Combination Therapy with Thalidomide, Temozolomide and Tamoxifen Improves Quality of Life in Patients with Malignant Astrocytomas

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Abstract. Background: Patients with malignant astrocytomas (MA) have a poor survival rate despite surgery, radiation therapy (RT), and chemotherapy (CT). Patients deteriorate rapidly with decreasing quality of life (QoL). The purpose of the current study was to determine the safety and efficacy, including QoL evaluation, of oral therapy with temozolomide, thalidomide, and tamoxifen (TTT) in patients with MA in an Institutional Review Board (IRB)-approved, prospective trial. Patients and Methods: Twenty-three patients met the eligibility requirements and were enrolled after informed consent was signed. After baseline testing, patients received temozolomide 75 mg/m2 orally (p.o.) for the first 21 days, thalidomide 100 mg p.o. daily, and tamoxifen 100 mg p.o. daily for each 28-day cycle. Treatment continued until disease progression. Primary outcome measurements were survival (Kaplan-Meier analysis), response to treatment, toxicity (National Cancer Institute’s Common Toxicity Criterion) and QoL evaluation. Results: The Kaplan-Meier analysis showed that survival time from diagnosis was 78.4±15 weeks with a median survival of 54.6 weeks and from date of enrollment was 46.1±10 weeks with median survival of 33.3 weeks. Toxicity was limited to 5 patients with deep venous thrombosis (DVT), 2 of whom had pulmonary emboli (PE). All recovered with anticoagulation therapy and none suffered long term sequelae. Several QoL measures, including the global health status scores (p=0.003), were significantly improved after 2 cycles of treatment compared to the baseline assessment. Conclusion: The combination of temozolomide, thalidomide and tamoxifen administered as outpatient oral therapy resulted in significantly improved QoL for patients with MA without significant toxicity.

Patients with malignant astrocytomas (MA), defined as glioblastoma multiforme (GBM) and anaplastic astrocytoma (AA), have a poor survival rate despite surgery and radiation therapy (RT) (1, 2). Adjuvant chemotherapy (CT) is often used but the impact on survival is limited (3). Patients deteriorate rapidly with decreasing quality of life (QoL) (4, 5). To date, the use of adjuvant CT has resulted in a definite survival advantage for patients with oligodendrogliomas and AA, while meta-analysis suggested a trend towards survival benefit in patients with GBM (6-14). However, most chemotherapy agents produce toxicities including myelosuppression, pulmonary fibrosis, myelinolysis and nephrotoxicity (3). These conditions further exacerbate the declining QoL of brain tumor patients.

The blood-brain-barrier (BBB) limits the effectiveness of most chemotherapeutic agents by limiting drug delivery to the tumor. As a result, innovative strategies have been tried including drug-impregnated wafer implantation (15), convection-enhanced CT delivery (CED) (16-18), BBB disruption (19-21) and stem cell rescue following high-dose chemotherapy (22). Alternative approaches have attempted to utilize understanding of the molecular pathogenesis of MA to develop novel agents or synergistic combinations of drugs to achieve greater efficacy (23-25). This approach using procarbazine, lomustine and vincristine (PCV) has proven highly effective for patients with anaplastic oligodendrogliomas (9, 26).

Ideally a combination CT for patients with MA would involve oral agents with favorable toxicity profiles, known efficacy in astrocytic tumors and diverse mechanisms of action. Temozolomide (Temodar, Schering Plough, Kenilworth, NJ, USA), tamoxifen (Zeneca Pharmaceuticals, Wilmington, DE, 0250-7005/2007 $2.00+.40

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USA), and thalidomide (Thalomid, Celgene, Summit, NJ, USA) (TTT) is a chemotherapy combination that has this potential (27, 28).

Temozolomide is a second-generation oral alkylating agent with predictable pharmacokinetics and a favorable toxicity profile. In a recent trial, use of temozolomide concurrent with RT in patients with newly diagnosed astrocytoma led to statistically significant and clinically meaningful survival benefit with minimal toxicity (29, 30). Tamoxifen has been shown to inhibit the growth rate of low-passage human glial cell lines (31) and phase I and II studies have demonstrated modest efficacy of tamoxifen in the treatment of recurrent MA (27, 32, 33). This benefit was generally seen with very little or no side-effects even in patients who were treated with high doses and an extended course (27, 33, 34). Thalidomide is an immunomodulatory agent with a broad spectrum of activity in neoplastic conditions. Thalidomide has been shown to inhibit angiogenesis in tumors and modulate cytokines that regulate the immune system (35-38).

The purpose of the current study was to determine the safety, efficacy, and the effect on the QoL of the combination chemotherapy with TTT in the treatment of patients with MA.

Patients and Methods

Study population. The phase II open label TTT study received Institutional Review Board (IRB) approval and began enrolling patients in 2001. Important inclusion criteria included histological confirmation of supratentorial MA, Eastern Cooperative Oncology Group (ECOG) performance status score from 0 to 2, age >18 years and measurable or evaluable disease on contrast-enhanced imaging. Prior radiation therapy did not preclude enrollment. Patients receiving more than two prior chemotherapy regimens or with documented hypersensitivity to any of the study therapeutic agents or components of their formulation were excluded from the study. The complete inclusion and exclusion criteria for study enrollment are outlined in Table I. All patients presenting to our institution who met eligibility criteria were offered enrollment in the study. IRB-approved informed consent was obtained from each study participant.

Study protocol. Baseline evaluation included complete history and physical examination, complete blood counts, blood chemistry, gadolinium-enhanced magnetic resonance imaging (MRI) of the brain within 30 days of the entry into the study, chest roentgenogram, and QoL assessment using EORTC QLQ-30 version 3.0 and EORTC BN-20 questionnaires. The patients received temozolomide 75 mg/m² orally (p.o.) daily for the first 21 days, thalidomide 100 mg/m² p.o. daily, and tamoxifen 100 mg p.o. daily throughout each 28-day cycle. The treatment was continued until disease progression or occurrence of severe toxic events. Supportive treatment followed common medical practice. The maintenance of a white blood cell (WBC) count above 3.0x10³/L and a platelet count above 1x10³/L was also required for treatment continuation. If necessary, the next treatment cycle was postponed until hematological recovery. The patients with failure of hematological recovery six weeks after the last treatment cycle were discontinued from the study. All severe adverse events were reported to the IRB. Pre-treatment evaluation sheets, observation sheets and periodic evaluation sheets were maintained and recorded. The response to the treatment was evaluated by MRI of the brain with gadolinium after every 2 cycles of treatment.

Outcome measurements. Patient survival, response to treatment, treatment-related toxicity, and changes in the QoL were the primary outcomes analyzed in this study. Patient survival was measured from the time of enrollment until the last date of follow-up or death. The time of diagnosis to the same end-point was also recorded. The response to treatment was defined by evaluation of the gadolinium-enhanced MRI scheduled at the end of every 2 cycles of treatment. Complete response (CR) was defined as resolution of all enhancing lesions from baseline. The progression of disease (PD) was defined as tumor growth or appearance of new tumors. All others were defined as stabilized disease (SD). Patient toxicity was closely monitored and was graded according to the National Cancer Institute’s Common Toxicity Criteria, Version 3 (ctep.cancer.gov/reporting/ctc.htm). Changes in QoL were assessed after every 2 cycles of treatment using the same questionnaire given at the baseline evaluation.

Statistical analysis. The overall survival and progression-free survival were measured from two time-points, date of histological diagnosis and date of enrollment. The Kaplan-Meier survival distributions were calculated using Statistical Analysis System (SAS). The categorical variables were assessed by the Chi-square test and continuous variables by the student’s t-test. The QoL data was also analyzed using SAS and in accordance with the EORTC recommendations (http://www.eortc.be/home/qol/downloads/).

Results

Patient characteristics. A total of 23 patients (14 male, 9 female) with a mean age of 58 years were enrolled between 2001 and 2005. Thirteen patients (56%) were
enrolled in the study between 9/2001 and 12/2002. Another 6 patients (26%) were entered in 2003 and the final 4 patients (17%) added in 2004. The mean follow-up between enrollment and end of the study was more than 2 years. The histology was defined as GBM in 18 (78%) and AA in 5 (22%) patients. The diagnosis was made through surgical resection in 19 (83%) and biopsy in 4 (17%) of the patients. Thirteen patients had prior treatments including combined RT and CT (4 patients), RT (7 patients), and CT (2 patients). The patient characteristics are described in Table II.

Survival. At the time of analysis in April 2005, 18 patients had died of progressive disease. Among the remaining 5 patients, 3 were still alive and 2 patients were lost to follow-up after 14 and 19 weeks and their survival status could not be determined. By Kaplan-Meier analysis, the mean survival time (±S.E.M.) from the date of diagnosis was 78.4±15 weeks with median survival of 54.6 weeks (95% confidence interval [CI], 44.7-82.6) (Figure 1). The mean survival from the date of enrollment was 46.1±10 weeks with median survival 33.3 weeks (95% CI, 25-47) (Figure 2). Excluding the 5 patients with AA did not significantly change the mean survival from the date of diagnosis and from the date of enrollment ($p<0.704$ and $p<0.123$, respectively).

Response to treatment. The response to treatment could be evaluated in 15 patients. Of the 8 patients unable to be evaluated, 2 were withdrawn prior to treatment (1 death and 1 voluntary withdrawal), and 6 were withdrawn prior to the first imaging time-point (2 disease progression, 2 medical complications, 2 voluntary withdrawals). In the 15 evaluable patients, SD was seen in 9 (60%) and PD was seen in 6 (40%) patients. The duration of SD was 8-135 weeks (median 12 weeks). One patient remained progression-free for 2.5 years.

The mean progression-free time from the date of diagnosis was 46±11 weeks and the median progression-free time was 32 weeks (95% CI: 19-46 weeks) (Figure 3).
The mean progression-free time from the time of enrollment was 18±5.6 weeks while the median progression-free time was 11 weeks (95% CI: 8-19 weeks) (Figure 4).

Toxicity. The most common treatment-related toxicity related to hypercoagulation. Five patients (22%) developed deep venous thrombosis (DVT) and 2 of these patients (9%) had pulmonary emboli (PE). All recovered with anticoagulation therapy and none suffered long term sequelae. One patient had an arterial thrombosis, which was probably not related to the treatment. One patient had a sustained drop in WBC requiring temozolomide to be withheld. The mean WBC in the patients was 9.4x10^3/L at the baseline, which fell to a mean of 5.58x10^3/L after 2 cycles of treatment. Hemoglobin and platelets were not significantly affected. Other events not felt to be treatment-related, but noted, included a seizure in 4 patients and lower extremity edema unrelated to DVT in 4 patients. Other grade 3 or 4 toxicities were not observed. Grade 2 toxicities included nausea, emesis, headache, dizziness, blurred vision and transient skin rash which all resolved spontaneously or with conservative measures.

Changes in quality of life (QoL). Among the 26 QoL scores, 5 scores were significantly improved after treatment. Sixteen of the remaining 21 scores improved with treatment, but the results did not reach statistical significance. The Global Health Status/QoL, which defines the overall health status and quality of life, was significantly improved after 2 cycles of treatment compared to the baseline (p=0.003, see Figure 5). The Functional Scores are shown in Figure 6 and showed overall improvement and the differences in the "role function" between baseline and post-treatment cycle 2 reached statistical significance (p=0.03). Of the Symptom Scores shown in Figure 7, the "thought about financial difficulties" improved significantly after 4 cycles of treatment when compared to baseline (p=0.04). Scores on the Brain Cancer module (EORTC BN20) were very stable over the study (Figure 8). Of these, headaches improved significantly after 2 cycles of treatment (p=0.003) and "thought about future uncertainty" improved significantly after 4 cycles of treatment (p=0.01).
Discussion

While there have been major steps toward understanding the biology of astrocytomas, cures or prolonged responses are rare. Despite this, most studies evaluating treatment protocols focus on survival as the primary end-point (39-41). The results with various treatments and protocols have shown only small survival advantage, mostly in younger patients (42, 43). While toxicity and complications are reported in all of these studies, specific QoL evaluations have largely been ignored. In other carcinomas with poor survival or with little apparent advantage of one therapy versus another, there is increasing evidence of assessment of QoL in the protocols (44-47). In this open label trial it was shown that TTT could be safely administered with survival equivalent to other studies (48-50) while maintaining or improving QoL measures.

Assessment of QoL in patients with MA presents special challenges since disease progression and progressive neurological deficits impact on QoL in addition to the treatment protocols. Clinical depression is commonly experienced by patients with MA and their families, further confounding QoL perceptions unrelated to treatment protocols (51). In previous studies of adjuvant treatment, much of the survival benefit was realized at the expense of hospitalization and intravenous chemotherapy. In light of the short survival times, it is no surprise that management with oral agents on an outpatient basis is preferred by patients (52). This study has demonstrated that the oral regimen of TTT is well-tolerated with acceptable toxicity which corroborates previous studies using the oral combination of temozolomide and thalidomide (28, 53).

The BBB represents a formidable block to the efficacy of most chemotherapy regimens. This has led to trials using different strategies including alternative delivery mechanisms such as wafers or CED, BBB disruption, chemotherapy using viral vectors, and high dose chemotherapy (54, 55). In addition to alternate delivery mechanisms, another approach has been to employ a multi-drug regimen with potential synergistic action either by combining different cellular targets or by direct drug-to-drug interaction. In this approach, however, toxicity may also be synergistic. In the present small study, overall toxicity was acceptable, however, the rate of hypercoagulation-related events was relatively high (5/23, 21%) suggesting the possibility of toxicity synergism (56-58). Hypercoagulation-related complications such as deep vein thromboses and pulmonary emboli have long been recognized as a major cause of morbidity and mortality in patients with MA, developing in 20% to 45% of patients (59, 60). Advanced age, the presence of paresis, and A or AB blood types have been identified as additional risk factors (59-61). Oral tamoxifen has a known risk factor for thromboembolism as evidenced from the International Breast Cancer Prevention Study (IBIS-I) (62). The anti-angiogenic properties of thalidomide may act as a
procoagulant leading to increased patient morbidity (63). This study underscores the need for DVT prophylaxis in many MA patients and the potential for unexpected synergy when multi-drug regimens are used.

In an era when multimodality treatment entailing surgery, RT, and CT is the accepted standard of therapeutic intervention for patients with MA, it remains critical to understand the momentous impact on QoL. Such treatment regimens can translate into extensive hospitalizations or other measures that may exacerbate physical and psychosocial suffering, despite excellent care. This study suggests that oral regimens have the potential to provide equivalent efficacy while concurrently improving QoL. In addition to evaluating survival, toxicity and complications, all studies of patients with MA should use QoL as an appropriate end-point for analysis.

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References


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