Efficacy and Toxicity of Postoperative Temozolomide Radiochemotherapy in Malignant Glioma

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Purpose: To evaluate the feasibility, safety and efficacy of daily temozolomide concurrent with postoperative radiotherapy in malignant glioma.
Patients and Methods: From 11/1999 to 03/2003, n = 81 patients aged 15–72 years (median 52 years, Karnofsky score 80–100% in 83%) suffering from primary glioblastoma (n = 47), anaplastic astrocytoma (n = 6), anaplastic oligodendroglioma (n = 16), and recurrent glioma (n = 12) were treated. Patients with primary gliomas received a combination of postoperative radiotherapy (60 Gy/1.8- to 2.0-Gy fractions) and daily oral temozolomide (75 mg/m^2) at all irradiation days (30–33 doses), while recurrent tumors were treated with 45–60 Gy and temozolomide. Initially, 6/81 patients had daily temozolomide doses of 50 mg/m^2.
Results: In total, 70/81 patients (86%) completed both radio- and chemotherapy. Grade 1 nausea/vomiting was seen in 28%, grade 2 in 11%, grade 3 in 1%. Antiemetics were applied in 41%. Hematologic toxicities were observed as follows: leukopenia grade 3/4 1%, lymphopenia grade 3/4 46%, thrombopenia grade 3/4 1%. Two patients under dexamethasone suffered herpes encephalitis after one and 16 doses of temozolomide (75 mg/m^2). Median survival was 15 months for glioblastoma. In oligodendroglioma patients, a 4-year survival rate of 78% was observed.
Conclusion: Postoperative radiochemotherapy with 30–33 daily doses of temozolomide (75 mg/m^2) is safe in patients with malignant glioma. The combined schedule is effective in oligodendroglioma patients and may prolong survival in glioblastoma. Effort should be taken to minimize corticosteroid doses, since both steroids and temozolomide lead to immunosuppression.

Key Words: Malignant glioma · Oligodendroglioma · Radiochemotherapy · Temozolomide

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Postoperative Radiochemotherapie mit Temozolomid beim malignen Gliom

Ziel: Bestimmung der Durchführbarkeit, Toxizität und Effektivität einer kombinierten postoperativen Radiochemotherapie mit täglicher oraler Applikation von Temozolomid beim malignen Gliom.
Patienten und Methodik: Von 11/1999 bis 03/2003 wurden n = 81 Patienten (Alter 15–72 Jahre, Median 52 Jahre, Karnofsky-Index 80–100% in 83%) mit primärem Glioblastom (n = 47), anaplastischem Astrozytom (n = 6), anaplastischem Oligodendrogliom (n = 16) oder Rezidivgliom (n = 12) behandelt. Patienten mit primären Gliomen erhielten simultan zur postoperativen Bestrahlung mit 60 Gy (1,8- bis 2,0-Gy-Fraktionen) an allen Bestrahlungstagen Temozolomid oral in einer Dosierung von 75 mg/m^2 (30–33 Dosen), Rezidive wurden mit 45–60 Gy und Temozolomid behandelt. Initial wurde 6/81 Patienten Temozolomid in einer Dosierung von 50 mg/m^2 verabreicht.
Ergebnisse: Insgesamt konnte die Radiochemotherapie bei 70/81 Patienten (86%) komplett durchgeführt werden. Übelkeit und Erbrechen waren selten (Grad 1 28%, Grad 2 11%, Grad 3 1%); bei 41% der Patienten wurden Antiemetika eingesetzt. Höhergradige hämatologische Toxizitäten waren: Leukopenie Grad 3/4 1%, Lymphopenie Grad 3/4 46%, Thrombopenie Grad 3/4 1%. Zwei Patienten mit Dexamethason entwickelten nach einer bzw. 16 Temozolomid-Einzeldosen eine Herpesenzephalitis. Die mediane Überlebenszeit betrug für Glioblastome 15 Monate, die 4-Jahres-Überlebensrate für Oligodendrogliome 78%.
Schlussfolgerung: Für Patienten mit malignen Gliomen ist die simultane postoperative Radiochemotherapie mit Temozolomid ein sicheres und wenig belastendes Verfahren. Wegen der immunsuppressiven Wirkung sollte die gleichzeitige Gabe von Dexamethason so weit wie möglich vermieden werden. Bei den chemosensiblen oligodendroglialen Tumoren ist die Radiochemotherapie effektiv; bei den Glioblastomen scheint eine Prognoseverbesserung möglich.

Schlüsselwörter: Maligne Gliome · Oligodendrogliom · Radiochemotherapie · Temozolomid

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Introduction

Despite long-lasting efforts to optimize the treatment for malignant glioma, the prognosis after standard therapy, comprising macroscopic resection and postoperative local radiotherapy, remains poor because almost all patients will die from local recurrences [2, 26]. As shown in the RTOG recursive partitioning analysis (RPA), the principal prognostic factors are histology (glioblastoma vs. grade III tumors), age and performance score [9], while other factors are of minor importance [19, 20, 31, 34]. Adjuvant chemotherapy increases survival by a small percentage [37]. Several substances have been applied simultaneously to irradiation in order to increase local control. Nitrosoureas, cytarabine (ARA-C) [1, 8, 15, 25], platinum plus etoposide or teniposide [4, 24, 29] have been used for intravenous or intraarterial [10, 14, 25, 32] infusion during the period of irradiation, but so far, none of these regimens has led to a significant increase in survival.

A new step was possible by the introduction of temozolomide which was shown to penetrate the blood-brain barrier to a significant amount and to sensitize glioma cells against irradiation [43]. This led to the development of a therapeutic scheme where temozolomide was used in a manner that aimed at maximal radiosensitization by daily chemotherapy application during fractionated radiotherapy [38]. The present investigation was undertaken to confirm the efficacy and safety of simultaneous radiochemotherapy with temozolomide in glioblastoma patients and to analyze its efficacy in grade III glioma patients. Special emphasis was put on the use of temozolomide in anaplastic oligodendroglioma, since these tumors are known to respond well to chemotherapy [6].

Patients and Methods

Treatment Schedule

Starting in November 1999, combined postoperative radiochemotherapy was offered to adult glioma patients as an individual medical treatment. Patients with a Karnofsky performance score ≥ 50% and no contraindications against the use of temozolomide (no severe liver or renal dysfunction, normal blood cell counts, no known hypersensitivity against temozolomide or darcarbazine, no local or systemic infection, no pregnancy) were offered temozolomide and irradiation as an individual treatment. All patients were given full information about the fact that temozolomide had shown monoactivity in recurrent glioma but was to be applied in a different schedule. Only patients who were mentally able to give their full informed consent were treated. From November 1999 to March 2003, 81 patients (28 women, 53 men) with primary or recurrent malignant glioma received combined radiochemotherapy. They comprised 39% (47/121) of all glioblastoma, 45% (22/45) of all anaplastic glioma and 67% (12/18) of all recurrent glioma patients referred for local irradiation to the radiotherapy department. Temozolomide was ordered from the hospital's pharmacy or from other regular drugstores.

All patients with primary tumors (glioblastoma n = 47, anaplastic astrocytoma n = 6, anaplastic oligodendroglioma/oligoastrocytoma n = 16) had tumor resection and postoperative radiotherapy (60 Gy in 1.8- to 2.0-Gy fractions) in combination with daily oral temozolomide. In all cases, megavoltage equipment, mask fixation and CT-based treatment planning were used for irradiation. Planning target volumes included the contrast-enhancing regions in the postoperative CT and/or the resection cavity with a margin of 1.5–2.5 cm. Temozolomide was applied as a single daily oral dose of 75 mg/m^2 1–2 h before each radiotherapy fraction (median 30 doses). Initially, six patients were treated with 50 mg/m^2. On the weekends, both irradiation and temozolomide were paused. The same schedule (radiation doses of 45–60 Gy) was used in twelve patients with recurrent or progressive malignant glioma after previous resection (12/12) and postoperative irradiation (10/12).

Supportive Therapy

Most of the patients received ambulatory treatment only (39%) while some were hospitalized for a short (1–2 weeks, 42%) or a longer (3–7 weeks, 19%) period for general supportive care. In order to prevent brain edema after irradiation, dexamethasone was applied. In total, 25% of the patients did not need any steroids at all, while 43% had low-dose (2–10 mg/d) or high-dose (12–32 mg/d) dexamethasone for some time during their therapy. As temozolomide may cause nausea, 41% of the patients were given prophylactic or therapeutic antiemetics for some days. Due to preexistent epileptic seizures, 53% of the patients had anticonvulsive drugs when starting radiochemotherapy with temozolomide. Blood cell counts and serum chemistry were performed weekly in hospitalized patients and also in the majority of ambulatory patients (see Table 2).

Statistical Analysis

Patients were followed up by clinical examination and CT/MRI scans every 3–6 months after therapy until deterioration. A retrospective analysis was carried out using the statistical software package SPSS 11.0 (Statistical Package for the Social Sciences, Chicago, IL, USA). A database was set up that registered date and type of resection, details of radiotherapy and temozolomide application, hemotologic and nonhematologic toxicity, time to progression, adjuvant chemotherapy, procedures for treatment of recurrences, and overall survival time. The cutoff date was April 30, 2004. Living patients were censored at the last date on which they were known to be alive.

Patients were grouped according to tumor type. Details of the patient characteristics are shown in Table 1. In addition, all glioblastoma and astrocytoma patients were retrospectively grouped into the six RPA classes using age, Karnofsky performance score, duration of symptoms, histology, mental status, neurologic function score, type of surgery, and radiotherapy dose as parameters [9].

Any tumor growth indicated by clinical deterioration or imaging was documented as progression. Progression-free survival was calculated from the time difference between date of surgery and date of progression, or date of death in cases where patients died without progression or where the date of progression was not known. For overall survival, the time difference between date of surgery and date of death was calculated. Progression-free and overall survival times were computed according to the Kaplan-Meier method for censored observations.

Table 1. Patient characteristics.

Tabelle 1. Patientengruppen.

	Glioblastoma	Anaplastic astrocytoma	Oligodendroglioma/ oligoastrocytoma	Recurrent glioma
Patients (n)	47	6	16	12
Age (years)	57 (29–72)	51 (26–67)	47 (18–65)	44 (15–61)
Karnofsky score (%)	80 (50–100)	95 (70–100)	90 (70–100)	80 (50–100)
Complete resection [n (%)]	34 (72)	0	8 (50)	3 (25)
Radiation dose (Gy)	60 (3.6–75)	59.4	59.4	59.4 (45–60)
Temozolomide doses (n)	30 (1–41)	32 (30–33)	30 (26–33)	29 (23–33)
Temozolomide 50/75 mg (n)	4/43	1/5	0/16	1/11

Results

Compliance

In total, 70/81 patients (86%) completed both radio- and chemotherapy without interruption. In these patients, 26–41 doses of temozolomide were applied. Reasons for interrupting or not continuing the therapy in eleven patients were both related to toxicity and unrelated to therapy. Toxicity was the dominant reason in six patients who experienced the following events: nausea for 1 day leading to refusal of therapy (n = 1), myelosuppression causing grade 2/grade 4 thrombopenia/leukopenia (n = 2), encephalitis caused by herpes simplex virus (n = 2), skin infection by herpes zoster (n = 1). Reasons probably unrelated to therapy (five patients) were: pneumonia by *Aspergillus* following an epileptic seizure (n = 1), sudden cardiac death due to unknown cause (n = 1), asthenia (n = 1), intracerebral hemorrhage at site of stereotactic biopsy (n = 1), tooth extraction (n = 1).

Toxicity

Hematologic toxicity is shown in Table 2. While leukopenia and thrombopenia were rare events (1% grade 3–4), severe lymphopenia was observed in almost half of the patients (grade 3: 38%, grade 4: 8%). The most frequent nonhematologic toxicities are shown in Table 3. Nausea was observed to some extent in the first days of treatment, but was usually mild. Serum enzymes expressing the secretory function (GGT) and integrity (GPT) of the liver cells showed abnormalities in a minority of patients (grade 3–4: 3–6%), but some of these events might have been caused by the simultaneous use of anticonvulsive drugs. All adverse events are shown in Table 4. Most of these were probably not caused by the addition of temozolomide to conventional radiotherapy.

An unexpected observation was the aforementioned occurrence of two cases of virus encephalitis. In the first patient, only one dose of temozolomide of 75 mg/m^2 had been applied 1 day before the patient became symptomatic, which almost excludes a causal relationship between the applied chemotherapy and the infection. In the second case, grade 3 lymphopenia had developed after 16 doses of temozolomide (75 mg/m^2) before the event. In the recurrent patients treated with reirradiation, unusual brain edema, symptomatic radionecrosis or other severe acute or subacute toxicities were not observed.

Table 2. Hematologic toxicity.

Tabelle 2. Hämatologische Toxizität.

	Leukopenia (n = 76)	Lymphopenia (n = 63)	Thrombopenia (n = 77)
Grade 1	5 (7%)	13 (21%)	1 (1%)
Grade 2	2 (3%)	14 (22%)	1 (1%)
Grade 3	0 (0%)	24 (38%)	0 (0%)
Grade 4	1 (1%)	5 (8%)	1 (1%)

Table 3. Nonhematologic toxicity.

Tabelle 3. Nichthämatologische Toxizität.

	Nausea (n = 81)	GGT (n = 74)	GPT (n = 74)
Grade 1	23 (28%)	26 (35%)	33 (45%)
Grade 2	9 (11%)	15 (21%)	4 (5%)
Grade 3	1 (1%)	3 (4%)	2 (3%)
Grade 4	0 (0%)	1 (2%)	0 (0%)

Table 4. Adverse events. HSV: herpes simplex virus.

Tabelle 4. Unerwünschte Ereignisse. HSV: Herpes-simplex-Virus.

Headache	11
Seizures	10
Neurologic deterioration	7
Asthenia	7
Vertigo	4
Myopathy	3
HSV encephalitis	2
Thrush	2
Hyperglycemia	2

Adjuvant and Salvage Therapy

As shown in Table 5, adjuvant chemotherapy was used infrequently (12/81 patients, 15%). Mainly, temozolomide was applied. Recurrences were predominantly treated by surgery (reresection in 20/81 patients, 25%) and temozolomide. In selected cases, brachytherapy (low-dose-rate temporary iodine-125-seed implant) was performed.

Table 5. Adjuvant chemotherapy and therapy for recurrence. AA: anaplastic astrocytoma; GBM: glioblastoma; OD: anaplastic oligodendro-/oligoastrocytoma.

Tabelle 5. Adjuvante Chemotherapie und Rezidivtherapie. AA: anaplastisches Astrozytom; GBM: Glioblastom; OD: anaplastisches Oligodendro-/Oligoastrozytom.

	GBM (n = 47)	AA (n = 6)	OD (n = 16)	Recurrent glioma (n = 12)
Adjuvant chemotherapy				
Temozolomide	6	1	3	0
PCV	0	0	0	1
Other	1	0	0	0
Total	7 (15%)	1 (17%)	3 (19%)	1 (8%)
Chemotherapy for recurrence				
Temozolomide	9	1	1	2
PCV	1	1	0	1
Other	2	1	1	3
Total	12 (26%)	3 (50%)	2 (13%)	6 (50%)
Surgery/irradiation for recurrence				
Resection	12	1	1	4
Brachytherapy	1	0	1	0
Surgery + brachytherapy	1	0	1	0
Reirradiation + brachytherapy	1	0	0	0
Total	15 (32%)	1 (17%)	3 (19%)	4 (33%)

Progression-Free and Overall Survival

Progression-free survival was highest in the oligodendroglial tumors (Figure 1a) with a median progression-free survival time of 34 months. In primary glioblastoma and anaplastic astrocytoma patients, median progression-free survival times amounted to 7.3 and 8.7 months, respectively.

Median follow-up time for surviving patients was 31 months (Figure 1b). In glioblastoma, a median survival time of 14.6 months was achieved. In the small group of patients suffering from primary anaplastic astrocytoma, a 2-year survival rate of 33% was observed. Median survival for recurrent gliomas was 14 months. The best result was achieved in anaplastic oligodendroglioma patients. In this group, a 4-year survival rate of 78% was seen (median not reached).

For all primary glioblastoma and astrocytoma patients, survival in the six RPA groups was compared to survival as reported by Curran et al. [9] (Table 6). A sufficient number of patients was only present in the RPA classes 3–5. In these classes, survival with temozolomide radiochemotherapy appeared superior to the RTOG data with a survival advantage of 2–6 months in classes 4 and 5.

Discussion

Besides altered fractionation radiotherapy schemes, adjuvant and simultaneous chemotherapy has been one of the most extensively followed directions in order to increase local control and survival in malignant glioma patients.

In *glioblastoma* patients, a meta-analysis found a total increase in the 2-year survival rate of 4% [37] for any kind of adjuvant chemotherapy. The most recent multicenter trial of the Medical Research Council, however, failed to show any advantage for adjuvant PCV (procarbazine, CCNU, vincris-

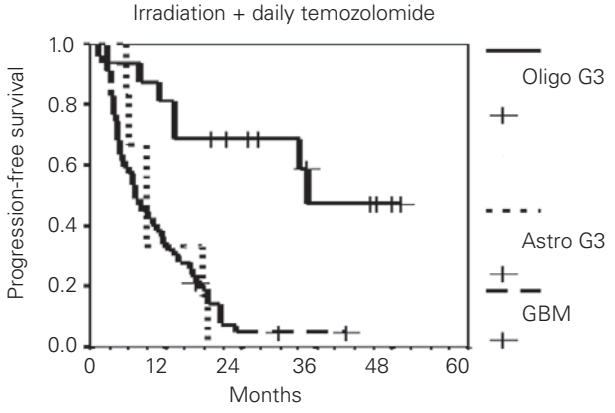

Figure 1a – Abbildung 1a

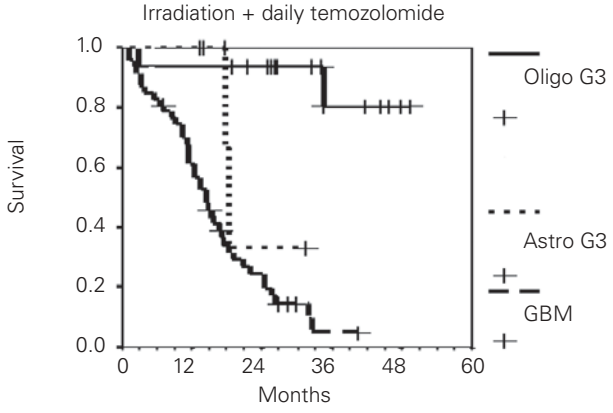

Figure 1b – Abbildung 1b

Figures 1a and 1b. Progression-free survival (a) and overall survival (b) in patients suffering from primary malignant glioma treated with postoperative radiotherapy and daily temozolomide. Oligo G3: anaplastic oligodendroglial tumors (n = 16), Astro G3: anaplastic astrocytomas (n = 6), GBM: glioblastoma multiforme (n = 47).

Abbildungen 1a und 1b. Progressionsfreies Überleben (a) und Gesamtüberleben (b) der Patienten mit primären malignen Gliomen nach postoperativer Radiochemotherapie mit Temozolomid. Oligo G3: anaplastische oligodendrogliale Tumoren (n = 16), Astro G3: anaplastische Astrozytome (n = 6), GBM: Glioblastoma multiforme (n = 47).

tine) in these patients [33]. Adjuvant chemotherapy with nitrosoureas or PCV has been shown to increase survival after 1 or 2 years by about 5%. Many groups have tried to increase the efficacy of postoperative radiotherapy by simultaneous radiochemotherapy, either by i.v. infusion of nitrosoureas [1, 8, 15, 25], platinum derivatives [4, 24, 29], taxanes [11, 13, 16, 28, 35] or topotecan [12, 17] or by intraarterial infusion [10, 14, 25, 32]. In most of these schemes, chemotherapy was applied only at some days during radiotherapy, and no schedule showed a significant increase in overall survival.

The Neuro-Oncology Working Group of the German Cancer Society carried out a study (NOA 01) where malignant glioma patients with a Karnofsky performance score ≥ 70% were treated with postoperative radiotherapy and adjuvant ACNU/VM26 or ACNU/ARA-C. In glioblastoma patients, median survival times of 16.2 months were achieved, while anaplastic astrocytoma patients had a median survival of 60 months. Although these patients were selected according to one of the major prognostic factors, these results were superior to those from the RTOG trials when patients were grouped into RPA classes [44] (Table 6).

A more radiobiologically oriented schedule was used by others who, by applying daily low doses of chemotherapy, tried to sensitize every radiotherapy fraction. Daily doses of cisplatinum [36] and topotecan [18] both lead to median survival times of 15 months. This kind of scheme was also applied by Stupp et al. [38] by using daily temozolomide (75 mg/m^2) for simultaneous radiochemotherapy in glioblastoma patients and monotherapy with temozolomide in the adjuvant setting. Thus, a promising median survival time of 16 months was achieved. This result has now been confirmed in a randomized trial (14.6 months, [39]). In the present investigation, however, comparable survival times (15 months) were achieved by simultaneous radiochemotherapy alone, which suggests that adjuvant chemotherapy is of minor importance in this disease. In addition, comparison of survival in the RPA classes seems to demonstrate that short-term concomitant radiochemotherapy with temozolomide is at least as effective as long-term adjuvant chemotherapy as applied in the NOA 01 trial [44].

In patients with *anaplastic astrocytoma*, the situation is different. In a large historical RTOG trial, median survival times of 3–4 years were achieved by accelerated hyperfractionated radiotherapy and concomitant/adjuvant BCNU [45]. Both the meta-analysis [37] and the MRC trial [33] showed a survival advantage when using adjuvant chemotherapy after resection and radiotherapy, but median survival times were in the range of only 1.5 years. Probably, the RTOG trial included also patients with oligodendroglial components, which have a much better prognosis. At present, it is difficult to estimate the efficacy of simultaneous radiochemotherapy in anaplastic astrocytoma, since most reports do not separate these tumors from glioblastoma when reporting survival. Recently, the M.D. Anderson Cancer Center, Houston, TX, USA, performed a phase II study of accelerated radiotherapy and concomitant daily carboplatin, followed by adjuvant PCV in anaplastic gliomas. For anaplastic astrocytomas, results seemed to be below the expectation [30]. The present data concerning combined radiochemotherapy using temozolomide does not add much information to this question, since only six patients were treated.

Table 6. Median survival (months) according to RPA classes (95% confidence interval in brackets).

Tabelle 6. Mediane Überlebenszeit in den RPA-Klassen (95%-Vertrauensbereich in Klammern).

RPA class	Patients (n)	Present study	RTOG [9]	NOA 01 [44]
1	2	–	58.6	59.2
2	1	–	37.4	61.6
3	7	32.0 (7.8–56.3)	17.9	24.1
4	20	17.3 (14.5–20.2)	11.1	15.8
5	21	11.3 (9.8–12.9)	8.9	14.5
6	2	–	4.6	7.4

For patients with *anaplastic oligodendroglioma* or *mixed anaplastic astrocytoma/oligodendroglioma*, the role of chemotherapy is far better defined. Since the work of Cairncross et al. [6], these tumors are looked upon as chemosensitive. The standard therapy, comprising resection, postoperative radiotherapy and adjuvant PCV, leads to 3-year survival times of 70–85% [23, 27, 40]. So far, temozolomide was mainly used as first-line [7, 22, 42] and second-line [41] salvage chemotherapy in recurrent oligodendroglial tumors. Response rates of 25–50% have been reported, leading to median survival times of 10–13 months. The results achieved in the present investigation for primary and recurrent oligodendroglial tumors compare well with these figures and suggest that radiotherapy combined with short-term simultaneous temozolomide is at least as effective as radiotherapy plus long-term adjuvant PCV in the primary setting.

The relative effectiveness of sequential radiotherapy – temozolomide compared to the sequential temozolomide – radiotherapy is now being tested in a randomized trial of the Neuro-Oncology Working Group of the German Cancer Society [3]. Although it is, at present, uncertain whether results can be improved by simultaneous radiochemotherapy, the latter should be offered to patients with an oligodendroglial tumor outside clinical trials. It has, however, to be considered that these tumors present a heterogeneous group within itself, since cytogenetic analyses have shown a strong dependence of prognosis on specific chromosomal aberrations. Patients with a combined 1p/19q loss have a 10-year survival rate of 80%, while all others have median survival times between 1.5 and 5 years [21].

The protracted, daily application of temozolomide with doses of 75 mg/m^2 was found to be safe in a dose-finding phase I study in 1998 [5]. Temozolomide combined with radiothera-

py was first investigated by Stupp et al. [38]. In this study, however, opportunistic lung infections caused by *Pneumocystis carinii*, probably secondary to lymphopenia, were observed in two patients. Therefore, the prophylactic use of antibiotics was recommended. In the present series, lymphopenia was the dominant side effect as well. Antibiotics were not applied prophylactically, but no patient developed opportunistic bacterial infections. The most unexpected toxicity was the occurrence of herpes simplex encephalitis which, however, at least in one patient was not caused by temozolomide, since that patient had only received one dose of 75 mg/m^2 the day before. The other patient had grade 3 lymphopenia. Immunosuppression caused by high-dose steroids may have been, at least in part, responsible for these events. Therefore, care should be taken to reduce corticosteroids as much as possible during daily chemotherapy with temozolomide.

Combined and adjuvant radiochemotherapy with temozolomide has now been tested in a randomized, multicenter, multinational trial for glioblastoma by the EORTC and was found to increase 2-year survival from 10% to 26% [39]. Although glioblastoma is the most frequent type of malignant gliomas in adults, it would probably be more interesting to set up a randomized trial comparing postoperative radiotherapy to radiochemotherapy in oligodendroglial tumors and perhaps in anaplastic astrocytoma. In addition, the role of adjuvant temozolomide in glioblastoma still remains unclear.

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