Published in final edited form as:

J Neurooncol. 2018 December ; 140(3): 717–725. doi:10.1007/s11060-018-03003-z.

Pre-irradiation Intensive Induction and Marrow-ablative Consolidation Chemotherapy in Young Children with Newly Diagnosed High-Grade Brainstem Gliomas: Report of the "Head-Start" I and II Clinical Trials

Diana S. Osorio[1], **Neha Patel**[2], **Lingyun Ji**[3], **Richard Sposto**[3], **Joseph Stanek**[1], **Sharon L. Gardner**[4], **Jeffrey C. Allen**[4], **Albert Cornelius**[5], **Geoffrey B. McCowage**[6], **Amanda Termuhlen**[3], **Ira J. Dunkel**[7], **Melanie Comito**[8], **James Garvin**[9], **Jonathan L. Finlay**[1]

[1]Division of Pediatric Hematology/Oncology, Nationwide Children's Hospital, The Ohio State University, Columbus, Ohio

[2]Division of Pediatric Hematology/Oncology, University of Wisconsin, Madison, Wisconsin

[3]Department of Preventive Medicine, University of Southern California, Los Angeles, California

[4]Division of Pediatric Oncology, New York University Langone Medical Center, New York, New York

[5]Division of Pediatric Hematology/Oncology, Helen DeVos Children's Hospital, Grand Rapids, Michigan

[6]Department of Oncology, The Children's Hospital at Westmead, Sydney, Australia

[7]Department of Pediatrics, Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College, New York, New York

[8]Division of Pediatric Hematology/Oncology, Penn State Hershey Medical Center, Hershey, Philadelphia

[9]Division of Pediatric Hematology/Oncology & Stem Cell Transplant, Columbia University Medical Center, New York, New York

Abstract

Diana S. Osorio: Diana.Osorio@nationwidechildrens.org.

Conflict of Interest: **Ira J. Dunkel:** Consultant, current: Apexigen (May 26, 2017 to present), Bayer Healthcare Pharmaceuticals (March 30, 2016 to March 30, 2020), Celgene (May 2, 2017 to March 31, 2020). The Celgene agreement is actually not finalized, but has a pending start date of May 2, 2017 despite that being in the past. Consultant, past: Bayer Healthcare Pharmaceuticals (October 1, 2011 to October 1, 2012), Bristol-Myers Squibb (June 11, 2012 to June 11, 2013; April 24, 2015 to April 24, 2017), Ipsen (August 20, 2014 to August 20, 2015), Eisai (October 1, 2015 to October 1, 2016). Pfizer (January 20, 2016 to January 20, 2017). All other authors have no conflicts of interest to declare.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethical approval: This article does not contain any studies with animals performed by any of the authors.. Informed consent was obtained from all individual participants included in the study.

BACKGROUND: The dismal outcome in children with high-grade brainstem gliomas (BSG) accentuates the need for effective therapeutic strategies. We investigated the role of intensive, including marrow-ablative, chemotherapy regimens in the treatment of young children with newly-diagnosed high-grade BSG.

METHODS: Between 1991-and-2002, 15 eligible children less than 10 years of age with a diagnosis of high-grade BSG were treated on "Head-Start" I and II protocols (HSI and HSII). Treatment included Induction with 4-5 cycles of one of three intensive chemotherapy regimens followed by Consolidation with one cycle of marrow-ablative chemotherapy (thiotepa, carboplatin and etoposide) with autologous hematopoietic cell rescue (AHCR). Irradiation was required for children over 6 years of age or for those with residual tumor at the end of Consolidation.

RESULTS: We had two long-term survivors who were found *retrospectively* to harbor low-grade glial tumors and thus were not included in the survival analysis. Of the remaining 13 patients, the 1-year event-free (EFS) and overall (OS) survival for these children were 31% (95% CI: 9-55%) and 38% (95% CI: 14 to 63%), respectively. Median EFS and OS were 6.6 (95% CI: 2.7, 12.7) and 8.7 months (95% CI: 6.9, 20.9), respectively. Eight patients developed progressive disease during study treatment (seven during Induction and one at the end of Consolidation). Ten children received focal irradiation, five for residual tumor (three following Induction and two following Consolidation) and five due to disease progression.

CONCLUSIONS: Children with high-grade BSG did not benefit from this intensive chemotherapy strategy administered prior to irradiation.

Keywords

Marrow-ablative therapy; high-dose chemotherapy; high-grade glioma; brainstem; brainstem glioma; diffuse intrinsic pontine glioma; DIPG

INTRODUCTION

Ten to 15% of childhood intracranial tumors are located in the brainstem and the majority of these tumors are gliomas.[1] Eighty-percent of gliomas are high-grade and diffusely involve the pons, known as a diffuse intrinsic pontine glioma (DIPG). The remaining 15-20% are low-grade gliomas and arise primarily in the midbrain and medulla.[2,3] The majority of children are diagnosed between 5 and 10 years of age with an equal predilection for males and females. Children present with a short period of symptoms between 2 weeks to 2 months prior to their diagnosis, typically with gait imbalance, dysmetria, dysarthria, long-tract signs and/or 6^{th}, 7^{th} cranial nerve palsies.[4]

DIPGs are one of the only brain tumors diagnosed by characteristic findings seen on magnetic resonance imaging (MRI). These tumors are widely infiltrative showing diffuse expansion of more than 50% of the pons and basilar artery encroachment. They are hypo- or iso-intense on T1-weighted images and hyperintense on T2-weighted MRI, with minimal to no-enhancement with gadolinium.[5]

Prior to the current molecular diagnostic era, surgical biopsy was rarely performed due to the potential for peri-operative complications without providing a significant rationale for

treatment assignments.[4] Recent trials have brought tumor biopsy at diagnosis back to the forefront to molecularly profile these tumors.

Nonetheless, children with high-grade BSG continue to have a dismal prognosis, with a median OS of less than 1 year, and fewer than 20% of children are alive beyond 2-years from diagnosis.[6,7] Radiation therapy is the standard treatment of these tumors, which at best provides temporary neurological and radiographic improvement.[8,9] Various strategies for delivering radiation therapy (i.e.: hypo- or hyperfractionated irradiation +/−sensitizers) have failed to improve OS for these children, at times with unacceptable toxicities.[10–18]

The “Head-Start” prospective, multi-center chemotherapy trials have been utilized in infants and children to treat highly aggressive brain tumors in young children with irradiation-avoiding strategies to prevent irradiation-induced deleterious side effects and hopefully improve survival. In this manuscript we report the impact upon survival of two prospective, sequentially conducted “Head-Start” trials on children with high-grade BSG. At the time of initiating this protocol, there were no clinical precedents exploring intensive chemotherapy regimens in DIPG, especially in very young patients. The delay in completion of this manuscript for publication reflected the difficulty in retrospectively retrieving original MRI studies from archival records and several different institutions to perform centralized confirmation that tumors represented true diffuse intrinsic pontine gliomas versus other, more focal or atypical brainstem tumors.

PATIENTS AND METHODS

Patient Selection

Children who were less than 10-years of age with newly diagnosed previously *untreated* tumors, with radiographic and clinical characteristics of DIPG were enrolled on one of the following non-randomized, prospective, multi-institutional studies, HSI (1991-1997) or HSII (1997-2002).

An MRI of the brain with-and-without gadolinium was required at diagnosis but an MRI of the spine and lumbar cerebrospinal fluid cytology was not mandated. There was no central radiology review prior to enrollment, diagnostic MRI characteristics were defined per institutional radiology review and treating clinician. Chemotherapy was required to begin within 21-days of the diagnostic MRI and/or any definitive surgical diagnostic procedure. Enrollment criteria included no prior exposure to chemotherapy or irradiation and adequate hepatic and renal function.

Surgery and Pathology

Children with presumed BSG were eligible for entry without tumor biopsy provided the tumors demonstrated the characteristic radiological features of DIPG. Patients with largely exophytic BSG or localized to the midbrain or cervico-medullary junction required surgical confirmation of a glioma grade 2-4. The degree of surgical resection was determined by central review of operative reports and of the pre-operative and post-operative MRI reports. If biopsy or resection was performed, tumor pathology was centrally reviewed retrospectively by neuropathologists on the study committee.

Chemotherapy Regimens

The treatment plan included one of these three Induction Regimens followed by one cycle of the Consolidation Regimen. INDUCTION REGIMEN A (HSI) consisted of 5 cycles of chemotherapy at 21-day intervals with cisplatin (3.5mg/kg/dose intravenously (IV) on day 1), cyclophosphamide (65mg/kg/day and mesna on days 2 and 3), etoposide (4mg/kg/day IV on days 2 and 3), vincristine (0.05mg/kg/dose IV on days 1, 8 and 15 of cycles 1 to 3); INDUCTION REGIMEN B (HSII before amendment to Regimen C below) which consisted of 4 cycles of chemotherapy at 28-day intervals with procarbazine (10mg/kg/day orally once daily on days 0, 1, 2, 3 and 4), carboplatin (20mg/kg/day IV on days 3 and 4), lomustine (3.5mg/kg/day orally on days 3 and 4), vincristine (0.05mg/kg/dose IV on days 1, 8 and 15 of cycles 1 to 3); or REGIMEN C (HSII after amendment) which consisted of 4 cycles at 28-day intervals with carboplatin (20mg/kg/day IV on days 3 and 4 or an AUC of 8 using the Calvert Formula dosing[19]), temozolomide (6.5mg/kg/day orally once at bedtime on days 1 to 5) and vincristine (0.05mg/kg/dose IV on days 1, 8 and 15 of cycles 1 to 3, max dose 2mg). Patients without progressive tumor growth at the completion of Induction chemotherapy were eligible to proceed with one cycle of the CONSOLIDATION REGIMEN which consisted of carboplatin (calculated using the Calvert formula for a desired area under the curve of 7mg/ml/min on days −8 through −6 to a maximum of 500 mg/m2/day), thiotepa (300mg/m^2/day or 10mg/kg/day on days −5 through −3), and etoposide (250mg/m^2/day on days or 8.3mg/kg/day −5 through −3). (See Table 1)

Filgrastim (5μg/kg/day) was to be administered subcutaneously 24-hours after the last dose of chemotherapy with each Induction cycle and continued until recovery of the neutrophil count. Induction chemotherapy was to be discontinued if there was evidence of disease progression or if unacceptable toxicity occurred. Bone marrow or autologous peripheral blood hematopoietic cell harvesting was to be undertaken upon recovery from Induction cycles 1 and/or 2.

Extent of disease evaluation was to be performed following completion of two cycles of Induction and following completion of the entire Induction phase of chemotherapy. Any patient who had radiographically stable to better residual tumor was eligible to proceed to Consolidation provided the patient was not corticosteroid dependent. If this criterion could not be met, the patient was considered for off-study therapy. Any patient who developed radiographic evidence of tumor progression at any time was also not eligible to proceed and was considered for off-study therapy.

Seventy-two hours after completion of the Consolidation Regimen, bone marrow or leukapheresed peripheral blood hematopoietic cells (PBHC) were to be re-infused (Day 0). A minimum cell dose of 2 x 10^6 $CD34^+$ cells/kg was required for successful re-infusion. All patients were to receive filgrastim 5μg/kg/day starting 24 hours after hematopoietic cell reinfusion and continued until there was neutrophil engraftment.

After complete recovery from Consolidation, patients were to receive radiotherapy if they were older than 6 years of age at the time of diagnosis and/or had residual tumor at the completion of Induction chemotherapy. Irradiation was to be initiated no earlier than day

+42 following hematopoietic cell reinfusion. Patients were to receive focal irradiation to the tumor bed plus a 2.5 cm margin to a total dose not to exceed 59.4 Gy.

After completion of therapy, patients were to undergo brain MRI scans with-and-without gadolinium once every 3 months for the first 2 years, once every 6 months for the next 3 years and annually thereafter.

Response and Toxicity Criteria

Pre-study MRI scans were compared with studies performed after completion of Induction chemotherapy and approximately 6 weeks after Consolidation chemotherapy. Tumor size was estimated as the product of the greatest diameter and its perpendicular. Responses were categorized as follows: progressive disease (PD), greater than 25% increase in tumor size or the appearance of new area of tumor; partial response (PR), greater than 50% decrease in tumor size; minor response (MR), between 25% and 50% decrease in tumor size; complete response (CR), complete disappearance of all previously assessable tumors; stable disease (SD), less than 25% decrease in tumor size Toxicity criteria were graded according to the Common Terminology Criteria for Adverse Events version 3.0.

Study Evaluations

Complete blood cell counts and biochemical screening profiles were to be obtained at prescribed intervals. Audiograms or brainstem auditory-evoked potentials were to be performed before each of the Induction cycles, before Consolidation, at 3 months and 1 year post-Consolidation and annually thereafter.

Supportive Care

Platelet counts were to be maintained above 30,000/μL and hemoglobin was to be maintained above 8.0 g/dL. Febrile neutropenic patients were to be treated with broad-spectrum intravenous antibiotics and antifungal agents when appropriate. Patients were to receive appropriate prophylaxis for *pneumocystis jerovecii* pneumonia.

Informed Consent

Parents or legal guardians for each child signed an informed consent approved by the Institutional Review Board (IRB) or equivalent committee at each treating center.

Statistical Considerations

The primary aim from these prospective HSI and HSII trials was to determine EFS and OS of these patients from the time of study enrollment and after administration of the intensive chemotherapeutic regimen. Primary endpoints for analysis were: 1) EFS – the time from date of diagnosis to progression, relapse or death from any cause; 2) OS – the time from date of diagnosis to death; and 3) irradiation-free survival – the time from date of diagnosis to death or the receipt of radiotherapy for any reason. These were estimated using the Kaplan-Meier method and presented using corresponding 95% confidence intervals. Patient characteristic and response data were summarized using descriptive statistics.

RESULTS

Patient Characteristics

Between June 1992 and August 2002, a total of 15 children less than 10 years of age with newly diagnosed high-grade BSG were enrolled on either HSI or HSII. See Table 2 for more demographic information.

Diagnostic/Imaging Work-up—Of the 15 patients, two underwent a biopsy, and two patients had partial resections. Pathology in three of these four cases was consistent with a high-grade glioma (glioblastoma multiforme (GBM), malignant glioma and anaplastic astrocytoma) confirmed upon central pathological review; one patient however, was ultimately deemed to be a pilocytic astrocytoma upon central review following completion of study therapy and was therefore ultimately not included in the overall survival analysis. The majority of the children were, by institutional report “classic” DIPGs. Six of the 15 patients underwent MRI of the total spine and had no evidence of disseminated disease.

At the time, central review of MR imaging studies was made available following completion of all study therapy. Of the two patients who proved to be long-term survivors, one patient’s tumor was located in the lower pons and upper medulla, and at diagnosis was diffusely enhancing suggestive of a high-grade glioma. It was only after a period of 6 years did we note that the tumor no longer demonstrated any contrast enhancement and was described only by a fusiform enlargement of his lower pons and medulla and was also not included in the final survival analysis. The second patient, who underwent biopsy had a low-grade glioma confirmed on central review with MR imaging findings not typical of a DIPG. The patient who underwent a partial resection at diagnosis of a pathologically confirmed GBM, had MRI findings typical of a high-grade exophytic BSG with irregular gadolinium enhancing areas. The patient with a confirmed brainstem anaplastic astrocytoma had classic DIPG findings on MRI.

Response to Induction Chemotherapy—Eight of the 15 children (53%) completed Induction (Regimen A: n=4 of 6, Regimen B: n=1 of 3, Regimen C: n=3 of 6) the remaining seven (Regimen A: n=2; Regimen B: n=2; Regimen C: n=3) developed progressive disease three of which proceeded directly to irradiation.

Three patients all treated on Regimen C, achieved partial responses. One patient, treated on Regimen A, achieved a minor response. Four patients had stable disease at the end of Induction therapy (Regimen A: n=3, Regimen B: n=1). All three patients from Regimen A with stable disease at the end of Induction discontinued study therapy due to large residual disease and proceeded to receive focal irradiation, one of whom (ultimately deemed ineligible due to pathology of pilocytic astrocytoma) became a long-term survivor.

Response to Consolidation Chemotherapy—Five of the 15 children with BSG proceeded to Consolidation, of whom three maintained stable disease for 5 months, 7 months and one other long-term survivor (ultimately reviewed radiographically as a low-grade medullary tumor). One patient achieved partial response following Consolidation and

survived for two years before expiring of tumor progression. One patient developed progressive disease two days into the conditioning regimen and removed from the study.

Toxicity—Toxicities observed were similar to those observed for other children enrolled on HSI and HSII Regimens as previously reported.[4,20] No patients were removed off-study or had dose reductions because of chemotherapy-related persistent grade 3 or 4 toxicities. There were no toxic deaths. One long-term survivor who received craniospinal irradiation (36 Gy) after what deemed to be a recurrence after completion of HSII therapy developed secondary growth-hormone and thyroid deficiency and resides in a group home at 23 years of age as of his last follow up.

Event-Free Survival, Overall Survival and Irradiation-Free Survival—Three of the four patients who completed Induction and Consolidation therapy ultimately developed progressive disease and expired. There were two long-term survivors who were found to have low-grade gliomas and were ultimately excluded from the survival analysis. One of these survivors never received irradiation post-Consolidation and is a long-term survivor (in excess of 14 years) and was ultimately deemed to have a low-grade glioma of the medulla on central imaging review. He developed tumor progression 18 months following completion of Consolidation, and received maintenance treatment with Thalidomide (3 years) and Celebrex (1 year). The one other long term survivor (in excess of 14 years); completed Induction but proceeded directly to irradiation without Consolidation because of a large residual was ultimately deemed ineligible for the study on the basis of central pathology review favoring a pilocytic astrocytoma.

For all patients eligible for survival analysis (n=13 of 15 enrolled), the 1-year and 2-year EFS were 31% (95%-CI: 9-55%), 0%, respectively; and 1-year and 2-year OS were 38% (95% CI: 14-63%) and 7.7% (95% CI: 0.4 to 29.2%); respectively, with a median EFS and OS of 6.6 and 8.7 month (Figure 1).

DISCUSSION

The clinical outcome for patients with DIPG remains dismal. Treatment strategies employed over the last three decades for these children have continually failed to prolong their survival. Indeed, with the progressive implementation of advanced imaging techniques, the outcomes of children with DIPG in successive cooperative group clinical trials appears to have worsened, due to exclusion of patients with lower-grade gliomas by MRI criteria.[10,21–23] Focal irradiation remains the only modality that provides transient radiological responses and symptom improvement, but without providing cure. Cohen et al ACNS0126 study demonstrated no apparent survival benefit to the addition of temozolomide having a mean 2-year EFS and OS are 1.7% ± 1.7% and 3.6%± 2.5%, respectively[18].

In recent years, classification of these diffusely infiltrating gliomas has integrated genetic and epigenetic characteristics [24] with clinical-pathological characteristics; these were unknown at the time HSI and HSII were launched, and are therefore outside of the scope of this paper. The role of chemotherapy remains unproven for children with DIPG. The results of our HSI and HSII trials are in concordance with this, and demonstrate that in spite of

utilizing the most intensive chemotherapy regimens available, in addition to irradiation, no survival advantage was observed.

We have compared BSG outcomes from our HS trials with other trials where chemotherapy was administered prior to irradiation (Table 3).[21,22,25–28] In 1993, Duffner *et al* demonstrated benefit of chemotherapy in delaying irradiation in a small proportion of infants with malignant brain tumors. Frappaz *et al* delayed irradiation until the time of clinical progression with intensive Induction chemotherapy, including high-dose systemic methotrexate (BSG98-Study). Although the median OS was increased by 8 months, patient quality of life was impaired.[28] Gokce-Samar *et al* compared the BSG-98 strategy with targeted therapy approaches including erlotinib, cilengitide and nimotozumab after stereotactic biopsy and reported an increase in median progression-free survival (3 months *versus 8.6* months) for the BSG-98 group and a significant increase in median OS (8.8 months versus 16.1 months, p = 0.0003)[29]. Other pre-irradiation chemotherapy strategies have failed to show improved EFS and OS.[22,26,27] In addition to the pre-irradiation chemotherapy strategies detailed above, numerous efforts over the years have attempted to use chemotherapy during irradiation, but this also failed to provide any additional survival benefit.[11–18]

The application of marrow-ablative chemotherapy in children with high-grade gliomas was based on the premise that higher doses of chemotherapy could overcome the physiological blood-brain-barrier as well as resistance, thereby enhancing both delivery and efficacy of these cytotoxic agents to these tumors.[12,30]

There is evidence for a steep-dose response curve of brain tumors to chemotherapy.[31] Initial studies using single-agent carmustine in high doses followed by marrow rescue in patients with high-grade gliomas reported tumor responses to this agent with longer duration of survival. [32–34] Subsequent conditioning regimens added thiotepa and etoposide to BCNU; however this combination resulted in significant toxicities and increased treatment-related mortality.[35] Therefore, BCNU was subsequently replaced by carboplatin.

Studies have shown that thiotepa readily penetrates the brain parenchyma due to its lipid solubility making it an ideal drug of choice to treat brain tumors.[36–40] Thiotepa has been used in combination with other drugs at marrow-ablative doses in treating patients with recurrent and newly diagnosed high-grade glioma.[41,42] Given the modestly encouraging outcomes of marrow-ablative chemotherapy with thiotepa and etoposide-containing regimens in the treatment of recurrent high-grade astrocytomas in locations other than the brainstem, this was also utilized in patients with high-grade BSG.[43–47] Marrow-ablative chemotherapy has been explored for relapsing or newly diagnosed high-grade BSG either in pre-irradiation or post-irradiation schedules, with the aim of tumor reduction before delivering radiotherapy or as radiotherapy consolidation (Table 4).[35,43,48–50]

CONCLUSIONS

The results from the HSI and HSII trials for BSG are disappointing and show similar poor EFS and OS compared with previously reported studies (Table 4). Based on these data, we

no longer enroll children with BSG on the “Head-Start” clinical trials (HSIII and HSIV). This therapeutic strategy should not be utilized in children with classical DIPG either at initial diagnosis or at tumor recurrence/progression.

Acknowledgments

No funding sources.

REFERENCES

1. Walker DA, Punt JA, Sokal M. Clinical management of brain stem glioma. Arch Dis Child. 1999;80(6):558–564. [PubMed: 10332008]
2. Cartmill M, Punt J. Diffuse brain stem glioma. A review of stereotactic biopsies. Childs Nerv Syst. 1999;15(5):235–237. [PubMed: 10392494]
3. Maria BL, Rehder K, Eskin TA, et al. Brainstem glioma: I. Pathology, clinical features, and therapy. J Child Neurol. 1993;8(2):112–128. [PubMed: 8505473]
4. Espinoza JC, Haley K, Patel N, et al. Outcome of young children with high-grade glioma treated with irradiation-avoiding intensive chemotherapy regimens: Final report of the Head Start II and III trials. Pediatr Blood Cancer. 2016;63(10):1806–1813. [PubMed: 27332770]
5. Zimmerman RA. Neuroimaging of primary brainstem gliomas: diagnosis and course. Pediatr Neurosurg. 1996;25(1):45–53. [PubMed: 9055335]
6. Hargrave D, Bartels U, Bouffet E. Diffuse brainstem glioma in children: critical review of clinical trials. Lancet Oncol. 2006;7(3):241–248. [PubMed: 16510333]
7. Jansen MH, van Vuurden DG, Vandertop WP, Kaspers GJ. Diffuse intrinsic pontine gliomas: a systematic update on clinical trials and biology. Cancer Treat Rev. 2012;38(1):27–35. [PubMed: 21764221]
8. Eifel PJ, Cassady JR, Belli JA. Radiation therapy of tumors of the brainstem and midbrain in children: experience of the Joint Center for Radiation Therapy and Children’s Hospital Medical Center (1971-1981). Int J Radiat Oncol Biol Phys. 1987;13(6):847–852. [PubMed: 3583855]
9. Freeman CR, Suissa S. Brain stem tumors in children: results of a survey of 62 patients treated with radiotherapy. Int J Radiat Oncol Biol Phys. 1986;12(10):1823–1828. [PubMed: 3759533]
10. Packer RJ, Boyett JM, Zimmerman RA, et al. Outcome of children with brain stem gliomas after treatment with 7800 cGy of hyperfractionated radiotherapy. A Childrens Cancer Group Phase I/II Trial. Cancer. 1994;74(6):1827–1834. [PubMed: 8082086]
11. Packer RJ, Prados M, Phillips P, et al. Treatment of children with newly diagnosed brain stem gliomas with intravenous recombinant beta-interferon and hyperfractionated radiation therapy: a childrens cancer group phase I/II study. Cancer. 1996;77(10):2150–2156. [PubMed: 8640684]
12. Jakacki RI, Siffert J, Jamison C, Velasquez L, Allen JC. Dose-intensive, time-compressed procarbazine, CCNU, vincristine (PCV) with peripheral blood stem cell support and concurrent radiation in patients with newly diagnosed high-grade gliomas. J Neurooncol. 1999;44(1):77–83. [PubMed: 10582673]
13. Broniscer A, Leite CC, Lanchote VL, Machado TM, Cristofani LM. Radiation therapy and high-dose tamoxifen in the treatment of patients with diffuse brainstem gliomas: results of a Brazilian cooperative study. Brainstem Glioma Cooperative Group. J Clin Oncol. 2000;18(6):1246–1253. [PubMed: 10715294]
14. Bernier-Chastagner V, Grill J, Doz F, et al. Topotecan as a radiosensitizer in the treatment of children with malignant diffuse brainstem gliomas: results of a French Society of Paediatric Oncology Phase II Study. Cancer. 2005;104(12):2792–2797. [PubMed: 16265674]
15. Estlin EJ, Lashford L, Ablett S, et al. Phase I study of temozolomide in paediatric patients with advanced cancer. United Kingdom Children’s Cancer Study Group. Br J Cancer. 1998;78(5):652–661. [PubMed: 9744506]

16. Broniscer A, Iacono L, Chintagumpala M, et al. Role of temozolomide after radiotherapy for newly diagnosed diffuse brainstem glioma in children: results of a multiinstitutional study (SJHG-98). Cancer. 2005;103(1):133–139. [PubMed: 15565574]
17. Sharp JR, Bouffet E, Stempak D, et al. A multi-centre Canadian pilot study of metronomic temozolomide combined with radiotherapy for newly diagnosed paediatric brainstem glioma. Eur J Cancer. 2010;46(18):3271–3279. [PubMed: 20656474]
18. Cohen KJ, Heideman RL, Zhou T, et al. Temozolomide in the treatment of children with newly diagnosed diffuse intrinsic pontine gliomas: a report from the Children's Oncology Group. Neuro-oncology. 2011;13(4):410–416. [PubMed: 21345842]
19. Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol. 1989;7(11):1748–1756. [PubMed: 2681557]
20. Mason WP, Grovas A, Halpern S, et al. Intensive chemotherapy and bone marrow rescue for young children with newly diagnosed malignant brain tumors. J Clin Oncol. 1998;16(1):210–221. [PubMed: 9440745]
21. Fouladi M, Nicholson HS, Zhou T, et al. A phase II study of the farnesyl transferase inhibitor, tipifarnib, in children with recurrent or progressive high-grade glioma, medulloblastoma/primitive neuroectodermal tumor, or brainstem glioma: a Children's Oncology Group study. Cancer. 2007;110(11):2535–2541. [PubMed: 17932894]
22. Jennings MT, Sposto R, Boyett JM, et al. Preradiation chemotherapy in primary high-risk brainstem tumors: phase II study CCG-9941 of the Children's Cancer Group. J Clin Oncol. 2002;20(16):3431–3437. [PubMed: 12177103]
23. Jenkin Rd Fau - Boesel C, Boesel C Fau - Ertel I, Ertel I Fau - Evans A, et al. Brain-stem tumors in childhood: a prospective randomized trial of irradiation with and without adjuvant CCNU, VCR, and prednisone. A report of the Childrens Cancer Study Group. 1987;66(2).
24. Jones C, Karajannis MA, Jones DT, et al. Pediatric high-grade glioma: biologically and clinically in need of new thinking. Neuro-oncology. 2016.
25. Duffner PK, Horowitz ME, Krischer JP, et al. Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. N Engl J Med. 1993;328(24):1725–1731. [PubMed: 8388548]
26. Doz F, Neuenschwander S, Bouffet E, et al. Carboplatin before and during radiation therapy for the treatment of malignant brain stem tumours: a study by the Societe Francaise d'Oncologie Pediatrique. Eur J Cancer. 2002;38(6):815–819. [PubMed: 11937316]
27. Kretschmar CS, Tarbell NJ, Barnes PD, Krischer JP, Burger PC, Kun L. Pre-irradiation chemotherapy and hyperfractionated radiation therapy 66 Gy for children with brain stem tumors. A phase II study of the Pediatric Oncology Group, Protocol 8833. Cancer. 1993;72(4):1404–1413. [PubMed: 8339231]
28. Frappaz D, Schell M, Thiesse P, et al. Preradiation chemotherapy may improve survival in pediatric diffuse intrinsic brainstem gliomas: final results of BSG 98 prospective trial. Neurooncology. 2008;10(4):599–607.
29. Gokce-Samar Z, Beuriat PA, Faure-Conter C, et al. Pre-radiation chemotherapy improves survival in pediatric diffuse intrinsic pontine gliomas. Childs Nerv Syst. 2016;32(8):1415–1423. [PubMed: 27379495]
30. Donelli MG, Zucchetti M, D'Incalci M. Do anticancer agents reach the tumor target in the human brain? Cancer Chemother Pharmacol. 1992;30(4):251–260. [PubMed: 1643692]
31. Postmus PE, Holthuis JJ, Haaxma-Reiche H, et al. Penetration of VP 16-213 into cerebrospinal fluid after high-dose intravenous administration. J Clin Oncol. 1984;2(3):215–220. [PubMed: 6321690]
32. Hochberg FH, Parker LM, Takvorian T, Canellos GP, Zervas NT. High-dose BCNU with autologous bone marrow rescue for recurrent glioblastoma multiforme. J Neurosurg. 1981;54(4):455–460. [PubMed: 6259300]
33. Mbidde EK, Selby PJ, Perren TJ, et al. High dose BCNU chemotherapy with autologous bone marrow transplantation and full dose radiotherapy for grade IV astrocytoma. Br J Cancer. 1988;58(6):779–782. [PubMed: 2852028]

34. Johnson DB, Thompson JM, Corwin JA, et al. Prolongation of survival for high-grade malignant gliomas with adjuvant high-dose BCNU and autologous bone marrow transplantation. J Clin Oncol. 1987;5(5):783–789. [PubMed: 3553437]
35. Papadakis V, Dunkel IJ, Cramer LD, et al. High-dose carmustine, thiotepa and etoposide followed by autologous bone marrow rescue for the treatment of high risk central nervous system tumors. Bone Marrow Transplant. 2000;26(2):153–160. [PubMed: 10918425]
36. Edwards MS, Levin VA, Seager ML, Pischer TL, Wilson CB. Phase II evaluation of thioTEPA for treatment of central nervous system tumors. Cancer Treat Rep. 1979;63(8):1419–1421. [PubMed: 225030]
37. Heideman RL, Cole DE, Balis F, et al. Phase I and pharmacokinetic evaluation of thiotepa in the cerebrospinal fluid and plasma of pediatric patients: evidence for dose-dependent plasma clearance of thiotepa. Cancer Res. 1989;49(3):736–741. [PubMed: 2491958]
38. Tartaglia RL CD, Heideman R, Balis F, . Chemosensitivity of central nervous tumors to thiotepa and tepa. Proc Am Assoc Cancer Res. 1989;30:1833.
39. Ascendo J Feldman AT. High dose thiotepa with autologous bone marrow transplantation and localized radiotherapy for patients with astrocytoma grade III-IV. Proc Am Assoc Cancer Res. 1989;9:90.
40. Heideman RL, Packer RJ, Reaman GH, et al. A phase II evaluation of thiotepa in pediatric central nervous system malignancies. Cancer. 1993;72(1):271–275. [PubMed: 8508417]
41. Heideman RL, Douglass EC, Krance RA, et al. High-dose chemotherapy and autologous bone marrow rescue followed by interstitial and external-beam radiotherapy in newly diagnosed pediatric malignant gliomas. J Clin Oncol. 1993;11(8):1458–1465. [PubMed: 8336185]
42. Kalifa C, Hartmann O, Demeocq F, et al. High-dose busulfan and thiotepa with autologous bone marrow transplantation in childhood malignant brain tumors: a phase II study. Bone Marrow Transplant. 1992;9(4):227–233. [PubMed: 1534708]
43. Finlay JL, Goldman S, Wong MC, et al. Pilot study of high-dose thiotepa and etoposide with autologous bone marrow rescue in children and young adults with recurrent CNS tumors. The Children's Cancer Group. *J Clin Oncol*. 1996;14(9):2495–2503.
44. Finlay JL, August C, Packer R, et al. High-dose multi-agent chemotherapy followed by bone marrow 'rescue' for malignant astrocytomas of childhood and adolescence. J Neurooncol. 1990;9(3):239–248. [PubMed: 1964962]
45. Bouffet E, Mottolese C, Jouvet A, et al. Etoposide and thiotepa followed by ABMT (autologous bone marrow transplantation) in children and young adults with high-grade gliomas. Eur J Cancer. 1997;33(1):91–95. [PubMed: 9071906]
46. Fagioli F, Biasin E, Mastrodicasa L, et al. High-dose thiotepa and etoposide in children with poor-prognosis brain tumors. Cancer. 2004;100(10):2215–2221. [PubMed: 15139067]
47. Guruangan S, Dunkel IJ, Goldman S, et al. Myeloablative chemotherapy with autologous bone marrow rescue in young children with recurrent malignant brain tumors. J Clin Oncol. 1998;16(7):2486–2493. [PubMed: 9667268]
48. Kedar A, Maria BL, Graham-Pole J, et al. High-dose chemotherapy with marrow reinfusion and hyperfractionated irradiation for children with high-risk brain tumors. Med Pediatr Oncol. 1994;23(5):428–436. [PubMed: 8084310]
49. Dunkel IJ, Garvin JH Jr., Goldman S, et al. High dose chemotherapy with autologous bone marrow rescue for children with diffuse pontine brain stem tumors. Children's Cancer Group. J NeurooncoL 1998;37(1):67–73. [PubMed: 9525840]
50. Bouffet E, Raquin M, Doz F, et al. Radiotherapy followed by high dose busulfan and thiotepa: a prospective assessment of high dose chemotherapy in children with diffuse pontine gliomas. Cancer. 2000;88(3):685–692. [PubMed: 10649264]

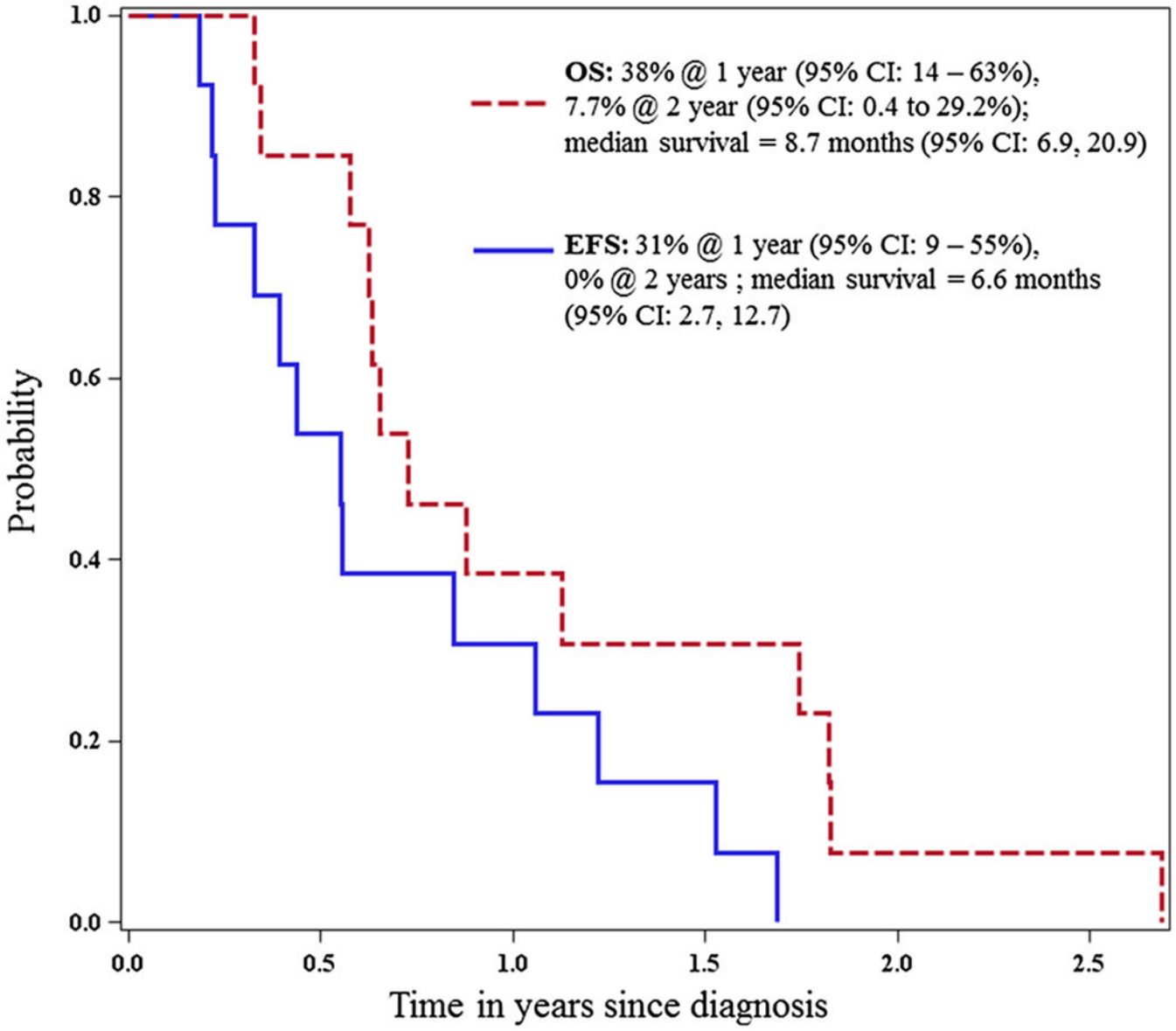

Figure 1.
Kaplan Meier Analysis of OS and EFS
OS: 38% @ 1 year (95% CI: 14 – 63%), 7.7% @ 2 year (95% CI: 0.4 to 29.2%); median survival = 8.7 months (95% CI: 6.9, 20.9)
EFS: 31% @ 1 year (95% CI: 9 – 55%), 0% @ 2 years ; median survival = 6.6 months (95% CI: 2.7, 12.7)

Table 1.

Treatment-Induction and Consolidation Chemotherapy Regimen

Part 1: INDUCTION REGIMEN	
Regimen A (HSI)	5-cycles at 21 days interval of: Cisplatin 3.5mg/kg IV on day 1 Etoposide 4mg/kg/day IV on days 2 and 3 Cyclophosphamide 65mg/kg/day and mesna on days 2 and 3 Vincristine 0.05mg/kg IV on days 1, 8 and 15 of cycles 1 to 3
Regimen B (HSII before amendment)	4-cycles at 28 days interval of: Procarbazine 5mg/kg orally once daily on days 0, 1, 2, 3 and 4 Lomustine 3.5mg/kg orally on days 3 and 4 Carboplatin 20mg/kg IV on days 3 and 4 Vincristine 0.05mg/kg IV on days 1, 8 and 15 of cycles 1 to 3
Regimen C (HSII after amendment)	4-cycles at 28 days interval of: Carboplatin at AUC of 8mg/ml/min based on pediatric Calvert formula[31] IV on days 1 and 2 Temozolomide 6.5mg/kg orally once at bedtime on days 1 to 5 Vincristine 0.05mg/kg IV on days 1, 8 and 15 of cycles 1 to 3
Part 2: CONSOLIDATION REGIMEN	
Enrolled in HS I and II trials	Carboplatin at AUC of 7 mg/ml/min based on pediatric Calvert formula[31]on days −8 through −6 Thiotepa 300mg/M^2/day or 10mg/kg on days −5 through −3 Etoposide 8.3mg/kg or 250mg/M^2/day on days −5 through −3

Table 2.

Demographics of the Study Population (15 patients) including the two long-term survivors.

			Regimen		
		Total	**A**	**B**	**C**
Number of Patients		15	6	3	6
Age (years)					
	0.0<1.5	1	0	0	1
	1.5<3.0	3	2	1	0
	3.0<6.0	8	4	1	3
	6.0<10.0	3	0	1	2
Sex					
	Female	8	3	1	4
	Male	7	3	2	2
Race					
	Asian	1	0	0	1
	African	4	2	1	1
	Hispanic	0	0	0	0
	White	9	4	1	4
	Unknown	1	0	1	0

Table 3.

Response to Pre-irradiation Chemotherapy of Published Studies Including Newly-diagnosed High-grade BSG; Carbo-carboplatin; CCNU-lomustine; CDDP-cisplatin; CPM-cyclophosphamide; Tamox-Tamoxifen; VP-16-etoposide; VCR-vincristine; FHF: focal hyperfractionated; FRT-focal involved-field conventional radiation therapy ranging from 50.4-59.4 GY; RT Radiation therapy; CR-complete responses; MR-minimal responses; OR-total objective response; PD-progressive disease; PR-partial responses; SD-stable disease; m-months; N= total number of radiologically evaluable patients

				Response to chemotherapy						
Study	**N**	**Chemotherapy Regimen**	**Post-Chemotherapy RT**	**CR**	**PR**	**MR**	**SD**	**PD**	**OR%**	**Median Survival (OS)**
Duffner et al.[24]	8	Reg A: CPM/VCR Reg B: CDDP/VP-16 (AABAAB sequence)		0	0	0	4	4	0	-
Jakacki et al.[12]	6	4-cycles: CCNU/VCR/ Procarbazine	FRT	0	3	1	1	1	50	13m
Kretschmar et al.[27]	37	4-cycles: CDDP/CPM	FHF 66Gy	0	3	3	20	6	8.1	9m
Doz et al.[25]	21	2-cycles: Carbo x 3days	FRT+Carbo	0	0	2	6	13	9.5	11m
Jennings et al.[28]	27	3-cycles: Carbo/ VP-16/VCR	FHF 72Gy	0	2	1	12	12	11	-
Jennings et al.[28]	22	3-cycles: CDDP/ VP-16/CPM/VCR	FHF 72Gy	0	1	4	8	9	22.7	-
Frappaz et al.[29]	23	Cycle-1: Tamox/BCNU/ CDDP; cycle-2&3 :high-dose MTX	FRT+Hydroxyurea/ tamoxifen	-	-	-	-	-	-	17m
Osorio et al. This study *	15	HS I and II	Focal, no greater than 59.4Gy	0	0	0	7	8	-	8.7m

* Chemotherapy responses after completion of induction +/−consolidation to reflect response to entire chemotherapy regimen.

Table 4.

Outcome of Myeloablative Chemotherapy in High-grade BSG from Published Clinical Trials. B-BCNU; Bu-busulphan; C-carboplatin; CPM-cyclophsphamide; DF-disease free; E-etoposide; EFS-event-free survival; N-total number of radiologically evaluable patients; NA-not available; OS-overall survival; RT-radiation therapy; T-thiotepa; m-months; WD-with disease

Recurrent or Refractory High-grade BSG								
Study	**N**	**Prior therapy**	**Conditioning Regimen**	**Post-RT**	**Median survival**	**1-year EFS/OS**	**2-year EFS/OS**	**Long-term survivor**
Papadakis et al.[57]	3	RT & chemotherapy	BTE	No	1.1m (0.4-18.7m)	NA	NA	none
Finlay et al.[48]	6	RT & chemotherapy	TE	No	4.9m (1.6-23.6m)	7%	0%	none
Dunkel et al.[55]	10	RT & chemotherapy	TE(6); BTE(2); CTE(2)	FHF 72-78 Gy	4.7m (0.1-18.7m)	NA/10±7%	NA/0%	none
Newly-Diagnosed High-grade BSG								
Study	**N**	**Induction Chemo**	**Conditioning Regimen**	**Pre/Post-RT**	**Median Survival**	**1-year EFS/OS**	**2-year EFS/OS**	**Long-term survivor**
Papadakis et al.[57]	8	none	BTE	Post RT	14.1m (7.6-46m)	NA	NA	none
Kedar et al.[54]	6	none	CPM/T	Post: FHF 70-75 Gy	12.5m (77d-24+m)	NA	NA	2 (1 DF/ 1WD)
Dunkel et al.[55]	5	none	BTE	FHF 72-78 Gy	11.4m (7.6-17.1m)	NA/50±18%	NA/0%	none
Bouffet et al.[56]	23	none	BuE	Pre: FRT 50-55 Gy	10m (7.4-12.6m)	7%/7%	0%/7%	none