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CLINICAL STUDY

A phase II trial of tamoxifen and bortezomib in patients with recurrent malignant gliomas

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Abstract NF-kB inhibition by bortezomib enhances tamoxifen-induced apoptosis in preclinical glioma models. We conducted a single institution, phase II trial to evaluate efficacy and safety of high dose tamoxifen with bortezomib in adults with recurrent malignant gliomas. The primary endpoint was radiographic response. Concurrent enzyme inducing anticonvulsants and grade ≥2 peripheral neuropathy were exclusion criteria. Patients received tamoxifen (120 mg PO twice daily) and bortezomib (1.3 mg/m2 IV on days 3, 6, 10, 13, 24, 27, 31, and 34) per 6-week cycles. We enrolled 42 patients with anaplastic gliomas (AGs, n = 12) and glioblastomas (GBMs, n = 30), 32 males and 10 females. Median age was 38 years (range 22–65) and 48 years (range 19–68) for AGs and GBMs, respectively. median karnofsky performance status was 90 % (range 70–100) for AGs and 80 % (range 60–100) for GBMs. Median prior therapies was 3, ranging 1–7. Grade ≥3 toxicities included lymphopenia (4/42), hypophosphatemia (3/42), thromobocytopenia (2/42), and 1/42 with hyponatremia, headache, dyspnea, or DVT. One patient withdrew consent, two were removed for toxicity, and all others discontinued for progression. Among 40 patients evaluable for response, only one achieved stable disease for 3 months; all others progressed rapidly. For AGs and GBMs respectively, median progression-free survival was 5.9 and 5.7 weeks and median overall survival was 25.6 and 14.7 weeks. The study was closed due to poor accrual and therapeutic futility. Combination tamoxifen and bortezomib has no activity in recurrent malignant gliomas. Poor penetration across blood brain barrier of bortezomib likely limited efficacy.

Keywords Tamoxifen · Bortezomib · Glioma · Glioblastoma

Introduction

Based on the Central Brain Tumor Registry of the United States, gliomas are the most frequent adult primary brain tumors with an incidence of 6.03 per 100,000 adults per year [1]. Malignant gliomas are the second leading cause of cancer mortality in adults under 35 years of age [2]. Despite advances in imaging, anesthesia and surgical techniques, the prognosis of malignant gliomas treated by surgical resection alone is dismal with a median survival of 4–6 months [3–5]. Radiotherapy remains the most effective treatment, extending median survival to 8–9 months [6–8]. Adding temozolomide extends median survival to 15 months for glioblastomas and 2–5 years for anaplastic gliomas (AG) [9, 10]. Cytotoxic agents have limited efficacy in recurrent disease [5]. Oncology clinical trials now focus on targeting key molecular targets in order to personalize therapy and increase efficacy of treatment.

High dose tamoxifen, a member of the selective estrogen receptor modulator (SERM) family, is cytotoxic to

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glioma cells by inhibiting protein kinase C. SERM activity, however, is also associated with up-regulation of a number of anti-apoptotic genes, particularly the nuclear factor kappa light-chain-enhancer of activated B cells (NF-kB) pathway. NF-kB activation is a proven mechanism of resistance to tamoxifen and other antiestrogen therapy in both glioma and breast cancer models [11–14]. Suppression of NF-kB by salicylates markedly enhanced SERM-induced apoptosis, further supporting a role for NF-kB in overcoming glioma resistance to SERM-induced toxicity [12]. Bortezomib is a potent reversible inhibitor of 26S proteasome and the NF-kB pathway, proven effective and approved for multiple myeloma and mantle cell lymphoma [15]. Recent pharmacodynamic and pharmaco-kinetic studies in xenograft models proves that drug exposure is crucial for bortezomib efficacy in solid tumors [16]. In preclinical studies, combination bortezomib and tamoxifen has synergistic cytotoxic effect and overcomes resistance to hormone therapy [11].

We conducted a single institution phase II clinical trial to evaluate safety and efficacy of high dose tamoxifen with bortezomib in recurrent malignant gliomas due to modest activity of both drugs against glioma, spectrum of non-overlapping toxicities, and marked synergistic cytotoxicity by the combination in preclinical studies.

Methods

Study population

We enrolled 42 patients between 2005 and 2011, 18 years of age or greater, and with pathologically-confirmed glioblastoma (GBM, n = 30) or AG (AG, n = 12). Radiographically-confirmed tumor progression by MRI following standard external beam fractionated radiotherapy and adjuvant temozolomide chemotherapy was required. A minimum karnofsky performance status (KPS) of 60 %, normal metabolic and end-organ function, and an expected survival of 2 + months were required for enrollment. Measurable disease was required as radiographic response was the primary endpoint. Competent patients or their designated Power of Attorney/Health Care Proxy (POA/HCA) were required to sign the informed consent for this National Cancer Institute (NCI) Institutional Review Board-approved trial. There were no limits on the number of prior therapies, but a minimum wash out period of 2 or 4 weeks was required after molecularly targeted or cytotoxic agents, respectively. A minimum of 4 weeks after radiation and full recovery after surgery were also required. Exclusion criteria included grade 2 or more peripheral neuropathy, prolonged corrected QT interval (QTc), hypersensitivity to components of the study drugs, or significant medical illness. Concurrent use of enzyme-inducing anti-epileptics was strictly prohibited. A stable dose of corticosteroids was required for 5 + days prior to the baseline MRI scan within 14 days of enrollment. Patients with a history of intracranial hemorrhage or stroke within 6 months were ineligible.

Study design

The primary endpoint was treatment response rates, including stable disease, partial response or complete response. A min–max phase II design assumed ineffective response rate (stable disease or objective response at 6 weeks after 6 weeks on treatment) of 10 or 20 % and a targeted 25 or 40 % response rate for glioblastoma or AG patients, respectively. We also assumed that the probability of declaring an ineffective treatment effective (alpha) is 10 % and the probability of declaring an effective treatment ineffective (beta) is 10 %. Target enrollment was, thus, 27 and 19 for glioblastoma or AG patients, respectively. Accrual was stopped due to poor accrual and no therapeutic responses (goal >2 or >3 for glioblastoma and AG patients, respectively). Secondary endpoints included frequency and grade of adverse events as well as median progression-free and overall survival.

Treatment and patient assessment

Each cycle of therapy consisted of 6 weeks of oral tamoxifen 120 mg twice daily and intravenous bortezomib 1.3 mg/m2 on days 3, 6, 10, 13, 24, 27, 31, and 34 of every 6-week cycle. Dose delays were permitted for reversible and preventable toxicity. All patients underwent a perfusion MRI at baseline and at the end of each 6-week cycle. Peripheral blood mononuclear cells were collected for NF-kB activity as a surrogate marker of bortezomib activity. As no responses were noted, no assays were processed nor correlations performed between NF-kB activity inhibition by bortezomib and tumor response as proposed.

A full metabolic screen, history, physical and neurological exam was performed prior to each cycle. MRI scans were assessed using the response assessment in neuro-oncology (RANO) criteria [17]. Specifically, stable or decreasing dose of corticosteroids and stable or improved fluid-attenuated inversion recovery (FLAIR) abnormality were required to be scored a complete response, partial response or stable disease based on complete, partial or no decrease in the enhancing tumor burden based on standard post-gadolinium T1-weighted sequences. Disease progression by RANO criteria was sufficient to terminate treatment, as was a determination of clinical progression in the absence of radiographic progression or any drug-related serious intracranial bleeding.

Results

Forty-two patients were included in this analysis: 12 AG and 30 glioblastomas (GBM), of which 32 were males and 10 were females. Only 12/19 of target enrollment for the anaplastic cohort were accrued due to poor accrual. The median age was 38 years (range 22–65) for AG, and 48 years (range 19–68) for GBM. The median KPS at study entry was 90 for AG (range 70–100) and 80 for GBM (range 60–100). Patients were treated with a median of 3 prior therapies (range 1–7), while 19/42 (45 %) received prior bevacizumab therapy. Refer to Table 1 for detailed demographic data. Grade 3 or greater treatment related toxicities included lymphopenia (4, 9.5 %), hypophosphatemia (3, 7.1 %), thrombocytopenia (2, 4.8 %), and 1 (2.4 %) each with hyponatremia, headache, dyspnea, infection, somnolence, and DVT (Table 2). Two GBM patients were removed for toxicities, and all others had progression of disease. Among 40 patients evaluable for response, only one achieved stable disease unstained beyond the first response assessment. All others had rapid progression of disease, of which only 2/39 GBM and 1/12 AG patients even remained on study beyond the first 6-week clinical assessment. Median progression free survival was 5.9 and 5.7 weeks, while median overall survival was 25.6 and 14.7 weeks for AG and GBM respectively. Refer to Table 3 for details of response and survival. The study was closed to accrual early due to poor enrollment and therapeutic futility.

Table 2 Treatment-related toxicities

Grade and Frequency	1	2	3	4	Total	Fraction
Thrombocytopenia	19	3	1	1	24	0.75
Lymphopenia	4	4	4	0	12	0.38
Hypophosphatemia	0	6	3	0	9	0.28
ALT/sGPT	6	1	0	0	7	0.22
Anemia	6	0	0	0	6	0.19
Hyponatremia	4	0	1	0	5	0.16
Headache	0	2	1	0	3	0.09
Leukopenia	1	2	0	0	3	0.09
AST/sGOT	2	0	0	0	2	0.06
Dyspnea	1	0	1	0	2	0.06
Fatigue	2	0	0	0	2	0.06
Fever	1	1	0	0	2	0.06
Hyperkalemia	2	0	0	0	2	0.06
Cough	1	0	0	0	1	0.03
Depression	0	1	0	0	1	0.03
Diarrhea	0	1	0	0	1	0.03
Dizziness	1	0	0	0	1	0.03
Venous thrombosis	0	0	1	0	1	0.03
Edema	1	0	0	0	1	0.03
Hyperbilirubinemia	1	0	0	0	1	0.03
Hypermagnesemia	1	0	0	0	1	0.03
Hypocalcemia	1	0	0	0	1	0.03
Hypokalemia	1	0	0	0	1	0.03
Hypotension	1	0	0	0	1	0.03
Elevated creatinine	1	0	0	0	1	0.03
Infection (unknown ANC)	0	0	1	0	1	0.03
Neutropenia	0	1	0	0	1	0.03
Pain	0	1	0	0	1	0.03
Rash	1	0	0	0	1	0.03
Hemorrhage (rectal)	1	0	0	0	1	0.03
Somnolence	0	0	1	0	1	0.03
Urinary frequency	1	0	0	0	1	0.03

Discussion

Our study suggests that combination tamoxifen and bortezomib has a benign toxicity profile, but no therapeutic benefit in adults with recurrent malignant gliomas. Only 3 glioblastomas and 1 AG patients remained on therapy beyond the 6-week clinical assessment, of which only 1 GBM had stable disease at the 12-week MRI assessment. While only 12 of the 19 targeted for enrollment in the anaplastic cohort were accrued, it is unlikely to find 3 objective responses among the remaining 7 patients given the lack of response among the 30 glioblastoma patients enrolled. Bortezomib monotherapy or in combination therapy is associated with up neuropathy in up to 34 % of a meta-

Table 1 Patient demographics

		Anaplastic gliomas (n = 12)	Glioblastomas (n = 30)
Age (years)	Median (range)	38 (22–65)	48 (19–68)
Sex (M:F)	Frequency (percent)	9 (75 %):3 (25 %)	23 (77 %):7 (23 %)
KPS (%)	Median (range)	90 % (70–100 %)	80 % (60–100 %)
Prior therapies	Median (range)	3 (1–7)	3 (1–7)
Prior bevacizumab	Frequency (percent)	5 (42 %)	14 (47 %)
Time from completion of XRT (weeks)	Median (range)	77 (17–211)	32 (1–183)

Table 3 Treatment response and survival

	Anaplastic gliomas (n = 12)	Glioblastomas (n = 30)
Evaluable for response (n, %)	12 (100 %)	28 (93 %)
Response at 12 weeks (n, %)	1 (8.3 %)	0
Complete response	0	0
Partial response	0	0
Stable disease	1 (8.3 %)	0
Treated beyond 6 weeks	1 (8.3 %)	3 (10 %)
Median PFS (weeks, range)	5.9 (3.0–8.0)	5.7 (1.0–11.7)
Median OS (weeks, range)	25.6 (0–44)	14.7 (4–142)
6 month PFS (%)	0	0

PFS progression free survival, *OS* overall survival

analysis of 6492 patients enrolled in 34 clinical trials [18], but our glioma cohort did not experience any clinically significant neuropathy. The extremely short duration of bortezomib treatment in our trial may, at least in part, explains the infrequency of neuropathy in our glioma cohort. In addition, high-dose tamoxifen was previously a salvage treatment choice for recurrent malignant gliomas based on case series or pre-clinical studies [19]. Our study suggests that high dose tamoxifen monotherapy also has no significant therapeutic role in malignant gliomas, as supported by other negative early phase trials of high-dose tamoxifen in combination with chemotherapy and/or radiation for newly diagnosed or recurrent malignant gliomas [20–26].

The poor response of combination tamoxifen and bortezomib was likely influenced, at least in part, by the poor penetration of bortezomib across the blood brain barrier. Prior xenograft studies suggests tumor vessel perfusion, permeability, and architecture limit bortezomib exposure that then correlated with response and efficacy of bortezomib in these solid tumor models [16]. This combination was recently studied in patients with endocrine-resistant and progressive metastatic breast cancer and proved similarly ineffective, with only 22 % patients stable disease with no responses, despite effective target inhibition as suggested by peripheral blood mononuclear cell and tumor assays [27]. Either incomplete NF-kB suppression by bortezomib or alternative feedback pathways must also contribute to resistance of breast cancer and gliomas to SERM-mediated cytotoxicity. The demonstrated proteasome inhibition in tumor tissue provided evidence that the lack of clinical responses in solid tumors was not solely attributed to insufficient drug exposure. Since there was no limit on prior therapies, our glioma cohort was highly pretreated, half of which had received bevacizumab. The high frequency of prior bevacizumab failure may have impacted response rates in our cohort, though the remaining 7/12 AG and 16/30 GBM bevacizumab-naïve patients also failed to respond to combination tamoxifen and bortezomib therapy. Whether our cohort was enriched for poor molecular prognostic factors, such as IDH1 wild-type or unmethylated MGMT, is unknown since no molecular data was available for our cohort. Better results may have been observed with a less treatment resistant and molecular favorable population, but we conclude that combination tamoxifen and bortezomib has no significant activity in recurrent malignant gliomas.

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Compliance with ethical standards

Conflict of interest None.

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