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Tolerability of Temozolomide in Conjunction with Craniospinal Radiation for the Treatment of Pediatric CNS Embryonal Tumors

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Abstract

Background: Temozolomide (TMZ) is effective in CNS embryonal tumors and well tolerated. The aim of this study is to evaluate tolerability of temozolomide in conjunction with craniospinal irradiation (CSI) in this patient group.

Methods: Retrospective chart review conducted of patients from 1/1/02-10/31/12. Nine charts reviewed; Information obtained included: tumor type, treatment regimen, side effects and management.

Results: Eight of nine patients completed CSI with minimal side effects. Two experienced delay in treatment secondary to myelosuppression, one requiring premature discontinuation of temozolomide. All patients tolerated maintenance chemotherapy with minor adjustments.

Conclusions: CSI with temozolomide was well tolerated. Further investigation is warranted.

Keywords: Temozolomide; CNS embryonal tumors; Medulloblastoma; Craniospinal irradiation

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Introduction

The incidence of embryonal CNS tumors (medulloblastoma, primitive neuroectodermal tumors (PNET), and pineoblastoma) in the pediatric population is 0.6 per 100,000 person-years, with medulloblastoma being the most common malignant CNS tumor (20%) [1]. Event free survival for medulloblastoma has improved in the past decades. Overall survival has also improved: 80% for patients with standard risk and 60-70% for high risk [2]. This improvement is attributed to the change in standard treatment [2-7]. With the increase in survival rates, more concern is given to quality of life. Multiple morbidities include permanent neurologic, endocrinologic, neurocognitive and hearing deficits. The combination of tumor location, surgery, radiation and chemotherapy is responsible for multiple morbidities. With such significant morbidities in long term cancer survivors, research to alter treatment in order to minimize sequelae as well as increase efficacy should be conducted.

In the early 1990s, temozolomide, a second generation alkylating agent, was studied in adult patients with glioblastoma multiforme (GBM), anaplastic astrocytoma and other high grade gliomas [8-10]. It is also a radiosensitizer and has been used in combination with radiation therapy for aggressive tumors. It was used concomitantly with focal radiation therapy in adult patients with GBM. These studies showed that temozolomide in combination with focal radiation was well tolerated with side effects including myelosuppression [11,12]. Stupp et al. reported 4 of 62 patients in one study and 37 of 284 patients in another study discontinuing temozolomide early with concomitant focal radiation secondary to toxicity including infection and myelosuppression [11,12].

Pediatric studies have shown similar tolerability and have demonstrated that temozolomide had a response to medulloblastoma/PNET [13,14]. Currently, the Children's Oncology Group is conducting a Phase II trial for recurrent/refractory embryonal tumors with temozolomide and irinotecan versus temozolomide, irinotecan, bevacizumab, again with the rationale that temozolomide has been shown to be active as a single agent for recurrent embryonal tumors [13].

Limited studies have been conducted to evaluate the tolerability and efficacy of temozolomide in combination with CSI. Our aim was to evaluate this treatment regimen in patients with embryonal CNS tumors. Our hypothesis was that it would be well tolerated with mild to moderate side effects consisting of myelosuppression. Patients were treated with temozolomide as off-label use given the preliminary data regarding efficacy.

Methods

We performed a retrospective chart review evaluating patients with embryonal CNS tumors who received temozolomide in conjunction with CSI. Chart review from 2002 till October 2012 was conducted. Data collected consisted of: age, sex, type of tumor, age at diagnosis, treatment regimen, side effects and management. In order to objectively identify side effects, the Common Terminology Criteria for Adverse Events version 4.0 was used as a reference.

The results are descriptive, evaluating primary outcomes. The methods of Kaplan and Meier were used to analyze outcomes for this cohort.

Results

Please see **Table 1** for detailed information regarding patient characteristics and treatment regimens along with side effect profiles. Of the nine patients, eight (89%) completed CSI and temozolomide with minimal side effects. Five patients received temozolomide and CSI immediately after diagnosis while four patients received some chemotherapy prior to this combination. The most common adverse reactions included grade 2 nausea and vomiting, seen in all patients, which responded well to antiemetics. No patients required platelet transfusions. Two (22%) of the nine patients had grade 2 thrombocytopenia during the course of CSI and temozolomide. Patient 3 had temozolomide held for five days for platelet recovery. This patient also had a delay in CSI for one day secondary to gastroenteritis requiring hospitalization. Patient 5 required cessation of temozolomide after 22 days secondary to grade 2 thrombo-cytopenia and grade 3 esophagitis. This patient also had a two week delay of CSI due to inpatient admission to treat the esophagitis. No patients required discontinuation of CSI. One patient suffered radiation necrosis with subsequent epidural hemorrhage (treated with decompressive suboccipital craniectomy, steroids, hyperbaric chamber). All 9 patients received subsequent adjuvant chemotherapy. One patient had discontinuation of cisplatin for ototoxicity, two required dose reduction and five had delay in chemotherapy for toxicity.

To date, of the nine patients evaluated in this study, five are still alive. Four of the five patients have minimal sequelae. Patient 4 has multiple neurological deficits likely due to surgical intervention for radiation necrosis and requires full assistance.

Discussion

The combination of temozolomide and CSI was well tolerated, requiring discontinuation of treatment in one of nine patients (11%). The most common adverse effects included grade 2 nausea and vomiting. Only one patient required cessation of temozolomide for grade 2 thrombocytopenia and grade 3 esophagitis and a 2 week delay in radiation for hospitalization for esophagitis. The esophagitis may be secondary to a combination of CSI and temozolomide, which is rare adverse event. One patient had grade 3 anemias likely due to a combination of 4 months of Head Start II followed by CSI and temozolomide. One patient had grade 2 neutropenia but this patient was also pretreated with vincristine/cisplatin. The only late effect seen was radiation necrosis with subsequent epidural hemorrhage. Radiation necrosis is a rare, but concerning, side effect reported and it is unclear why this patient developed it. Previous studies using this combination therapy have been conducted, with no reported toxicity of radiation necrosis.

In a study of pediatric patients with aggressive CNS tumors, one patient with medulloblastoma received CSI and had tolerable side effects consisting of myelosuppression [15]. The German Society of Pediatric Oncology and Hematology high grade glioma group treated six patients with diffuse intrinsic pontine glioma (DIPG) and primary metastatic high grade glioma (HGG) with CSI and concurrent metronomic temozolomide. This study also reported myelosuppression. All patients suffered Grade III or higher myelotoxicity and four of six patients had to discontinue temozolomide [16]. This same group treated a patient with DIPG with CSI and concomitant temozolomide and nimotuzumab and had similar side effects requiring disruption of temozolomide due to myelotoxicity [17]. These limited studies have shown that this treatment regimen causes significant myelosuppression requiring discontinuation of treatment with temozolomide in majority of patients. The possible explanation for the difference in toxicity profiles for our study compared to the group in Germany may be disease related. Our patients all had embryonal tumors while the other group treated patients with DIPG and high grade gliomas.

Our study was very limited in that it was a retrospective chart review with a small number of patients treated over a period of 10 years. These patients received temozolomide and a different CSI dose depending on disease risk, which makes it difficult to interpret the data, but what is notable, is the overall tolerability of this combination. Temozolomide with radiation is standard of care for patients with newly diagnosed high grade gliomas, not on clinical trials, because of tolerability as well as feasibility [18]. Therefore it may be valuable to further investigate this combination as a potential option for patients requiring aggressive therapy in high risk embryonal tumors.

Prospective studies consisting of larger population of pediatric patients with embryonal tumors receiving temozolomide in conjunction with CSI should be considered. Temozolomide has been proven effective in embryonal tumors and combination with CSI has been tolerable with side effects mainly consisting of myelosuppression, which is treatable and reversible.

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Conflict of Interest Disclosure

There authors have no conflicts of interest to disclose.

Table 1 Patient Characteristics.

Pt	Age/ Sex	Tumor	CSI dose plus TMZ (90mg/m^2/day)	Adjuvant chemotherapy regimen	Side effects (CSI and TMZ) CTCAE 4.0 Grades	Management of Side effects from CSI/ TMZ	Side effects from adjuvant chemotherapy CTCAE 4.0 Grades
1	4/M	Brainstem PNET	23.4 Gy + local boost of 55.8 Gy (4 months of chemo prior)	Head Start II, dose reduced VCR for toxicity	nausea (II), vomiting (II), anemia (III), diarrhea (I), chemo induced alopecia (II), dermatitis (II)	antiemetics, PRBC transfusions to keep Hgb >10, aquaphor	anemia (III), neutropenia (II), ototoxicity (III), nausea (II), thrombocytopenia (II), vomiting (II)
2	4/M	LCA medulloblastoma	36 Gy + local boost of 55.8 Gy (one dose of VCR, CDDP prior)	CTX, VP-16, VCR, CDDP- d/c for ototoxicity, (Head Start II) , progressed- TMZ, VP16, progressed- hospice	nausea (II), vomiting (II) (NG fed CN 9,10 palsy), alopecia (II), neutropenia (II)	antiemetics, GCSF injections	anemia (III), nausea (II), thrombocytopenia (IV), febrile neutropenia (III), vomiting (II), ototoxicity (II), seizure (II)
3	6/M	Pineoblastoma	23.4 Gy + local boost of 55.8 Gy (2 months of chemo prior)	VCR, CDDP, VP16, CTX	nausea (I), thrombocytopenia (II), chemo induced alopecia (II), scalp dermatitis (II)	antiemetics, TMZ held for 5 days for platelet recovery, CSI held one day for gastroenteritis	thrombocytopenia (II), neutropenia (II), tremor (I), hypomagnesemia (II)
4	5/M	LCA medulloblastoma	36 Gy + local boost of 55.8 Gy & maximum of 45.86 Gy to cord metastases (1.5 months of chemo prior)	VCR, CDDP, VP-16, CTX, high dose MTX prior to CSI, then VCR, CDDP, VP-16 (Head Start II), ASCR, delayed for thrombocytopenia	nausea (II), vomiting (II), scalp dermatitis (II), head bobbing after 2nd wk of CSI, radiation necrosis	antiemetics, aquaphor	anemia (III), neutropenia (III), thrombocytopenia (III), nausea (III), vomiting (III), sepsis (IV), febrile neutropenia (III)
5	15/M	Desmoplastic medulloblastoma	23.4 Gy + local boost of 54 Gy	VP-16, CDDP, CTX, VCR, CBCDA, progressed- topotecan, CTX, IT thiotepa, ASCR, delayed for neutropenia	nausea (II), vomiting (II), thrombocytopenia (II), esophagitis (III)	Antiemetics, TMZ d/c after 22 days thrombocytopenia (II) and esophagitis (III), radiation delayed 2 wks for esophagitis	anemia (III), neutropenia (III), thrombocytopenia (III), nausea (II), vomiting (II), esophagitis (III), ataxia (II), peripheral neuropathy (II), jaw/ear pain (II), seizures (II),
6	5/F	Medulloblastoma focally desmoplastic/ nodular	23.4 Gy + local boost of 54 Gy	CDDP, VP-16, VCR, CBCDA, delayed for myelosuppression	nausea (II), vomiting (II), maculopapular rash (II)	antiemetics, benadryl for symptomatic relief of rash	neutropenia (III), thrombocytopenia (II), mucositis (II), nausea (III), seizure (II)
7	11/M	Medulloblastoma	23.4 Gy +local boost of 54 Gy	CDDP, VP-16, VCR, CBCDA, delayed for thrombocytopenia	nausea (II),vomiting (II)	antiemetics	jaw/ear pain (II), neutropenia (III), thrombocytopenia (II) paresthesias (II), nausea (III), vomiting (II)
8	6/M	Medulloblastoma with anaplasia	36 Gy + local boost of 55.8 Gy	VP-16, CDDP, VCR, CTX, CBCDA- dose reduced and delayed for myelosuppression	nausea (II), vomiting (II), dermatitis (II)	antiemetics, aquaphor	nausea (II), vomiting (II), thrombocytopenia (II), neutropenia (II), anemia (II)
9	9/M	Desmoplastic medulloblastoma	23.4 Gy + local boost of 55.8 Gy	CDDP, VP-16, VCR, CBCDA, CTX	dermatitis (I), weight loss (I), nausea (II), vomiting (II)	antiemetics	thrombocytopenia (II), hearing loss (II), anemia (III), neutropenia (IV)

Abbreviations- CTX: Cyclophosphamide, VCR: Vincristine, VP-16: Etoposide, CDDP: Cisplatin, MTX: Methotrexate, ASCR: Autologous Stem Cell Rescue, CBCDA: Carboplatin, IT: Intrathecal, TMZ: Temozolomide, CTCAE: Common Terminology Criteria for Adverse Events.

References

1 Lau C (2014) Epidemiology of central nervous system tumors in children. Uptodate pp: 1-3.

2 Gottardo NG, Hansford JR, McGlade JP (2014) Medulloblastoma down under 2013: A report from the third annual meeting of the International Medulloblastoma Working Group. Acta Neuropathol 127: 189-201.

3 Tait DM, Thornton-Jones H, Bloom HJG (1990) Adjuvant chemotherapy for medulloblastoma: the first multi-centre control trial of the International Society of Paediatric Oncology (SIOP I). European Journal of Cancer 26: 464-469.

4 Packer RJ, Goldwein J, Nicholson S (1999) Treatment of children with medullo blastoma with reduced dose craniospinal radiation therapy and adjuvant chemotherapy: A Children's Cancer Group Study. Journal of Clinical Oncology 17: 2127-2136.

5 Evans AE, Jenkin RD, Sposto R (1990) The treatment of medullo blastoma. Journal of Neurosurgery 72: 572-582.

6 Packer RJ (1990) Chemotherapy for medulloblastoma/primitive neuroectodermal tumors of the posterior fossa. Annals of Neurology 28: 823-828.

7 Packer, RJ, Gajjar A, Vezina G (2006) Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. Journal of Clinical Oncology 24: 4204-4208.

8 Newlands ES, Blackedge GRP, Slack JA (1992) Phase I trial of temozolomide. British Journal of Cancer 65: 287-291.

9 Friedman HS, McLendon RE, Kerby (1998) TDNA mismatch repair and O^6 – Alkylguanine- DNA Alkyltransferase analysis and response to temodar in newly diagnosed malignant glioma. Journal of Clinical Oncology 16: 3851-3857.

10 O'Reilly SM, Newlands ES, Glaser MG (1993) Temozolomide: a new oral cytotoxic chemotherapeutic agent with promising activity against primary brain tumours. European Journal of Cancer 29A: 940-942.

11 Stupp R, Dietrich PY, Ostermann Kraljevic S (2002) Promising survival for patients with newly diagnozed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. Journal of Clinical Oncology 20: 1375-1382.

12 Stupp R, Hegi ME, Mason WP (2009) Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival of glioblastoma in a randomized phase III study: 5 year analysis of the EORTC-NCIC trial. Lancet Oncology 10: 459-466.

13 Nicholson HS, Kretschmar C, Krailo M (2007) Phase 2 study of temozolomide in children and adolescents with recurrent central nervous system tumors. A report from the Children's Oncology Group. Cancer 110: 1542-1550.

14 Nicholson HS, Krailo M, Ames MM (1998) Phase I study of temozolomide in children and adolescents with recurrent solid tumors: A report from the Children's Cancer Group. Journal of Clinical Oncology. 16: 3037-3043.

15 Loh KC, Willert J, Meltzer H (2005) Temozolomide and radiation for aggressive pediatric central nervous system malignancies. Journal of Pediatric Hematology Oncology 27: 254-258.

16 Muller K, Schlamann A, Guckenberger M (2014) Craniospinal irradiation with concurrent temozolomide for primary metastatic pediatric high grade or diffuse intrinsic pontine gliomas. A first report from the GPOH-HIT-HGG study group. Strahlenther Onkol 190: 377-381.

17 Muller K, Schlamann A, Seidel C (2013) Craniospinal irradiation with concurrent temozolomide and nimotuzumab in a child with primary metastatic diffuse intrinsic pontine glioma. A compassionate use treatment. Strahlenther Onkol 189: 693-696.

18 Cohen KJ, Pollack IF, Zhou T (2011) Temozolomide in the treatment of high grade gliomas in children: a report from the Children's Oncology Group. Neuro-Oncol 13: 317-323.