Prolonged Administration of Temozolomide in Adult Patients with Anaplastic Glioma

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Abstract. *Purpose: Prolonged administration of temozolomide is widely used in patients with glioblastoma; whereas the treatment of anaplastic glioma differs between neurooncological centres. The safety, feasibility and efficacy of prolonged temozolomide administration in patients with anaplastic gliomas was evaluated. Patients and Methods: Forty-two patients with primary, recurrent or secondary anaplastic glioma were retrospectively analysed for the course of their disease. Treatment mostly consisted of surgery, followed by radiotherapy with concomitant and adjuvant temozolomide. In five patients with recurrence of primary anaplastic glioma, chemotherapy was initiated without previous surgery. Temozolomide was administered until evidence of tumour recurrence, appearance of serious side-effects or patients´ wish to finish chemotherapy. Results: The median overall survival (OS) was 39 months with a median cycle number of 7.5 (1-42). Treatment with temozolomide was stopped in 12 patients due to side-effects in general, whereas in only three patients (7.1%) treatment had to be discontinued due to haematological side-effects. There was no evidence of treatment related infections or grade IV toxicity. Extent of surgery had a significant influence on OS in anaplastic gliomas, the number of adjuvant temozolomide cycles showed a positive influence as well on time to progression (TTP) and OS. Conclusion: Prolonged administration of adjuvant temozolomide is safe and can be favorable for patients with anaplastic gliomas.*

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The standard treatment for patients with anaplastic glioma is surgery, followed by radiotherapy with or without adjunctive chemotherapy (1). To date there is no defined standard radio- or chemotherapy regimen. Treatment algorithms used in clinical practice are heterogenous.

For anaplastic oligodendrogliomas adjuvant chemotherapy with alkylating drugs was thought to be superior to radiotherapy, but recent molecular findings showed that combined losses on chromosomes 1p and 19q are solely prognostic markers though not predictive for a response to chemotherapy (2). This reflects the uncertainty of the best treatment modality. Until 2005 the chemotherapy regimens in the treatment of anaplastic gliomas were mainly nitrosourea-based. The implementation of a combined radiochemotherapy for glioblastoma multiforme (GBM) increased the median survival in these tumours to 14.6 months and led to a 2-year survival of 26.5% (3) with a low toxicity profile. Considering the favourable toxicity profile compared to nitrosourea-based regimens, such as PCV (procarbazine, lomustine, vincristine) combined radiochemotherapy with temozolomide might be a promising approach also in anaplastic glioma. Although there is no data indicating that temozolomide is superior to PCV or radiotherapy alone, temozolomide as treatment in first recurrence of anaplastic glioma has been reported in many neurooncological centres, thus the Stupp scheme for GBM has been transferred to patients with anaplastic gliomas.

Following promising data on prolonged administration of temozolomide in GBM (4, 5) the ideal duration of treatment in anaplastic glioma patients is in question, since these patients have a better prognosis than patients with GBM and the impact of possible cumulative toxicity with prolonged administration might be more severe.

In our centre, the treatment of anaplastic gliomas is identical to that for GBM. Therefore the number of cycles administered in patients with histologically proven anaplastic glioma (WHO°III) who received 6 or more cycles of concomitant and adjuvant temozolomide or temozolomide

for recurrent disease, was analysed. In this retrospective study, the safety and efficacy of prolonged treatment with temozolomide in 42 well-documented patients with primary, secondary or recurrent anaplastic gliomas was investigated.

Patients and Methods

All patients with either newly diagnosed anaplastic glioma, recurrent disease or secondary anaplastic glioma, transformed from an initially low-grade glioma (WHO°II), were included in this retrospective survey (diagnosis and treatment between 1999 and 2010). Treatment mainly consisted of surgery (GTR=gross total resection, STR=subtotal resection or biopsy; all confirmed by early postoperative MRI within 48 hours) followed by percutaneous radiotherapy (3D conformal or intensity modulated radiotherapy applied with a daily dose of 2 Gy up to a cumulative dose of 60 Gy), concomitant temozolomide (75 mg/m^2) and adjuvant temozolomide (150-200 mg/m^2 in a 5/28 cycle). Five patients with progressive disease of a previously diagnosed anaplastic glioma were treated with temozolomide (150-200 mg/m^2 in a 5/28 cycle) without surgical intervention.

The patients were followed by MRI and clinical visits (every 3 months) and blood samples for haematological toxicity were drawn every 2 weeks. Adverse events were graded following the National Cancer Institute Common Toxicity Criteria (CTC) Version 3 (6). Upon tumour progression according to the MacDonald (7) criteria or severe side-effects of temozolomide treatment the patients were evaluated for repeat surgery or the treatment modality was changed.

In total, 42 patients (25 men and 17 women, median age of 38.5 years with a range from 25 to 76 years) were included in the retrospective analysis (see Table I).

Statistical analysis. The outcome parameters, TTP and OS were calculated from the time of diagnosis until progression of disease or death, according to the Kaplan-Meier method. For the quantitative data a two tailed *t*-test or Mann-Whitney *U*-test were performed as appropriate. The influence of several variables (number of adjuvant chemotherapy cycles, patient's age, surgical treatment modality) on OS and TTP were tested with the Logrank test. In addition, the Cox proportional hazards model was used as a multiple model in order to gain information about the influence of adjuvant chemotherapy cycles and patients' ages simultaneously. A p-value <0.05 was considered as statistically significant. Statistical calculation was made with the SAS System, release 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Surgical treatment and histology. Three basic groups of patients were identified: primary anaplastic glioma, recurrent anaplastic glioma and secondary anaplastic glioma (see Table I).

Gross-total resection was performed in 22 patients whereas 15 patients underwent subtotal resection or stereotactic biopsy. In all the operated patients, histological workup revealed the diagnosis of an anaplastic glioma (8 anaplastic oligodendrogliomas, 29 anaplastic astrocytomas). Five patients were not surgically treated, due to missing mass effect, deep seated or eloquent location of the process and radiologically proven progress of an initially diagnosed anaplastic glioma (1 anaplastic oligodendroglioma, 4 anaplastic astrocytomas).

Table I. *Patient characteristics*.

Characteristics	n=42	
Age, years; mean (range)	38.5	(25-76)
Gender, n (%)		
Male	25	(59.5%)
Female	17	(40.5%)
Surgery, n (%)		
GTR	22	(52.3%)
STR or biospy	15	(35.7%)
No surgery	5	(11.9%)
Histology, n (%)		
Anaplastic astrocytoma	33	(78.5%)
Anaplastic oligodendroglioma	9	(21.5%)
Anaplastic oligoastrocytoma	0	(0%)
Tumor type, n (%)		
Primary AG	16	(38.1%)
Recurrent primary AG	9	(21.5%)
Secondary AG	17	(40.4%)
Median no. of cycles (range)	7,5	(1-42)
≥6 cycles, n (%)	31	(73.8%)
<6 cycles, n (%)	11	(26.2%)

AG, Anaplastic glioma; GTR, gross total resection; STR, subtotal resection.

Temozolomide administration. In all patients, 508 cycles of temozolomide were administered with a median cycle count of 7.5 (range 1-42). Most patients received 6 or more cycles, whereas in only 11 patients treatment was stopped before the 6th cycle.

Treatment related side effects. At the time of evaluation, 26 patients were under temozolomide chemotherapy without evidence of progressive disease. Four patients died within the observation period due to tumour progress or other reasons not related to therapy. Temozolomide treatment was stopped in 12 patients (28.5%). Due to side-effects the treatment was stopped in 6 patients (14.2%) because of non-haematological minor side-effects, *e.g.* nausea and in three patients (7.1%) because of haematological toxicity not exceeding a grade III toxicity according to CTC criteria. In three patients (7.1%) with documented progressive disease treatment was discontinued and changed.

There was no evidence of treatment related infections or gastrointestinal toxicity. The side-effects leading to treatment discontinuation and considered to be treatment-related occurred within the first 6 cycles, in 7 out of 12 patients (58.3%).

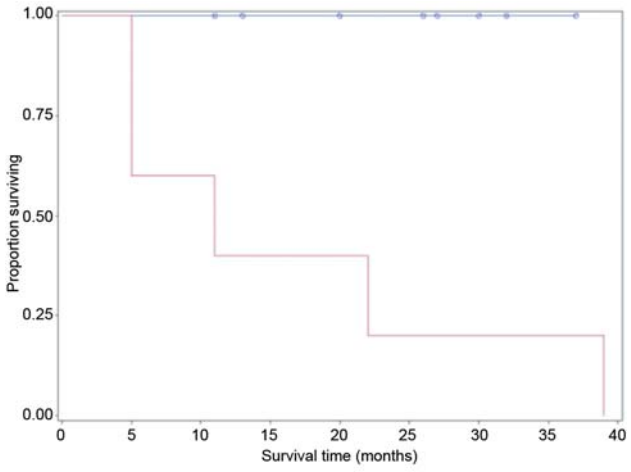

Figure 1. *Kaplan-Meier curves highlighting the influence of treatment length on overall survival (primary anaplastic gliomas). (blue curve: long term administration of temozolomide without treatment discontinuation) and red curve: treatment discontinuation (for any reason)), p-value=0.0002.*

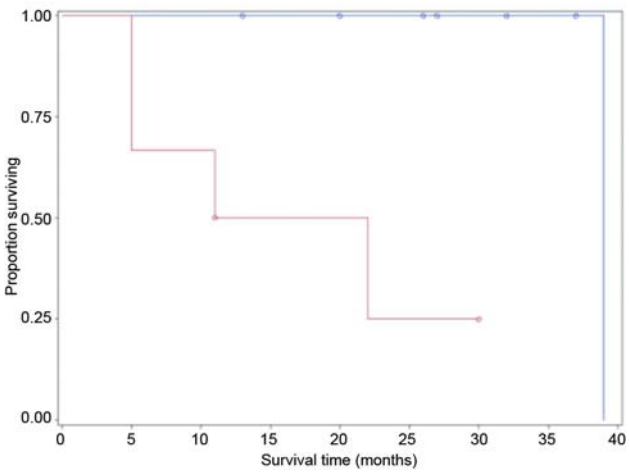

Figure 2. *Influence of the surgical procedure on overall survival in primary anaplastic gliomas. (blue curve: gross total resection documented in early postoperative MRI, red curve: subtotal resection or biopsy), p-value=0.0024.*

Overall survival and time to progression. The median OS was 39 months, although 26 patients were still alive and under temozolomide medication at the time of evaluation. Their survival times have been censored from the Kaplan Meier analysis.

In the primary anaplastic glioma subgroup, the median overall survival was 24 months (range 5-39). Within the recurrent primary anaplastic glioma subgroup, the median OS was 61 months (range 11-109), in this group 50% of patients were alive under temozolomide chemotherapy and have been censored for the Kaplan-Meier analysis. The third subgroup, secondary anaplastic gliomas, showed a median OS of 86 (range 29-235) months with 59% of patients being alive and therefore censored for the Kaplan-Meier analysis.

The median TTP in all three groups was 22.2 months, progression-free survival at 6 months was 90.4% in all the patients. The median follow up of all patients was 65 months with a range from 12 to 273 months.

Stratified for histological diagnosis, there was no difference between anaplastic oligodendrogliomas and astrocytomas with regard to OS and TTP (OS: p=0.6018 for primary, p=0.0933 for recurrent and p=0.1661 for secondary anaplastic gliomas and TTP: p=0.5286 for primary, p=0,8877 for recurrent and p=0.2912 for secondary anaplastic gliomas).

A factor with positive influence on OS time in all the subgroups of anaplastic gliomas was progression free survival of 6 months (p=0.0082 for primary, p<0.0001 for secondary and p=0.0462 for recurrent anaplastic gliomas). Within the group of primary anaplastic gliomas, the number of cycles showed a significant influence on OS (p=0.0455). Furthermore the patients receiving less than 6 cycles (p=0.0128) and patients whose treatment stopped (p=0.0002) for any reason had a worse outcome in any group (see Figure 1).

The extent of surgery had a positive influence in all the subgroups, whereas only for primary anaplastic gliomas was there a strong significance concerning OS (p=0.0024 for primary, p=0.0951 for secondary and p=0.0570 for recurrent primary anaplastic gliomas) (see Figure 2).

Discussion

Temozolomide as treatment in first recurrence of anaplastic glioma has been reported by Yung *et al*. (8) leading to a median OS of 13.6 months. Median survival of 3 years in primary anaplastic astrocytoma has been reported (1), whereas a 5-year survival rate of 21,9% was found for patients with anaplastic astrocytomas and 36,5% for patients with anaplastic oligodendrogliomas (9).

In the present study, the median OS of all three groups was 39 (range 5-235) months. The fact that more than 50% of the patients were still alive (with a median follow-up of these surviving patients of 61 months (range 11-157)) and had no evidence of progression at the time of evaluation and were therefore censored from the Kaplan-Meier analysis may have caused the discrepancy with the data of Hau *et al*. (4), who reported a median OS of 43,2 months.

A randomized trial of anaplastic gliomas found a median time to treatment failure of 54 months in 42.7% of patients, with high toxicity due to the PCV-treatment, causing discontinuation or dose reduction in 25 out of 68 patients

(36.7%) (10). In the present cohort, treatment discontinuations for any reason lead to a significant (p=0.002) worsening of prognosis. Therefore the absence of temozolomide could be proposed as the cause and vice versa.

The available literature showing beneficial effects on the extent of surgery is limited. Generally, the extent of resection as a positive prognostic factor in malignant glioma has been shown (11), although only 8 patients with anaplastic gliomas were included. Interestingly, extent of resection was highly significant (p=0.0024) for primary anaplastic gliomas but not for primary recurrent or for secondary anaplastic gliomas in the present study.

Treatment with PCV additional to radiotherapy, as shown in the EORTC study (2), had a high rate of side-effects and treatment was stopped due to haematological side-effects in 33% and due to non-haematological side-effects in 5% respectively. A grade IV (CTC) toxicity was observed in 32% of these patients. In a randomized trial addressing anaplastic glioma (NOA-4) (10), comparing the adverse effects between temozolomide and PCV, the temozolomide group showed 6 adverse events only, whereas 54 events were registered in the PCV treatment arm. Recently published studies (4, 5, 12) have reported low rates of side-effects and all patients tolerate prolonged therapy without cumulative toxicity, demonstrating that a long-term administration of temozolomide has a favourable safety profile. Leukopaenia in 7% and thrombocytopaenia in 10% of patients has been found (4), whereas the EORTC/NCIC study demonstrated 3% of CTC grade III and IV leukopaenia, 4% neutropaenia and 3% thrombocytopaenia (3). The long term administration of adjuvant temozolomide thus seems to be safe and effective in patients with anaplastic gliomas.

Due to the retrospective character of the present study and the absence of molecular analysis, clearer profiling of patients remaining sensitive for temozolomide-treatment was not possible.

Therefore prospective studies with longer follow-up periods are warranted to analyse the effects of prolonged chemotherapy with temozolomide on TTP and OS. Additional molecular profiling might filter such patients that remain sensitive to prolonged temozolomide administration. This approach seems to be justified due to the low toxicity profile and absence of cumulative toxicity. Moreover the optimal duration of adjuvant treatment could be addressed in such prospective trials.

Conclusion

Anaplastic glioma patients with stable disease and no treatment-related side-effects under adjuvant temozolomide chemotherapy can continue the prolonged administration far beyond 6 cycles, without any evidence of cumulative toxicity. The long-term administration of temozolomide seems to be safe and effective in these patients. Any treatment-related side-effects, mostly occur within the first six cycles of treatment.

Conflict of Interest

None.

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