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Irinotecan and BCNU-Impregnated Wafers Used in Combination, for the Treatment of Patients with Recurrent Glioblastoma Multiforme

Sheri Dewan[1]*, Edward Stopa[2], Lloyd Alderson[4] and Prakash Sampath[1,3]

[1]*Department of Neurosurgery, Warren Alpert Medical School of Brown University and Rhode Island Hospital Providence, Rhode Island, USA*
[2]*Division of Neuropathology and Department of Pathology, Warren Alpert Medical School of Brown University and Rhode Island Hospital, Providence, Rhode Island, USA*
[3]*Department of Neurosurgery, Roger Williams Hospital, Providence, Rhode Island USA*
[4]*Department of Neurosurgery, Lahey Clinic, Burlington, Massachusetts, USA*

Abstract

Introduction: This retrospective study examines the toxicity of the combination of intravenous irinotecan, (CPT-11; Camptosar®; Pharmacia & Upjohn, Kalamazoo, Mich.) and BCNU (1,3-bis(2-chloroethyl)-1-nitrosurea) impregnated wafers (Gliadel®) following implantation at the time of tumor recurrence in patients with glioblastoma multiforme (GBM).

Method: Ten patients with recurrent GBM were examined in this study. The inclusion criteria were histologically confirmed GBM, Karnofsky's Performance Scale (KPS) greater than or equal to 60, and a single focus of recurrent tumor. All patients underwent resection of their tumor at the time of first recurrence with placement of BCNU wafers. Postoperatively, patients were treated with irinotecan. One cycle constituted of 125 mg/m^2 once weekly for 4 weeks followed by a 2-week rest. The patients were followed for toxicity, tumor progression and survival. Treatment was discontinued if intolerable side effects ensued.

Results: The mean time to tumor progression was 4.35 months. The mean survival from the time of BCNU wafer placement was 12.1 months. The overall mean survival was 18.9 months. The average number of cycles of CPT-11 that patients received was 2.7. The toxicity associated with the CPT-11 was as follows: two patients reported Grade 2 diarrhea and one patient experienced grade 3 pancytopenia, three patients reported deep vein thromboses and one patient suffered a non-life threatening pulmonary embolism.

Conclusions: The combination of systemic irinotecan along with local intratumoral BCNU is well tolerated and may be more efficacious than either treatment alone. Our data support the need for a future prospective study designed to confirm the effectiveness of this combined treatment strategy.

Keywords: Irinotecan; BCNU; Glioblastoma multiforme; Impregnated wafers

Introduction

Malignant gliomas remain refractory to the standard therapy of surgical debulking followed by radiation. They are also universally fatal with a median survival still under 12 months and death usually occurring 40 to 50 weeks from initial diagnosis [3,7]. Both single and combination chemotherapeutic treatments have been attempted. Although some combination treatments appear to show promise as effective strategies, clinical trials confirming their safety and efficacy remain to be performed.

The introduction of intratumoral chemotherapy with the use of biodegradable polymers has proven to be a promising new strategy for treating patients with local recurrent disease. The data from randomized multicenter trials reveals modest improvement in survival both at reoccurrence and when used at initial surgery [23]. More importantly, the toxicity, both systemic and local, is minimal [12]. This fact makes this treatment option an ideal one to use in combination with systemic chemotherapy, thereby preventing potential synergies of toxicities. Nitrosureas including lomustine and carmustine administered as monotherapy or as part of a regimen are widely used [6,8,10,11,21,25]. Of multiple systemic chemotherapies, the camptothecins may prove to be one of the more effective antiglioma treatments. Other studies have suggested an additional potential benefit of CPT-11 due to its ability to cross the blood brain barrier and its relatively well-tolerated toxicities.

Combination therapy is a treatment strategy designed to provide more favorable results than a single drug alone [19]. The combination of BCNU-impregnated wafer along with CPT-11 is an attractive option for a number of reasons. Firstly, BCNU can be directly delivered to the brain minimizing toxicity. Secondly, CPT-11, a topoisomerase inhibitor, exerts its antineoplastic effect in a different part of the cell cycle potentially adding to the synergism with an alkylating agent [7]. Thirdly, CPT-11 along with this active metabolite SN38 has been shown to cross the blood-brain barrier to cytotoxic concentrations, therefore, greatly increasing its bioavailability [4,13,20].

In this study, we show that the combination of CPT-11 with BCNU wafer is safe, and that it may improve survival in some patients.

Materials and Methods

We retrospectively studied ten patients with recurrent malignant

***Corresponding author:** Sheri Dewan M.D., Department of Neurosurgery, Warren Alpert Medical School of Brown University and Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island, USA, Tel: (401) 455-1749; Fax: (401) 444-7146; E-mail: Sheri_Dewan@Brown.edu

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glioma who were treated at our center between 1998-2001. All patients studied had histologically confirmed glioblastoma multiforme, Karnofsky's Performance Scale (KPS) great than or equal to 60, a single focus of tumor recurrence with a potential for resection, and the ability to provide informed consent. Patients were predominantly male, a total of seven patients; the rest were female. The median age was 46 years old; with a range from 40-75 years old. The mean KPS score was 90, with a range from 70-100. Tumor location was left-sided in seven patients and right-sided in three patients. Of the left-sided tumors; two were located in the temporal region, one was in the frontal lobe, three were located in the parietal region and one was fronto-parietal. Of the right- sided tumors; one was located in the temporal lobe, one was parietal and one was fronto-parietal. Tumors were eloquent in eight of the locations; the majority of patients had hemiparesis associated with their tumors, one patient having a quadrantanopsia. Many of these patients had been treated with other modalities prior to/or in addition to surgery. Nine patients had additional external beam radiation; four of the ten patients underwent stereotactic gamma knife radiosurgery. (Table 1) summarizes basic patient characteristics.

At the time of surgery, patients underwent craniotomy for microsurgical resection of recurrent glioblastoma. Three patients required the assistance of motor mapping; two required intraoperative ultrasound and the other five were aided with neuronavigation. In all cases a gross total resection was the intended outcome, and in nine patients this was achieved by the surgeon's direct vision, later confirmed with MRI imaging. In one patient gross total resection was not achieved due to the presence of the ventricular surface. After complete resection of the recurrent tumor, Gliadel® wafers, were placed in the tumor resection cavity and were adhered to the brain surface using Surgicel®. In all patients eight Gliadel® wafers were placed in the intracavitary space.

Number of patients	10
Female	3
Male	7
Tumor Location	
Left	7
Right	3
Age	
Mean	46
Range	40-75

Table 1: Patient Characteristics.

Time between recurrence (months)	
Mean	6.18
Range	2.3-13.5

Table 2: Time of recurrence.

CPT-11 cycles (number)	
Mean	2.7
Range	1-6

Table 3: CPT-11 cycles.

Time from Gliadel placement to progression (months)	
Mean	4.35
Range	1-9

Table 4: Gliadel Placement.

Time of survival gliadel placement to death (months)	
Mean	12.1
Range	2.5-21

Table 5: Time of Survival

ime of survival from diagnosis to death (months)	
Mean	18.9
Range	12-26

Table 6: Time of Survival Overall.

Approximately two weeks after surgery, once the wound had completely healed, all patients were evaluated in the outpatient setting and were treated intravenously with CPT-11 (125 mg/m^2 weekly). CPT-11 was administered intravenously over a 90-minute period.

Patients were monitored for signs of systemic toxicity, tumor progression and overall survival at weekly intervals. Statistically, we calculated mean times for recurrence, giving ranges between treatments. Time of overall survival was also calculated using mean time from date of diagnosis.

Results

In our retrospective study, the mean time for recurrence was 6.18 months, ranging from 2.3 to 13.5 months (Table 2). This was the length of time between surgical resections and Gliadel wafer placement. The average number of cycles of CPT-11 that each patient received was 2.7, with a range between 1 and 6 (Table 3). Toxicity played a factor in the ability to tolerate CPT-11 cycles.

Table 4 demonstrates the mean progression time for tumor regrowth after Gliadel placement; 4.35 months with a range from 1 to 9 months (Table 4). In terms of survival after Gliadel placement and CPT-11 cycles; the mean survival was 12.1 months, with a range between 2.5 and 21 months (Table 5). The time of overall survival was on average 18.9 months with a range from 12 to 26 months (Table 6). This suggests a possible survival advantage with the combination of CPT-11 and BCNU wafers.

In terms of toxicity associated with CPT-11: Grade 2 diarrhea was reported by two patients, one patient experienced grade 3 pancytopenia, three patients reported deep vein thromboses and one patient suffered a non- life threatening pulmonary embolism. The presence of Grade 2 diarrhea was severe enough to warrant cessation of treatment in one patient. In addition, anemia, weight loss, dehydration, fever and pneumonia were also reported. However these findings did not interrupt chemotherapy treatments. No patients reported significant neurologic deterioration due to Gliadel® or any intracranial signs of infection. One patient developed a subgaleal seroma, which began draining, however was never infected and required no antibiotic therapy.

In regards to response, one patient experienced a partial response, and three patients had stable disease. The remaining six patients had evidence of tumor progression on MRI after the second cycle of chemotherapy.

Discussion

Using a retrospective analysis, we demonstrate that the combination of intratumoral BCNU (an alkylating agent) and systemic administration of CPT-11 (a topoisomerase inhibitor) is well tolerated and may improve survival with minimal toxicity. Little has been published on the usage of Gliadel wafers in combination with irinotecan. Most neuro-oncology studies have used the IV infusion form of BCNU as well as irinotecan to increase survival.

The introduction of biodegradable polymers has proven to be one such novel strategy that initially met with great promise and has had statistically significant efficacy both at tumor recurrence and at initial presentation. This strategy is important because it does allow

for delivery of chemotherapeutic agents as well as potentially other antineoplastic agents directly into the central nervous system and minimizes systemic toxicity. As a result, it is an ideal form of treatment to be used in combination with another systemic antitumor therapy.

Salvage chemotherapy with CPT-11 for recurrent glioblastoma multiforme has been shown to have a lack of response or minimal activity when used alone in treatment [5]. This could be due to several factors including sub-optimal dosing or increased clearance due to anticonvulsants or dexamethasone. Other studies have shown that CPT-11 appears to be active in treating malignant glioma, medulloblastoma and ependymoma but have postulated the addition of other agents to enhance efficacy [22]. More recently, irinotecan monotherapy has demonstrated efficacy, however when enhanced with other chemotherapeutics has shown promise [24].

The idea of combining agents and using available data to support such combination has become prevalent in the neuro-oncological research in recent years. Temozolomide (Temodar in the United States, Temodal globally; Schering Corporation, Kenilworth, NJ) has shown to be effective in combination with irinotecan than either agent alone [14,18]. The challenge has been to identify optimal dose patterns that will maintain the efficacy seen in trials. Recently a Phase II clinical trial involving temozolomide and irinotecan showed that the combination of the two was toxic and poorly tolerated, that TMZ and CPT-11 were comparable in efficacy to TMZ alone [16]. It seems that multi-center trials are still needed to elucidate this further.

Another agent, bevacizumab, a humanized immunoglobulin G1 monoclonal antibody to vascular endothelial growth factor, has been shown to provide safe and effective activity in combination with irinotecan for the treatment of malignant glioma [1,9]. Zuniga et.al, postulates that decreased efficacy over time may be due to the high rate of distant tumor progression allowing adaption to inhibition of the vascular growth factor [26].

The usage of BCNU and irinotecan in combination has been described in the medical literature. The regimen seems to be active in patients with recurrent GBM and also appears to be non-cross-resistant [2,15]. Recently a Phase II clinical trial involving BCNU and irinotecan showed that the activity of BCNU plus CPT-11 appears comparable to that of CPT-11 alone, and may be more toxic [17]. In all cases, BCNU was administered by IV infusion at 100mg/m^2 as part of a cycle regimen. Our retrospective study examined the utility of BCNU in the form of gliadel wafers.

Conclusion

The combination using systemic CPT-11 along with local intratumoral BCNU appears to be well tolerated and may be more efficacious than either treatment alone for patients harboring malignant glioma. A prospective multicenter analysis of this combination therapy is warranted in order to confirm these preliminary retrospective observations.

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