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Original Article

Haematotoxicity of Craniospinal Radiochemotherapy for Metastatic Paediatric High-Grade Glioma

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Highlights

- Craniospinal radiochemotherapy (CSI-RCT) was feasible in 19 pediatric patients with metastatic high-grade glioma (pedHGG).
- Grade 3–4 hematotoxicity occurred in 42% of patients, but most cases were manageable without interrupting radiotherapy.
- Only 2 out of 19 patients required discontinuation of chemotherapy, one due to suspected temozolomide-induced aplastic anemia.
- The study supports the safety of combining CSI with temozolomide and informs future clinical trial design (e.g., SIOPE HGG-01).
- Use of advanced techniques such as proton therapy may further mitigate hematological toxicity in future treatment strategies.

Abstract

Aims

Paediatric high-grade gliomas (pedHGGs) have a dismal prognosis, often characterised by early and diffuse disease progression. Novel treatment approaches are urgently needed to improve outcomes. The upcoming SIOPE-HGG (High Grade Glioma)-01 trial will investigate upfront craniospinal radiochemotherapy (CSI-RCT) for newly diagnosed, nonmetastatic diffuse midline glioma/diffuse intrinsic pontine glioma (DMG/DIPG). As CSI-RCT is frequently avoided due to concerns over haematotoxicity, real-world feasibility data are critically needed.

Materials and methods

We retrospectively assessed haematological toxicity in 19 patients (aged 3-21 years) with metastatic pedHGG treated with CSI-RCT within the hirn tumor glioblastoma trial (HIT-HGG) and hospital in trial-glioblastoma (HIT-GBM) trial programmes (2002–2024). All patients received craniospinal irradiation (median dose: 35.2 Gy) using photon- or proton-based techniques, with concurrent chemotherapy: temozolomide (TMZ; n = 14) or PEI (cisplatin, etoposide, ifosfamide; n = 5). Haematological toxicities were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Results

Grade 3 to 4 haematotoxicity was observed in 7 of 19 patients (36.8%). Chemotherapy was discontinued in two cases—one due to TMZ-induced aplastic anaemia (TIAA) and another due to thrombocytopaenia. The remaining patients tolerated full-dose CSI-RCT with manageable side effects, and no unplanned radiotherapy interruptions occurred. The haematotoxicity rate was

comparable to or lower than previous reports, indicating that CSI-RCT is feasible with appropriate monitoring and management.

Conclusion

This is the largest cohort to date assessing haematological toxicity of upfront CSI-RCT in metastatic pedHGG. Despite notable haematotoxicity, treatment was largely feasible and well-tolerated. These findings support the integration of CSI-RCT into future clinical trials for newly diagnosed DMG/DIPG and provide a foundation for the upcoming SIOPE HGG-01 trial. Proton therapy may further reduce toxicity and warrants prospective evaluation.

Introduction

Paediatric high-grade gliomas (pedHGGs) usually present as focal disease [1], and craniospinal radiochemotherapy (CSI-RCT) is therefore only applied in rare cases with initial metastatic spread. Even then, focal irradiation to macroscopic tumour sites is often preferred over CSI due to expected major haematotoxicity in an overall predominantly palliative situation.

Recently, the risk of central nervous system (CNS) dissemination and its clinical impact has been revisited for the most frequent pedHGG, diffuse midline glioma, H3K27-altered, CNS grade 4 (DMG), and its pontine neuroradiological equivalent, diffuse intrinsic pontine glioma (DIPG) [2]. Current and earlier studies reported disseminated disease at first progression in 20% to 25% of DIPG patients [3,4] with even higher rates, up to 60% or more, during the further course of disease and at autopsy [[5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17]]. In nonpontine DMG, dissemination at first progression seems even higher with more than 60% [2]. Moreover, early dissemination at first progression was significantly associated with reduced overall survival (OS) in DMG/DIPG patients [2].

Since in murine DIPG models CSI significantly reduced the incidence of leptomeningeal spread compared to focal radiotherapy [18], the therapeutic efficacy and safety of upfront CSI will be investigated in the planned upcoming European pedHGG trial SIOPE HGG-01. With a randomisation to upfront CSI and concomitant temozolomide (TMZ) for DMG/DIPG, this trial aims to reduce the high rate of tumour dissemination at first progression. The planned combination of CSI with concomitant TMZ raised some critical concern since retrospective relative small patient series with this combination had indicated haematotoxicity, prompting treatment discontinuation in approximately 30% of cases [16,17,19].

To obtain more data regarding the haematotoxic potential of CSI with concomitant chemotherapy in pedHGG, we analysed the HIT-HGG database comprising data from six consecutive clinical trials for pedHGG. Thus, we were able to identify the largest series of patients with pedHGG receiving craniospinal radiochemotherapy to date (n = 19), allowing for further toxicity analyses to study the feasibility of this approach.

Section snippets

Material and Methods

The cohort comprised patients from the HIT-GBM and HIT-HGG trials (Supplement 1) with metastatic pedHGG, aged 3 to 21 years, enrolled from 2002 to 2024. All underwent central neuropathological and neuroradiological review. Collected data included patient demographics (age and sex), staging, tumour histology, treatment, side effects, and clinical outcomes. Diagnoses were made according to the respective World Health Organization (WHO) classification of tumours of the CNS applicable at the time …

Results

Nineteen patients with histologically or neuroradiologically confirmed diagnoses of metastatic pedHGG, classified as M2-M4 [22,23], were included in the present analysis.

While one patient received proton therapy, 18 patients underwent craniospinal irradiation using photon-based techniques. Among them, nine were treated with Intensity-modulated radiation therapy (IMRT)/Volumetric modulated arc therapy (VMAT)/tomotherapy, and nine received 3D-conformal radiation therapy. The median CSI dose …

Discussion

The present analysis significantly adds to the current knowledge about the haematotoxic potential of CSI in pedHGG. With 19 patients, it represents the largest series to date for this very rare, nonroutine treatment situation. The present study may therefore contribute to the discussion about the feasibility and acceptability of upfront CSI for the treatment of DMG/DIPG.

This discussion was started by the introduction of the planned European pedHGG trial SIOPE HGG-01. In this trial, upfront …

Patient Consent Statement

All patients included in this study were enrolled and treated within the framework of a clinical trial. Written informed consent for participation in the trial and publication of anonymized data was obtained from the patients' parents or legal guardians at the time of inclusion. The consent process complied with all applicable ethical and regulatory requirements. …

Author Contribution

Valentini C, data analysis, statistical analysis, manuscript preparation, literature research.

Perwein T, data analysis, manuscript editing.

Bison B, manuscript editing.

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Declaration of competing interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Christof Kramm reports a relationship with Deutsche Kinderkrebsstiftung, Bonn, Germany that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

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