. The pooled results showed that 28% patients achieved PR (95% CI = 0.19-0.37, P < 0.01; I² = 27%) (Figure 2A), 13% patients achieved CR (95% CI = 0.04. −0.22, P < 0.01; I² = 0%) (Figure 2B) and that combination therapy had a positive anti-tumour activity in children with intracranial tumours. Eleven studies reported the incidence rate of SD in combination therapy. The pooled results were encouraging, and at least 32% of patients achieved SD after combination therapy (95% CI = 0.22-0.42, P < 0.01; I² = 49.5%) (Figure 2C).

However, in addition to anti-tumour activity, combination therapy can also lead to disease progression. Ten studies were then included to assess disease progression in patients receiving combination therapy. The pooled results showed that 43% of patients had disease progression (95% CI = 0.29. −0.58, P < 0.01, I² = 76.9%) (Figure 2D).

2.6 | Statistical methods

Stata 14 was used for data combination and analysis and for evaluation of between studies heterogeneity tests (I²). We used a random effects model for meta-analysis, and the data are depicted as forest plots.

2.7 | Assessment of risk of bias

Since most of the studies included were single-arm cohort studies, the CASP-Cohort-Study-Checklist was used to assess the quality of the studies. Two investigators subjectively assessed the quality and bias of the studies, and the differences were resolved by consensus or arbitration by a third investigator. The critical appraisal skills programme (CASP) Cohort list is a quality assessment tool. In 2004, the Oxford Evidence-Based Medicine Center in the UK presented a list of CASP for cohort studies with 12 questions.

3 | RESULTS

3.1 | Search results and study characteristics

A total of 817 articles were identified following a systematic database search. Only 13 independent studies eventually met the analysis criteria and the PRISMA flow chart (Figure 1). A total of 272 subjects were enrolled, and all studies included were retrospective (Table 1). Among the 13 eligible studies, 9 studies reported PR, 4 studies reported CR, 11 studies discussed SD, and 10 studies discussed PD for evaluation of objective efficacy of BVZ combination therapy on recurrent, progressive or refractory intracranial tumours. There were 5 studies each that mentioned PFS or OS for the assessment of survival outcomes in paediatric patients with recurrent, progressive or refractory intracranial tumours treated with BVZ. The paper ultimately screened out 10 types of side effects, each involving 4 to 10 studies, and explored a combination of two or more chemotherapeutic drugs, including at least BVZ and irinotecan. The main paediatric intracranial tumours involved in this study were recurrent or refractory central nervous system (CNS) tumours (neuroblastoma, optic glioma, intrinsic pontine glioma, recurrent medulloblastoma, ependymoma, low-grade gliomas (LGG), high-grade gliomas (HGG), supratentorial HGG and diffuse intrinsic pontine glioma (DIPG) and recurrent malignant glioma). The average age of the population involved in the 13 included studies was >10 years in 7 studies and >15 years in 6 studies.

3.2 | Objective response

CR/PR/PD/SD were used as indicators of tumour response. Since not all four indicators can be analysed in each study, the number of studies included in each pooled result is different. Additionally, as various objective responses at different stages of treatment were provided by some studies, we selected ‘optimal objective response’ and used the random effects model in this meta-analysis without consideration of heterogeneity.

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3.3 | Survival outcomes

Survival outcomes including OS and PFS are other indicators of the efficacy of treatment. The pooled results showed that the average PFS (based on 5 studies) and OS (based on another 5 studies) of patients were 6.47 months (95% CI = 2.39-10.56, P < 0.05) (Figure 3A) and 11.9 months (95% CI = 6.07 to −17.78, P < 0.01) (Figure 3B), respectively.
Some studies reported average time of survival, whereas other studies reported the median time of survival. To facilitate the combined analysis, we converted the median value and its range into mean value and standard deviation (SD) values. As shown in Figure 3, the trends of PFS and OS are the same.

### 3.4 | Toxicity

The side effects of BVZ therapy in combination with other anti-tumour drugs was explored in the 13 included studies. We extracted 10 types of side effects for analysis after nearly 60 side effects mentioned in these 13 studies were carefully reviewed, re-screened and reclassified (the side effects mentioned in less than 3 studies were ignored). The number of included studies varied with each side effect. The 10 side effects were combined and their pooled incidence rates (Table 2) were as follows: gastrointestinal dysfunction, 36.7%; leukopenia, 33.6%; hypertension, 22.1%; anaemia, 21.5%; haemorrhage, 18.1%; thrombocytopenia, 17.9%; general, 16.9%; liver dysfunction, 15.0%; renal dysfunction (proteinuria), 13.4%; and musculoskeletal disorders (osteonecrosis), 3.9%, as shown in the forest plot (Figure 4). Among them, gastrointestinal dysfunction (including nausea, vomiting and diarrhoea) ranked first and had the highest incidence of toxic side effects, followed by leukopenia, hypertension and musculoskeletal disorders.
| Study          | Year | Study design   | Population                                                                 | Age                  | Male%  | Sample size | Country     |
|---------------|------|----------------|-----------------------------------------------------------------------------|----------------------|--------|-------------|-------------|
| Aguilera et al. | 2013 | Retrospective  | patients with relapsed medulloblastoma treated with bevacizumab (BV) and irinotecan (IRI), with or without temozolomide (TMZ), from 2006 until 2011. Children were <18 y old at initial diagnosis | age < 3, n = 3 age 3-18, n = 6 | 66.7%  | 9           | USA         |
| Couec et al.  | 2012 | Retrospective  | 28 children who received bevacizumab on a compassionate basis for refractory or recurrent brain tumours between June 2007 and August 2010 in 7 French centres | 11                   | –      | 28          | France      |
| Fangusaro et al. | 2013 | Retrospective  | Children with recurrent CNS tumours                                           | 10.3                 | –      | 92          | USA         |
| Gururangan et al. | 2010 | Retrospective  | Patients younger than 21 y with recurrent or progressive histologically confirmed malignant gloma or diffuse intrinsic pontine glioma (by clinical and imaging criteria) and measurable disease were eligible for this study | A 15.7 (5.6-20.1) B 8.7 (2.9-14.6) | –      | 35          | USA         |
| Gururangan et al. | 2012 | Retrospective  | Patients younger than 21 y of age with recurrent or progressive histologically confirmed EPN and measurable disease were eligible for this study | 9.7 (3-19.5) 57.1%  | –      | 13          | USA         |
| Hwang et al.  | 2013 | Retrospective  | Between September 2006 and July 2009, 14 children with recurrent LGG were treated with a bevacizumab-based regimen | 5.3 (1-12)           | –      | 14          | USA         |
| Kalra et al.  | 2015 | Retrospective  | children with refractory or progressive LGG who were treated at 2 institutions. Inclusion criteria were children younger than 18 y of age with or without NF1, and with either one of a documented clinical progression or progressive disease (PD) on magnetic resonance imaging (MRI) scan following at least 1 line of chemotherapy who were subsequently managed with BBT | 8.6 (1.8-15.3) 56.3% | –      | 16          | Australia   |
| Millan et al. | 2016 | Retrospective  | From 2006 to 2013, our paediatric institution treated sixteen patients who were <4 y of age with bevacizumab at the time of treatment initiation | 34.3 mo (4.9-47.3) 43.8% | –      | 16          | Spain       |
| Narayana et al. | 2010 | Retrospective  | conducted from clinical records for 12 consecutive patients who were diagnosed with recurrent paediatric HGG between September, 2005 and July, 2008 at New York University Langone Medical Center, New York, NY | 14.75 (4-22) 58.3% | –      | 12          | USA         |
| Okada et al.  | 2013 | Retrospective  | Patients with refractory or recurrent paediatric solid tumours or CNS tumours were eligible | 9 (3-22) 45.5%       | –      | 11          | Japan       |
| Parekh et al. | 2011 | Retrospective  | the medical records of patients less than 21 years of age diagnosed at Childrens Hospital Los Angeles with recurrent or progressive HGG who received a combination of bevacizumab and other conventional chemotherapeutic agents, including irinotecan, between January 2006 and September 2008. | 13.5 (5-19) 50.0% | –      | 8           | USA         |
| Venkatramani et al. | 2013 | Retrospective  | Patients >1 and <21 y of age with histologically confirmed solid tumour without known effective therapy, body weight ≥10 kg, a Karnofsky or Lansky performance score of >50%, and with an expected life expectancy of > 8 weeks were eligible. | 11 (3.9-19.4) 66.7% | –      | 12          | USA         |
| Zaky et al.   | 2013 | Retrospective  | Patients >21 y of age newly diagnosed with DIPG at Childrens Hospital Los Angeles between January 2007 and December 2007 who were treated with chemoradiotherapy followed by an adjuvant chemotherapy regimen consisting of irinotecan, temozolomide and bevacizumab and reviewed the treatment response, toxicity and outcome. Only six patients fit our inclusion criteria. | 6.6 (3.5-10.6) 33.3% | –      | 6           | USA         |
| Total         | 13   | studies        |                                                                             | 272                  | –      |             |             |
3.5 | Evaluation of research quality

We evaluated the quality of each study in three sections: Are the results of the study valid? (Section A); What are the results? (Section B); Will the results help locally? (Section C). After independent evaluation by two investigators and joint discussion on the differences, we could see that the quality of the 13 included studies was generally acceptable, and there were no serious quality problems and biases.

4 | DISCUSSION

In summary, 13 clinical trials involving 272 subjects younger than 21 years of age were included in our study that explored a combination of two or more chemotherapeutic drugs, including at least BVZ and irinotecan.

Although several treatments have been studied in the past decades, the prognosis of paediatric intracranial tumours has not improved satisfactorily. The use of hypofractionated radiotherapy, preirradiation chemotherapy, concurrent chemoradiotherapy, radiosensitizers, adjuvant chemotherapy and high-dose chemotherapy regimens has not resulted in significant responses or prolonged survival. Janssens et al. reported 5-month PFS and 8.5-month OS in patients with diffuse intrinsic pontine gliomas treated with standard chemotherapy.28 Our results showed that children with intracranial tumours responded to BVZ therapy in combination with irinotecan; 28% patients achieved PR, 13% achieved CR, and 32% were stable; PFS and OS were 6.47 months and 11.9 months, respectively.

In addition, haematological toxicity such as thrombocytopenia, elevated transaminase levels and other AEs were associated with irinotecan.17 According to our results, we believe the AEs were acceptable. The long-term health risks of radiation therapy and chemotherapy are usually unacceptable. These include cognitive dysfunction, neuroendocrine dysregulation, vascular insults, second malignancies, myelosuppression, peripheral

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**FIGURE 2** (A) Forest plot of rate of partial response (B) Forest plot of rate of complete response (C) Forest plot of rate of stable disease (D) Forest plot of rate of progressive disease
neuropathy and carboplatin allergy in the treatment phase, and secondary malignancies as late effects. Therefore, we believe that compared with radiation therapy or chemotherapy, BVZ combined with irinotecan-based chemotherapy has a better response and acceptable toxicity profiles.

This study has some limitations. Firstly, this paper lacks relevant randomized controlled trials, and as only single-arm studies have been included, the effect sizes comparable to other treatments are unavailable. The second limitation is the small number of related studies and sample sizes because of a relatively low incidence rate of paediatric tumours.

5 | WHAT IS NEW AND CONCLUSION

In summary, BVZ combined with irinotecan-based chemotherapy had a better response and prolonged survival in the treatment of paediatric intracranial tumours than radiation therapy or chemotherapy.

FIGURE 3 (A) Forest plot of median progression-free survival (B) Forest plot of median survival
Gastrointestinal dysfunction, leukopenia and hypertension were side effects with the highest incidence. This study provides information for the clinical application of BVZ combined with irinotecan in the treatment of paediatric intracranial tumours.

BVZ, used either alone or associated with conventional chemotherapy, is now part of the upfront treatment for several tumour types in adult patients. However, few paediatric studies have been reported so far. Our results show that BVZ combined with irinotecan-based chemotherapy has better response rates and acceptable toxicity profiles for paediatric brain tumour patients. This is a promising result. We anticipate that BVZ combined with irinotecan-based chemotherapy will provide new insights into paediatric brain tumours treated with antiangiogenesis therapies. We should encourage the inclusion of these patients in clinical trials using BVZ combined with irinotecan-based chemotherapy.

ACKNOWLEDGEMENTS

We would like to thank Beijing Zhiyun data technology co. LTD for providing the data analysis service.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

ETHICS APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.
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