Journal of Neuro-Oncology (2005) 72: 255–260
DOI 10.1007/s11060-004-2338-2

Clinical Study

P450 enzyme inducing and non-enzyme inducing antiepileptics in glioblastoma patients treated with standard chemotherapy

Stefan Oberndorfer[1], Maria Piribauer[2], Christine Marosi[3], Heinz Lahrmann[1], Peter Hitzenberger[1] and Wolfgang Grisold[1]
[1]*Department of Neurology, Kaiser Franz Josef Hospital, Vienna, Austria;* [2]*Ludwig Boltzman Institute for Neurooncology, Kaiser Franz Josef Hospital, Vienna, Austria;* [3]*Clinical Division of Oncology, Department of Medicine I, University Clinic, Vienna, Austria*

Key words: antiepileptic drugs, CCNU, Cytochrome P450, glioblastoma, haematotoxicity

Summary

The co-administration of antiepileptic drugs (AED) and chemotherapeutic agents in patients with glioblastoma multiforme (GBM) is common. Interactions of chemotherapeutic agents and AED have not been investigated sufficiently. The purpose of this study is to evaluate the effects of enzyme inducing (EI-AED) and non-EI-AED in patients with GBM treated with standard chemotherapeutic agents on survival and haematotoxicity. One hundred and sixty eight glioblastoma patients with standard treatment including surgery, radiotherapy and chemotherapy were retrospectively analysed. Patients were separated into three groups: *Group A* patients without AED ($n = 88$), *Group B* patients with EI-AED ($n = 43$), and *Group C* patients with non-EI-AED ($n = 37$). CCNU was the most frequently used first-line drug in all three groups (Group A: 77%; Group B: 81%; Group C: 78%). Second line treatment, mainly temozolomide, was applicated in 58% of patients and third-line treatment in 9%. Carbamazepine was the most frequently administered AED in Group B (81%) and valproic acid in Group C (85%). For statistical analysis, only patients with CCNU first line treatment were calculated. A significant difference regarding survival was detected between Group B (10.8 month) and Group C (13.9 month), as well as increased haematotoxicity for Group C. These results indicate that AED influence the pharmacokinetics of chemotherapeutic drugs in patients with GBM. Valproic acid might be responsible for increasing haematotoxicity. Whether the difference regarding survival between Group B and Group C is due to a decrease of efficacy of chemotherapeutic agents by EI-AED, or due to increased efficacy of chemotherapeutic agents caused by the enzyme inhibiting properties of valproic acid, has to be evaluated in future studies.

Introduction

The glioblastoma multiforme (GBM) is a fatal cerebral neoplasm despite aggressive treatment including surgical resection, radiotherapy and chemotherapy. Median overall survival in these patients is about one-year and ranges between 7 and 16 month [1–8]. Surgical procedures as well as radiotherapeutic techniques have been improved throughout the last years with the consequence of reducing side effects but have proven only little effect on life expectancy. Different chemotherapeutic agents are increasingly used in patients with GBM although the benefit on survival is marginal. Nitrosourea, such as CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosurea), which is an alkylating agent, is frequently administered to patients with GBM whether alone or in combination with other chemotherapeutic drugs such as procarbazine and vincristine.

Seizures are a common problem in patients with GBM and contribute substantially to the morbidity [9]. The frequency of seizures in glioblastoma patients ranges from 22% to 60% [10–12]. The majority of these patients are treated with antiepileptic drugs (AED). Usually monotherapy is used in high-grade gliomas to control seizures. In case of tumor progression or an increase of edema seizure control might becomes insufficient and a combined antiepileptic drug therapy can be necessary. Also surgery, radiotherapy, steroids and even chemotherapy should be considered, in order to control seizures.

The enzyme inducing antiepileptic drugs (EI-AED) enhance the metabolism of other concurrently used drugs like, steroids, warfarin, some antibiotics as well as antipsychotics and antidepressants, so that the efficacy of these co-administered drugs may be insufficient and the dosage has to be increased [13,14]. A concomitant medication of AED and chemotherapeutic agents is necessary in the majority of malignant glioma patients with seizures. In this regard, pharmacokinetic interactions of AED with chemotherapeutic agents, when metabolised by the cytochrome P450 (CYP) system in the liver, can cause insufficient seizure and/or tumor control or lead to increased haematotoxicity or other various side effects [15,16]. Several isoenzymes of the CYP system are involved in the metabolism of AED as well as in the metabolism of nitrosureas [17,18]. However, the knowledge about pharmacokinetic interactions between chemotherapeutic agents, such as CCNU and AED is very limited [19–21].

In the clinical setting, interactions of chemotherapeutic agents and antiepileptic drugs have not been investigated sufficiently, although the co-administration is very common. The purpose of this study is to evaluate effects of EI-AED and non-EI-AED in patients with GBM treated with standard chemotherapeutic agents, mainly CCNU, on survival and haematotoxicity.

Patients and methods

In a retrospective analysis, 168 patients with histologically confirmed GBM, according to the WHO classifications system, WHO [22], seen at the Department of Neurology, Kaiser Franz Josef Hospital, Vienna, and the Department of Oncology, University Clinic Vienna, between 1993 and 2003, were included in the study. Data from the Kaiser Franz Josef Hospital were analysed from an neurooncological database where age, gender, diagnosis, clinical data, therapy and survival of neurooncological patients are recorded. Data from the University Clinic were taken from a study protocol. All data were recorded by physicians engaged in the patients care. Hospital records were available for all patients.

Only patients who received radiotherapy and standard chemotherapy after biopsy or tumor resection were included for analysis. Patients without chemotherapy, or patients with chemotherapy but without radiotherapy, were excluded. Age, gender, Karnofsky Performance Status (KPS), cycles of chemotherapy, haematotoxicity and survival were documented. Seizures were retrospectively recorded from the database and hospital records. A classification regarding the type of seizure was not attempted, because retrospective data were inconclusive and not convincing. Regarding antiepileptic drug therapy, the drug, dosage and drug combinations were evaluated. The decision whether to use EI-AED or non-EI-AED was up the physicians involved in the patients care in each center and based upon individual experiences. According to the clinical guidelines of the two centers, no prophylactic antiepileptic medication was administered to patients with newly diagnosed glioblastoma.

For data analysis, patients were divided into three groups: Group A; patients without epileptic seizures. Group B; patients with seizures treated with EI-AED, and Group C; patients with seizures treated with non-EI-AED. In order to receive more homogenous subgroups for statistical analysis, we calculated also patients with CCNU up front in each group.

The same standard chemotherapy with CCNU 100 mg/m^2, or temozolomide (150 mg/m^2), or (PCV) procarbazine/CCNU/vincristine was administered to patients in both centers. Nineteen patients from the Department of Oncology at the University of Vienna were treated according to a protocol with fotemustine (100 mg/m^2) and dacarbazin (200 mg/m^2). Survival data were calculated from time of tumor diagnosis until death. Haematotoxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) toxicity scale (Version 2.0).

Statistics

The standard version of the SPSS/Inc. statistical package for Windows 7.0 (1995) was used for data evaluation. Differences regarding survival between controls (Group A), patients with EI-AED (Group B), and non-EI-AED (Group C) were calculated between the total number of patients in each group. A subgroup analysis regarding survival for patients with CCNU up front was also performed, in order to receive a more homogeneous samples. The inter-group differences were tested for statistical significance by means of the Mann–Whitney *U*-test. A *P*-value less than 0.05 was assessed as statistically significant.

Results

From 168 patients with GBM who underwent aggressive treatment including surgery (or biopsy), radiotherapy and standard chemotherapy, 80 patients (48%) experienced seizures during the course of the disease. Forty-three patients (54%) were treated with EI-AED and, 37 patients (46%) were treated with non-EI-AED. Antiepileptic polytherapy was administered in nine patients (11%).

Descriptive data of all three patient groups are summarized in Tables 1–3. Regarding age, and KPS, no statistical significant difference was observed.

All patients included had a standard first line chemotherapy. The majority of patients in Group A, B, and C received CCNU for first line treatment (Group A: 77%, Group B: 81%, Group C: 78%). More than half of patients received a subsequent second line treatment

Table 1. Group A (controls). Glioblastoma patients with standard therapy without epileptic seizures

	n	Median	Min/max
Age (years)	88	59	(23/83)
Overall survival (month)	75[a]	11.6	(2/51)
Karnofsky Performance Status (KPS)	82[b]	90%	(70/100)
Chemotherapy		Median cycles	
First line			
1st CCNU	68	5	(1/9)
1st Da/Fo	9	5	(4/7)
1st PCV	6	4	(2/6)
1st TMZ	5	5	(2/7)
Second line			
2nd TMZ	30	3	(1/6)
2nd CCNU	5	3	(1/5)
2nd Da/Fo	7	3	(2/5)
2nd others	7		
Third line			
3rd	9		

[a] Missing data: 13 patients.
[b] Missing data: 6 patients.
Da/Fo, dacarbazin, fotemustin; PCV, procarbazine/CCNU/vincristine; TMZ, temozolomide.

Table 2. Group B. Glioblastoma patients with standard therapy and seizures treated with enzyme inducing antiepileptic drugs (EI-AED)

	n	Median	Min/max
Age (years)	43	57	(26/75)
Overall survival (month)	37[a]	10.8	(3/39)
Karnofsky Performance Status (KPS)	39[b]	90%	(80/100)
Chemotherapy		Median cycles	
First line			
1st CCNU	35	5	(1/8)
1st (da(fo)[a]	5	6	(4/8)
1st PCV	1	4	(1/5)
1st TMZ	2	4	(2/6)
Second line			
2nd TMZ	16	2	(2/6)
2nd CCNU	3	3	(2/5)
2nd DaFo	6	3	(1/5)
2nd others	2		
Third line 3rd	3		
Antiepileptic drug		Median dosage	
Carbamazepine	35	750 mg	(400/1200)
Phenytoin	8	200 mg	(100/200)
Polytherapy	5		

[a] Missing data: six patients.
[b] Missing data: four patients.
Da/Fo, dacarbazin, fotemustin; PCV, procarbazine/CCNU/Vincristine; TMZ, temozolomide.

Table 3. Group C. Glioblastoma patients with standard therapy and seizures treated with non-enzyme inducing antiepileptic drugs (non-EI-AED)

	n	Median	Min/max
Age (years)	37	56	(31/79)
Survival (month)	33[a]	13.7	(3/49)
Karnofsky Performance Status (KPS)	33[b]	90%	(70/100)
Chemotherapy		Median cycles	
First line			
1st CCNU	29	4	(1/8)
1st (da(fo)[a]	4	6	(4/8)
1st PCV	3	4	(1/5)
1st TMZ	1	5	5
Second line			
2nd TMZ	14	3	(1/5)
2nd CCNU	1	3	(1/4)
2nd Da/fo	4	4	(2/5)
2nd others	2		
Third line 3rd	3		
Antiepileptic drug		Median dosage	
Valproic acid	32	900 mg	(600/1500)
Lamotrigine	7	100 mg	(50/200)
Levetiracetam	2	2000 mg	(2000)
Polytherapy	4		

[a] Missing data: four patients.
[b] Missing data: four patients.
Da/Fo, dacarbazin, fotemustin; PCV, procarbazine/CCNU/vincristine; TMZ, temozolamide.

(Group A: 56%, Group B: 63%, Group C: 57%). The most frequently used second line chemotherapeutic drug was temozolomide. (Group A: 61%, Group B: 59%, Group C: 67%). Patients with CCNU as the first line chemotherapy received in median 5 cycles of chemotherapy (Group A: 5, Group B: 5, Group C: 4), whereas temozolomide was administered only in median three times in the second line setting (Group A: 3, Group B: 2, Group C: 3).

Regarding antiepileptic treatment in Group B, carbamazepine (81%) was more frequently used than phenytoin (19%). In Group C, mainly valproic acid (85%) was applicated for antiepileptic treatment.

Survival data are shown in Table 4. There was no statistical significant difference in overall survival of controls (Group A), as compared to patients who received EI-AED (Group B), nor to patients who received non-EI-AED (Group C). But, there was a statistically significant difference in survival between Group B and Group C ($P = 0.016$, Mann–Whitney U-test). Also survival data for the entire groups are provided in Table 4, which showed also statistical significant difference in survival between Group B and Group C ($P = 0.042$, Mann–Whitney U-test). Median survival of all glioblastoma patients with epileptic seizures was 12.4 month, which was not statistically different from glioblastoma patients without epileptic seizures with a median survival of 11.8 month.

Blood toxicity was evaluated in Group B and C (Tables 5 and 6). Group B showed less frequent blood toxicity (G1: 6 ,G2 : 3, G3 : 1) than Group C (G1 : 7 ,G2 : 5, G3 : 4).

Discussion

It has been addressed in several papers that AED influence the pharmacokinetics of various concomitant medication as chemotherapeutic agents especially when metabolised by CYP system [14,23–30]. Therefore, from the recent literature it is recommended to avoid the classical EI-AED, such as carbamazepine and phenytoin, in neurooncological patients, and favour valproic acid or newer anticonvulsants like lamotrigine, levetiracetam, or topiramte [31,32]. The non EI-AED are not metabolised by the P450 system, although there may be unexpected interactions that do not involve known pathways.

This study investigated whether glioblastoma patients treated with standard chemotherapy, mainly CCNU, and concomitant EI-AED or non-EI-AED do have differences concerning overall survival, as well as concerning haematotoxicity as compared to GBM patients without seizures.

The results exhibited no significant difference in overall survival of GBM patients without epileptic seizures, compared to patients with EI-AED or non-EI-AED. But a significant difference in overall survival was found between patients treated with EI-AED compared to patients treated with non-EI-AED. Moreover, increased haematotoxicity could be demonstrated in patients treated with non-EI-AED as compared to patients with EI-AED. There was no statistical significant difference in overall survival between GBM patients with seizures

Table 4. Survival data (month) of Group A, B and C in patients with CCNU up front and the entire groups

	Group A	Group B	Group C	(*P* value)
CCNU up front	11.7 ($n = 66$)	10.8 ($n = 34$)	13.9 ($n = 28$)	*0.016 (B-C)
Total	11.6 ($n = 75$)	10.8 ($n = 37$)	13.7 ($n = 33$)	*0.042 (B-C)

(*$P < 0.05$, Mann–Whitney *U*-test).

compared to patients without seizures, which has been postulated previously [11–33]. Drug interactions of hepatic EI-AED with chemotherapeutic agents such as 9-aminocamptothecin, irinotecan, vincristine, and paclitaxel are reported in the literature [23–29,34]. They reduce blood levels by increasing their clearance, as well as haematotoxicity and probably the efficacy of chemotherapeutic agents. Concerning CCNU, the most frequently administered chemotherapeutic agent in Group A, B, and C, no data about pharmacokinetic interactions with EI-AED are available, which would suggest a decrease of CCNU plasma levels, haematotoxicity and efficacy. The shortened overall survival of Group B compared to control Group A, as well as the significant reduction in overall survival compared to Group C, would be in line with previous findings indicating decreased blood levels and probably efficacy of several chemotherapeutic agents concomitantly used with EI-AED [23–25,27,29]. These findings are also in accordance with animal studies on phenobarbital, a potent P450 enzyme inducer, which decreased CCNU related hepatotoxicity as well as anti-tumor activity in animal studies [21,35].

Valproic acid, the most frequently administered non-EI-AED, is an inhibitor mainly of the isoenzymes CYP2C9, CYP2C19, CYP2E1, CYP2A6 and possibly CYP3A4, but also inhibits other enzymatic systems such as the uridinediphosphate glucuronyltransferase for example UTG1A4, which glucuronates other drugs to usually inactive metabolites and epoxide hydrolase [14,17,18,36–37]. The impairment of hepatic metabolism, mainly the P450 system, can increase drug concentrations, which has been demonstrated for antiepileptic drugs like phenytoin, carbamazepine, benzodiazepines, and lamotrigine [36–38,40]. Regarding chemotherapeutic agents, such as irinotecan and SN-38, the toxicity profile and plasma disposition was not strongly influenced by valproic acid [30]. But high-grade glioma patients, who received valproic acid for antiepileptic treatment and a combination of fotemustine (a nitrosourea derivate), cisplatin and etoposide, experienced a threefold higher incidence of haematotoxicity [19]. However, besides those limited clinical experience, there are no available data concerning a possible mode of pharmacokinetic interaction between valproic acid and CCNU so far.

Table 5. Haematotoxicity (G0–G4) during chemotherapy in patients with enzyme inducing AED during first line chemotherapy with CCNU (Group B)

	G0	G1	G2	G3	G4
Erythrocyte		1	0	0	0
Leucocyte		2	1	0	0
Thrombocyte		3	2	1	0
Total		6	3	1	0

Table 6. Haematotoxicity (G0–G4) during chemotherapy in patients with non enzyme inducing AED during first line chemotherapy with CCNU (Group C)

	G0	G1	G2	G3	G4
Erythrocyte		2	0	0	0
Leucocyte		3	3	2	0
Thrombocyte		2	2	2	0
Total		7	5	4	0

Nitrosureas, such as CCNU, are a common standard first or second line treatment in patients with GBM. From the literature, it is reported that CCNU has some degree of hepatic activity. In the biotransformation of nitrosureas by the CYP system, isoenzymes such as CYP2C19, CYPP2D6, and CYP3A4, may be involved, which has been demonstrated in animal studies. Results of these studies indicate that CCNU leads to a prolonged decrease of liver cytochrome P450 mediated enzyme activities [35,41–43]. However, no available data in humans suggests that activation of the hepatic P450 system, for example due to EI-AED, would significantly affect the pharmacology of this agent.

Second line treatment may also be considered concerning survival data and haematotoxicity, but pharmacokinetics of temozolomide, which was the most frequently used second line agent in all three patient groups, are much more favourable compared to CCNU, and it is not metabolized by the P450 system. Another point is that more cycles of CCNU (median = 5 cycles) were applicated than cycles of temozolomide (median = 3 cycles) and more patients were treated with CCNU ($n = 132$) than patients with temozolomide ($n = 50$). Concerning other concomitant medication, dexamethasone is frequently applicated in patients with GBM to reduce brain edema. It is prescribed in most cases periodically and tapered as soon as possible due to its severe side effects. Dexamethasone is mainly a CYP3A3, but also CYP2B and CYPE1 isoenzyme inducers [44]. Drug interactions are described with phenytoin [45]. There are no data concerning drug interactions with chemotherapeutic agents or other AED. However, possible drug interactions of steroids with chemotherapeutic agents and AED have to be considered, although they are administered only periodically.

Concluding the data from this analysis, it seems evident that EI-AED and non-AED do have some effect on chemotherapeutic drug treatment. As CCNU was the

most frequently used chemotherapeutic agent, it can be assumed that enzyme inhibition of the CYP system by valproic acid, decreases the rate of metabolism of CCNU, which may leads to elevated plasma concentrations of the drug and possibly to increased haematological toxicity. Survival data indicating a significant difference between Group B and Group C, may be explained by impairment of CCNU metabolism and consecutively the efficacy of CCNU by EI-AED and non-EI-AED. Whether the decrease of efficacy of CCNU due to EI-AED or the increased efficacy of CCNU due to valproic acid was responsible concerning the significant difference in overall survival between Group B and Group C, has to be evaluated in future studies. Further studies should be obtained to evaluate plasma levels of CCNU in patients treated with EI-AED and non-EI-AED in order to confirm this observational data.

This observation has significant implications for patients with GBM when antiepileptic drug treatment becomes mandatory. Anti-tumor treatment with chemotherapeutic agents such as CCNU may become insufficient when used concurrently with EI-AED, and non-EI-AED, such as valproic acid, may amplificate haematotoxicity. We recommend to use newer antiepileptic drugs with a more favourable pharmacokinetic profile as levetiracetam, topiramate, or gabapentine in malignant glioma patients to avoid interactions with chemotherapy. However, EI-AED are potent anticonvulsants and may be preserved to selected patients with status epilepticus, epilepsia partialis continua, refractory seizures or patients with short live expectancy.

References

1. Brandes AA, Vistola F, Basso U, Berti F, Pinna G, Rotilio A, Gardiman M, Scienza R, Monfardini S, Ermani M: A prospective study on glioblastoma in the elderly. Cancer 1: 657–662, 2003
2. Chang EL, Yi W, Allen PK, Levin VA, Sawaya RE, Maor MH: Hypofractionated radiotherapy for elderly or younger low-performance status glioblastoma patients: outcome and prognostic factors. Int J Radiat Oncol Biol Phys 56: 519–528, 2003
3. Durando X, Lemaire JJ, Tortochaux J, Van-Praagh I, Kwiatkowski F, Vincent C, Bailly C, Vergelle P, Irthum B, Chazal J, Bay JO: High-dose BCNU followed by autologous hematopoietic stem cell transplantation in supratentorial high-grade malignant gliomas: a retrospective analysis of 114 patients. Bone Marrow Transplant 3: 559–564, 2003
4. Grossman SA, O'Neil A, Grunnet M, Mehta M, Pearlman JL, Wagner H, Gilbert M, Newton HB, Hellman R: Eastern Cooperative Oncology Group. Phase III study comparing three cycles of infusional carmustine and cisplatin followed by radiation therapy with radiation therapy and concurrent carmustine in patients with newly diagnosed supratentorial glioblastoma multiforme: Eastern Cooperative Oncology Group Trial 2394. J Clin Oncol 15: 1485–1491, 2003
5. Pech IV, Peterson K, Cairncross JG: Chemotherapy for brain tumors. Oncology 12: 537–543, 1998
6. Trippoli S, Pelagotti F, Messori A, Vacca F, Vaiani M, Maltoni S: Survival of patients with recurrent malignant glioma treated with temozolomide: a retrospective observational study. Drugs R D 4: 285–291, 2003
7. Stupp R, Dietrich PY, Kraljevic S, Pica A, Maillard I, Maeder P, Meuli R, Panzer R, Pizzolato G, Miralbell R, Porchet F, Regli L, de Tribolet N, Mirimanoff RO, Leyvraz S: Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. J Clin Oncol 1: 1375–1382, 2002
8. Westphal M, Hilt DC, Bortey E, Delavault P, Olivares R, Warnke PC, Whittle IR, Jaaskelainen J, Ram Z: A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. Neuro-oncol 5: 79–88, 2003
9. Moots PL, Maciunas RJ, Eisert DR, Parker RA, Laporte K, Abou-Khalil B: The course of seizure disorders in patients with malignant gliomas. Arch Neuro 52: 717–724, 1995
10. Greenberg HS, Chandler WF, Sandler HM: Brain Tumors. Contemporary Neurology Series. Oxford University Press, 1999, pp 299–317
11. Lote K, Stenwig AE, Skullerud K, Hirschberg H: Prevalence and prognostic significance of epilepsy in patients with gliomas. Eur J Cancer 34: 98–102, 1998
12. Oberndorfer S, Schmal T, Lahrmann H, Urbanits S, Lindner K, Grisold W: The frequency of seizures in patients with primary brain tumors or cerebral metastasis. Wien Klin Wochenschr 30: 911–916, 2002
13. Patsalos PN, Perucca E: Clinically important drug interactions in epilepsy: general features and interactions between antiepileptic drugs. Lancet Neurol 2: 347–356, 2003
14. Patsalos PN, Perucca E: Clinically important drug interactions in epilepsy: interactions between antiepileptic drugs and other drugs. Lancet Neurol 2: 473–481, 2003
15. Kivisto KT, Kroemer HK, Eichelbaum M: The role of human cytochrome P450 enzymes in the metabolism of anticancer agents: implications for drug interactions. Br J Clin Pharmacol 40: 523–530, 1995
16. Vecht CJ, Wagner GL, Wilms EB: Interactions between antiepileptic and chemotherapeutic drugs. Lancet Neurol 2: 404–409, 2003
17. Neuman MG, Shear NH, Jacobson-Brown PM, Katz GG, Neilson HK, Malkiewicz IM, Cameron RG, Abbott F: CYP2E1-mediated modulation of valproic acid-induced hepatocytotoxicity. Clin Biochem 34: 211–218, 2001
18. Patsalos PN, Froscher W, Pisani F, van Rijn CM: The importance of drug interactions in epilepsy therapy. Epilepsia 43: 365–385, 2002
19. Bourg V, Lebrun C, Chichmanian RM, Thomas P, Frenay M: Nitroso-urea-cisplatin-based chemotherapy associated with valproate: increase of haematologic toxicity. Ann Oncol 12: 217–219, 2001
20. Levin VA, Stearns J, Byrd A, Finn A, Weinkam RJ: The effect of phenobarbital pretreatment on the antitumor activity of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) and 1-(2-chloroethyl)-3-(2,6-dioxo-3-piperidyl-1-nitrosourea (PCNU), and on the plasma pharmacokinetics and biotransformation of BCNU. J Pharmacol Exp Ther 208: 1–6, 1979
21. Muller PJ, Tator CH, Bloom ML: Use of phenobarbital and high doses of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea in the treatment of brain tumor-bearing mice. Cancer Res 43: 2068–2071, 1983
22. World Health Organization: International Histological Classification of Toumors. Histological Typing of Tumours of the Central Nervous Sysrem. Geneva, WHO, No 2, 1979
23. Buckner JC, Reid JM, Wright K, Kaufmann SH, Erlichman C, Ames M, Cha S, O'Fallon JR, Schaaf LJ, Miller LL: Irinotecan in the treatment of glioma patients: current and future studies on the north central cancer treatment group. Cancer 97: 2352–2358, 2003
24. Cloughesy TF, Filka E, Kuhn J, Nelson G, Kabbinavar F, Friedman H, Miller LL, Elfring GL: Two studies evaluating irinotecan treatment for recurrent malignant glioma using an every-3-week regimen. Cancer 97: 2381–2386, 2003
25. Fetell MR, Grossman SA, Fisher JD, Erlanger B, Rowinsky E, Stockel J, Piantadosi S: Preirradiation paclitaxel in glioblastoma multiforme: efficacy, pharmacology, and drug interactions. New

Approaches to Brain Tumor Therapy Central Nervous System Consortium. J Clin Oncol 15: 3121–3128, 1997
26. Friedman HS, Petros WP, Friedman AH, Schaaf LJ, Kerby T, Lawyer J, Parry M, Houghton PJ, Lovell S, Rasheed K, Cloughsey T, Stewart ES, Colvin OM, Provenzale JM, McLendon RE, Bigner DD, Cokgor I, Haglund M, Rich J, Ashley D, Malczyn J, Elfring GL, Miller LL: Irinotecan therapy in adults with recurrent or progressive malignant glioma. J Clin Oncol 17: 1516–1525, 1999
27. Grossman SA, Hochberg F, Fisher J, Chen TL, Kim L, Gregory R, Grochow LB, Piantadosi S: Increased 9-aminocamptothecin dose requirements in patients on anticonvulsants. NABTT CNS Consortium. The new approaches to brain tumor therapy. Cancer Chemother Pharmacol 42: 118–126, 1998
28. Kramer RA: Cytochrome P450-inducing antiepileptics increase the clearence of vincristine in patients with brain tumors. Clin Pharmocol Ther 66: 589–593, 1999
29. Kuhn JG: Influence of anticonvulsants on the metabolism and elimination of irinotecan. A North American Brain Tumor Consortium preliminary report. Oncology 16: 33–40, 2002
30. Raymond E, Fabbro M, Boige V, Rixe O, Frenay M, Vassal G, Faivre S, Sicari E, Germa C, Rodier JM, Vernillet L, Armand JP: Multicentre phase II study and pharmacokinetic analysis of irinotecan in chemotherapy-naive patients with glioblastoma. Ann Oncol 14: 603–614, 2003
31. Hildebrand J, Michael Brada (eds). Epileptic seizures. In: Differential Diagnosis in Neuro-oncology. Oxford University Press, 2001, pp 47–58
32. Van den Bent MJ: The role of chemotherapy in brain metastases. Eur J Cancer 39: 2114–2120, 2003
33. Smith DF, Hutton JL, Sandemann D, Foy PM, Shaw MD, Williams IR, Chadwick DW: The prognosis of primary intracerebral tumours presenting with epilepsy: the outcome of medical and surgical management. J Neurol Neurosurg Psychiatry 54: 915–920, 1991
34. Villikka K, Kivisto KT, Maenpaa H, Joensuu H, Neuvonen PJ: Cytochrome P450-inducing antiepileptics increase the clearance of vincristine in patients with brain tumors. Clin Pharmacol Ther 66: 589–593, 1999
35. Ahmed AE, Grissom M, El-Azhary R, Haque A, Boor PJ, Costanzi J: Studies on the mechanism of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)-induced hepatotoxicity. II. Biochemical and morphological characterization of the injury and its prevention by phenobarbital. Cancer Chemother Pharmacol 19: 103–108, 1987
36. McKee PJ, Blacklaw J, Butler E, Gillham RA, Brodie MJ: Variability and clinical relevance of the interaction between sodium valproate and carbamazepine in epileptic patients. Epilepsy Res 11: 193–198, 1992
37. Perucca E: Clinical pharmacology and therapeutic use of the new antiepileptic drugs. Fundam Clin Pharmacol 15: 405–417, 2001
38. Perucca E, Hebdige S, Frigo GM, Gatti G, Lecchini S, Crema A: Interaction between phenytoin and valproic acid: plasma protein binding and metabolic effects. Clin Pharmacol Ther 28: 779–789, 1980
39. Perucca E, Dulac O, Shorvon S, Tomson T: Harnessing the clinical potential of antiepileptic drug therapy: dosage optimisation. CNS Drugs 15: 609–621, 2001
40. Samara EE, Granneman RG, Witt GF, Cavanaugh JH: Effect of valproate on the pharmacokinetics and pharmacodynamics of lorazepam. J Clin Pharmacol 37: 442–450, 1997
41. Chang TK, Chen H, Waxman DJ: 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosurea (CCNU modulates rat liver microsomal cyclophosphamide and ifosphamide activation by suppressing cytochrome P450 "C11 messenger RNA levels. Drug Metab Dispos 22: 673–679, 1994
42. Litterst CL: Prolonged depression of hepatic microsomal drug metabolism and hemoprotein levels following a single dose of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU). Biochem Pharmacol 30: 1014–1016, 1981
43. Tong S, Hirokata Y, Litterst CL, Gram TE: Interaction of the oncolytic drug, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea with the mixed-function oxidase system in rats. Chem Biol Interact 49: 105–119, 1984
44. Liddle C, Goodwin BJ, George J, Tapner M, Farrell GC: Separate and interactive regulation of cytochrome P450 3A4 by triiodothyronine, dexamethasone, and growth hormone in cultured hepatocytes. J Clin Endocrinol Meta 83: 2411–2416, 1998
45. Lackner TE: Interaction of dexamethasone with phenytoin. Pharmacotherapy 11: 344–347, 1991

Address for offprints: Stefan Oberndorfer, Department of Neurology and LBI for Neurooncology, KFJ-Hospital, SMZ-Süd, Kundratstr. 3, 1100, Vienna, Austria; Tel.: +43-1-60191-2008; Fax: +43-1-60191-2009; E-mail: stefan.oberndorfer@wienkav.at