Phase I/II Study of Imatinib Mesylate for Recurrent Malignant Gliomas: North American Brain Tumor Consortium Study 99-08

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Abstract

Purpose: Phase I: To determine the maximum tolerated doses, toxicities, and pharmacokinetics of imatinib mesylate (Gleevec) in patients with malignant gliomas taking enzyme-inducing antiepileptic drugs (EIAED) or not taking EIAED. Phase II: To determine the therapeutic efficacy of imatinib.

Experimental Design: Phase I component used an interpatient dose escalation scheme. End points of the phase II component were 6-month progression-free survival and response.

Results: Fifty patients enrolled in the phase I component (27 EIAED and 23 non-EIAED). The maximum tolerated dose for non-EIAED patients was 800 mg/d. Dose-limiting toxicities were neutropenia, rash, and elevated alanine aminotransferase. EIAED patients received up to 1,200 mg/d imatinib without developing dose-limiting toxicity. Plasma exposure of imatinib was reduced by ~68% in EIAED patients compared with non-EIAED patients. Fifty-five non-EIAED patients (34 glioblastoma multiforme and 21 anaplastic glioma) enrolled in the phase II component. Patients initially received 800 mg/d imatinib; 15 anaplastic glioma patients received 600 mg/d after hemorrhages were observed. There were 2 partial response and 6 stable disease among glioblastoma multiforme patients and 0 partial response and 5 stable disease among anaplastic glioma patients. Six-month progression-free survival was 3% for glioblastoma multiforme and 10% for anaplastic glioma patients. Five phase II patients developed intratumoral hemorrhages.

Conclusions: Single-agent imatinib has minimal activity in malignant gliomas. CYP3A4 inducers, such as EIAEDs, substantially decreased plasma exposure of imatinib and should be avoided in patients receiving imatinib for chronic myelogenous leukemia and gastrointestinal stromal tumors. The evaluation of the activity of combination regimens incorporating imatinib is under way in phase II trials.

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Despite optimal treatment, the prognosis of patients with malignant gliomas remains poor. Patients with glioblastoma multiforme have a median survival of 9 to 14 months, whereas those with anaplastic astrocytomas have a median survival of 24 to 36 months (1). Once patients develop tumor progression, conventional chemotherapy is generally ineffective, with a median time to tumor progression of 9 to 13 weeks (2). There is a need for more effective therapies.

Tyrosine kinases play a fundamental role in signal transduction, and deregulated activity of these enzymes has been observed in an increasing number of cancers. There is growing evidence that specific inhibitors of these tyrosine kinases have potential therapeutic applications in oncology.

Overexpression and activation of platelet-derived growth factor (PDGF) receptors (PDGFR) may contribute to the transformed phenotype of malignant gliomas (3–5). Inappropriate coexpression of PDGF and PDGFR is common in gliomas (5–8). Production of PDGF in cells that express PDGFR

potentially results in an autocrine or paracrine loop that may drive cell proliferation. The PDGFA and PDGFB ligands are expressed in most glioma cell lines and fresh surgical isolates. The PDGFRα subunit is overexpressed in virtually all glioma lines and primary cultures (5–7), whereas the PDGFRβ subunit is frequently expressed in glioma and endothelial cells (5). PDGFRα is overexpressed in low-grade astrocytomas (5), suggesting that it may be an early event in the "progressive" pathway to malignant gliomas. Because the PDGFRα is the "universal" PDGFR, sensitive to other isoforms of PDGF, activation of PDGFRα through an autocrine loop may be a pervasive feature of malignant gliomas. In contrast, only higher-grade tumors (anaplastic astrocytoma and glioblastoma multiforme) overexpress the PDGFA and PDGFB ligands (5, 7). The presence of these ligands allows the PDGF autocrine/paracrine loop to be closed in high-grade gliomas, potentially contributing to the pathogenesis of these tumors (9). Dominant-negative mutants of PDGF block the proliferation of U87MG glioma cells *in vitro* and *in vivo*, supporting a role for PDGF in the proliferation of malignant gliomas (10).

Imatinib mesylate (Gleevec; formerly known as STI571) is a potent inhibitor of the Bcr-Abl, PDGFRα, PDGFRβ, c-Fms, and c-Kit tyrosine kinases (11, 12). It has antitumor activity in chronic myelogenous leukemia by inhibiting Bcr-Abl (13) and in gastrointestinal stromal tumors by inhibiting c-Kit (14). Its ability to inhibit PDGFR with an IC_{50} of 0.1 μmol/L suggested that it might have therapeutic potential in malignant gliomas. Kilic et al. found that imatinib inhibited the growth of U343 and U87 glioblastoma cell lines *in vitro* and *in vivo* at concentrations achievable in man, providing support for its potential therapeutic value in patients with malignant gliomas (15).

There is increasing evidence that PDGF may have a proangiogenic effect by promoting pericyte recruitment and vessel maturation in many tumors (16). Inhibition of PDGFRβ on endothelial cells and pericytes by imatinib potentially contributes to an antitumor effect by inhibiting angiogenesis.

The North American Brain Tumor Consortium (NABTC) conducted a phase I/II study of imatinib in patients with recurrent malignant gliomas. Brain tumor patients receiving antiepileptic drugs that induce certain cytochrome *P*450 isoenzymes, such as CYP3A4, have accelerated drug metabolism that markedly alter the pharmacokinetics of antineoplastic agents that are substrates for cytochrome *P*450s. This increased metabolism decreases exposure to those drugs when administered at conventional doses (17, 18). Failure to achieve adequate plasma concentrations of those drugs may partially account for their lack of efficacy in previous brain tumor trials. Imatinib is primarily metabolized by CYP3A4/5 to the *N*-desmethyl derivative (CPG74588). It is likely that the patients taking enzyme-inducing antiepileptic drugs (EIAED) have increased hepatic metabolism and reduced exposure to imatinib when given at the same dose as patients not taking EIAED. In the phase I portion of the study, patients were stratified into those who received EIAED (group B) and those who did not (group A), with the goal of determining the maximum tolerated dose (MTD) for both groups of patients. A single phase II study was planned combining the response and toxicity data from all patients treated with the dose of imatinib that was appropriate for them based on their use of EIAEDs.

Patients and Methods

Patient eligibility

Adults (≥18 years old) with histologically confirmed supratentorial malignant gliomas with unequivocal tumor recurrence by magnetic resonance imaging scans were eligible. For the phase I component, meningioma patients were eligible, as there is evidence that PDGFR is expressed on these tumors (19, 20), and imatinib may have therapeutic potential. A baseline magnetic resonance imaging was done within 14 days of registration on a stable steroid dosage for ≥5 days. Patients must have failed prior radiotherapy and have an interval of ≥4 weeks from the completion of radiotherapy to study entry. Phase I patients may have had treatment for no more than three prior relapses; phase II patients may have had treatment for no more than two prior relapses. Additional eligibility criteria included Karnofsky performance score ≥60, life expectancy ≥8 weeks, adequate bone marrow function (absolute neutrophil count ≥1,500/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥10/dL), adequate liver function (alanine aminotransferase and alkaline phosphatase ≤2 times the upper limit of normal; bilirubin <1.5 mg/dL), and adequate renal function (blood urea nitrogen or creatinine ≤1.5 times upper limit of normal). Due to potential teratogenicity of imatinib, all patients of childbearing potential were required to use adequate birth control. Pregnant women and patients with serious intercurrent medical illnesses and conditions that could alter drug metabolism were excluded. Due to potential interaction with imatinib, patients on warfarin were excluded.

The study was approved by the institutional review board of each participating institution and conducted in accordance with institutional and federal guidelines for human investigations. Patients were informed of the investigational nature of this study and signed institutional review board–approved informed consent forms before enrollment.

Stratification

Patients were stratified according to whether they were taking EIAED and by tumor type. Group A patients were not taking EIAED; group B patients were on EIAED (carbamazepine, oxcarbazepine, phenytoin, phenobarbital, or primidone). Patients in group B had to be taking an EIAED while they remained on protocol. Patients switched from a non-EIAED to an EIAED before enrollment had to be on the EIAED for a minimum of 2 weeks before registration. Patients were also stratified according to tumor type: (*a*) glioblastoma multiforme or gliosarcoma and (*b*) anaplastic glioma, which included anaplastic astrocytomas, anaplastic oligodendrogliomas, and anaplastic oligoastrocytomas.

Evaluation during study

Medical history and physical examination were done at baseline and at the start of each 4-week cycle. Magnetic resonance imaging was done at baseline and before every other cycle (every 8 weeks). Determination of tumor status was made using the Macdonald criteria (21). Responses had to be present for two consecutive scans (8 weeks) and were centrally reviewed at the University of California-San Francisco. Central review of pathology was conducted by K.A.

Treatment plan

Imatinib was supplied by the Division of Cancer Treatment and Diagnosis, Cancer Therapy Evaluation Program, National Cancer Institute under a Cooperative Research and Development Agreement with Novartis Pharmaceuticals. Patients were administered imatinib orally once daily (≤600 mg) or twice daily (≥800 mg).

Phase I study

Patients initially received imatinib at a dose of 400 mg/d. Subsequent doses increased by 200 mg/d. Escalations were planned in groups of three patients, with an additional three patients to be added at the first indication of a dose-limiting toxicity (DLT). Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria

version 2.0 (http://ctep.info.nih.gov/reporting/index.html). DLT was defined as any grade 3 thrombocytopenia, grade 4 anemia and neutropenia, grade ≥3 nonhematologic toxicity (except for grade 4 hypophosphatemia), or failure to recover from toxicities to be eligible for retreatment within 2 weeks of the last dose of imatinib. The MTD was based on the tolerability observed during the first 4 weeks of treatment. The MTD of imatinib in each arm was that dose at which fewer than one third of patients experienced a DLT (i.e., the dose at which 0 or 1 of 6 patients experience DLT, with the next higher dose having at least 2 of 3 or 2 of 6 patients encountering DLT).

Phase II study

The initial plan was to conduct a single phase II study combining the response and toxicity data from all patients treated with the dose of imatinib that was appropriate for them based on their use of EIAEDs. However, the MTD for non-EIAED patients was determined first. The phase II study opened to non-EIAED patients who initially received 800 mg/d (400 mg twice daily) of imatinib in 4-week cycles. After hemorrhages were observed predominantly in glioblastoma multiforme patients receiving 800 mg/d imatinib, the study was amended and 15 additional anaplastic glioma patients were treated with 600 mg/d imatinib. The study completed accrual before the MTD for EIAED patients could be determined. Therefore, no EIAED patients were enrolled into the phase II study.

Pharmacokinetic studies

Plasma was collected for pharmacokinetic analysis from patients enrolled in the phase I component. For patients taking imatinib once daily, blood samples were collected before and at 1 to 4, 8, and 12 hours after ingestion of the first dose of imatinib. Blood samples were also obtained before imatinib ingestion on days 2 and 8 of cycle 1 and day 1 of cycle 2 (day 29). For patients taking imatinib twice daily, blood samples were collected before and at 1 to 4 and 8 hours after the first dose of imatinib. The second dose of imatinib was administered 8 hours after the first. Additional blood samples were then obtained 9, 10, 24, and 32 hours after the first dose of imatinib. No imatinib was administered on day 2 for patients receiving twice daily dosing of the drug. Blood samples were also obtained before imatinib ingestion on days 3 and 8 of cycle 1 and day 1 of cycle 2 (day 29). At each time point, venous whole-blood samples (7 mL) were collected into heparinized tubes and centrifuged immediately at 1,200 × *g* for 5 minutes. The plasma was removed, transferred to polypropylene screw-capped tubes, and frozen at −20°C until subsequent high-performance liquid chromatography analysis to determine total concentrations of imatinib and its metabolite CPG74588.

Measurement of imatinib levels. Plasma imatinib concentrations and metabolite CGP74588 were determined using a liquid chromatography/tandem mass spectrometry assay. Plasma samples were prepared using a protein precipitation procedure. Sample extracts were analyzed using reverse-phase chromatography with a Waters Symmetry column (Waters Corp., Milford, MA) followed by detection with a Sciex API 3000 mass spectrometer (PE Applied Biosystems, Foster City, CA). The lower limit of quantitation was 4 ng/mL, and the assay was fully validated (22). The accuracy and precision from prestudy validation were 104 ± 6% at the lower limit of quantitation and 98.9 ± 5% to 108 ± 5% over the entire concentration range of 4 to 10,000 ng/mL.

The concentration versus time curves of imatinib and metabolite CGP74588 in plasma were evaluated by noncompartmental analysis (WinNonlin Pro 3.1, Pharsight Corp., Mountain View, CA). Whenever feasible, the following pharmacokinetic variables were calculated from the plasma concentration versus time profiles of imatinib: T_{max} (sampling time when maximum measured plasma concentration occurs), C_{max} (maximum measured plasma concentration), λz (terminal disposition rate constant calculated by linear regression analysis to the log-linear concentration versus time plot), $t_{1/2}$ (apparent terminal disposition half-life), AUC_{last} and AUC_{inf} (areas under the concentration versus time curve from time 0 to the last sampling time point and from time 0 to infinity calculated using the linear/log trapezoidal rule), CL/F (apparent clearance calculated by oral dose divided by AUC_{inf}), and C_{min} (the trough concentrations following ≥8-day period of treatment). For AUC_{inf}, CL/F, and $t_{1/2}$ calculations, patients with extrapolated AUC (AUC_{last} − AUC_{inf}) >40% were excluded for summary statistics. Because the number of patients per dose group was small in this dose-finding study, the AUC, C_{max}, and C_{min} were dose normalized for statistical analysis (mean, SD, and geometric mean). A Student's unpaired *t* test with equal variance was used to evaluate the treatment effect on the dose-normalized AUC, C_{max}, CL/F, $t_{1/2}$, metabolite/parent AUC ratio, and C_{min}. $P < 0.05$ (one-tailed) was considered to be statistically significant.

Genotyping analysis

Paraffin-embedded tumor tissue was obtained from phase II patients when available. Laser-capture microdissection was done in areas containing normal tissue to ensure that >85% tumor cells were used for the genotyping analysis. In cases where the slides contained only tumor cells, dissection was carried out manually. DNA was obtained from tumors using standard methods. The following analyses were done: (*a*) epidermal growth factor receptor (EGFR) copy number measurement by real-time PCR in relation to a pool of four control genes using standard procedures (23), (*b*) EGFRvIII variant copy number on samples with EGFR amplification detected in (*a*), PCR and direct sequencing of (*c*) PTEN exons 2 to 9 and (*d*) p53 exons 2 to 11, and (*e*) kinase domain of PDGFRA and PDGFRB genes. All sequence reactions were done with standard dye terminator technology. Results were analyzed using the Mutation Surveyor software (Millenium Science, Surrey Hills, Victoria, Australia) followed by manual verification of traces. Sequence variants were repeated to confirm results.

Statistical considerations

The primary end points for the phase I component were to determine the MTD for group A (non-EIAED) and group B (EIAED) patients and characterize the toxicities and pharmacokinetics of imatinib. The primary end point in the phase II component was 6-month progression-free survival (6M-PFS) from the time of registration. In a retrospective review of eight consecutive negative phase II trials in recurrent malignant gliomas from the M.D. Anderson Cancer Center, the 6M-PFS was 15% for glioblastoma multiforme and 31% for anaplastic glioma (2). The phase II study included both glioblastoma multiforme and anaplastic glioma patients who were entered at an ~2:1 ratio. The study was sized to be able to discriminate between 20% and 40% rates of 6M-PFS for the entire cohort and 15% and 35% rates for the glioblastoma multiforme group alone. The glioblastoma multiforme comparison was the one of primary concern. With accrual of 32 glioblastoma multiforme patients, the trial would be considered a success if at least 8 glioblastoma multiforme patients showed 6M-PFS. This would give a 0.92 probability of detecting a 35% rate of 6M-PFS, with 0.9 probability of rejecting the agent if the 6M-PFS was only 15%. Assuming an accrual of ~16 anaplastic glioma patients, there would be a reasonable power to discriminate between 20% and 40% rates of 6M-PFS for the entire group. For the group as a whole, imatinib would be considered effective if at least 30% 6M-PFS was observed. This rule gave at least a 0.9 probability of detecting a 40% rate of 6M-PFS, with at least a 0.9 probability of rejecting the drug if the 6M-PFS was only 20%.

Results

Phase I component

Patient characteristics. Fifty eligible patients were enrolled into the phase I component. Patient characteristics are summarized in Table 1. Twenty-three patients were in group A (non-EIAED) and 27 were in group B (EIAED). There were 30

men and 20 women. Median age was 47 years (range, 18-73 years) and median Karnofsky performance score was 90 (range, 60-100). There were 35 glioblastoma multiformes and 15 anaplastic gliomas. Patients had a median of one prior chemotherapy regimen (range, 0-3).

MTDs and toxicities. The MTD for group A (non-EIAED) patients was 800 mg/d imatinib. DLTs included neutropenia, rash, and elevated alanine aminotransferase (Table 2). Group B (EIAED) patients received up to 1,200 mg/d imatinib without developing DLT. Additional dose escalation above 1,200 mg/d in EIAED patients was not pursued after the development of i.c. hemorrhages in five patients in the phase II study and lack of efficacy in non-EIAED patients became apparent. Other imatinib-related toxicities included hypophosphatemia, thrombocytopenia, leukopenia, lymphopenia, dyspnea, pneumonitis, and arthralgia (Table 2).

Response data. One glioblastoma multiforme patient who received 1,000 mg/d imatinib in the non-EIAED group had a partial response. There were 19 patients with stable disease at the first magnetic resonance imaging at 8 weeks [10 non-EIAED patients (9 glioblastoma multiforme and 1 anaplastic oligodendroglioma) and 9 EIAED patients (3 glioblastoma multiforme, 5 anaplastic oligodendroglioma, and 1 anaplastic astrocytoma)].

Pharmacokinetic results. Of the 50 patients enrolled into the phase I component, pharmacokinetic data were available from 25 patients [14 group A (non-EIAED) and 11 group B (EIAED)] following dosing on day 1 and steady-state trough pharmacokinetic samples from 15 patients (6 group A and 9 group B). Pharmacokinetic variables for imatinib and its metabolite CGP74588 are summarized in Tables 3 and 4. Comparison of AUCs for imatinib and CGP74588 between EIAED and non-EIAED patients is shown in Fig. 1A and B. Because of limited and unbalanced subject numbers at different dose levels, definitive conclusions about dose-exposure relationship could not be drawn. Nonetheless, it seemed that in group A (without EIAED), the plasma exposure of both imatinib and CGP74588 increased with dose. In group B (with EIAED), the AUC of imatinib showed a smaller increase at the same dose level, whereas CGP74588 showed a dose-exposure relationship comparable with group A up to 800 mg/d; the relationship at higher doses was unclear given the limited data.

Compared with group A, patients taking EIAEDs (group B) showed a 61% lower dose-normalized imatinib C_{max} and 72.5% lower dose-normalized AUC_{inf} (68.5% based on AUC_{last}). These results are consistent with those observed in the study of imatinib combined with rifampicin, a potent CYP3A inducer (24). The effect of EIAED on the dose-normalized CGP74588 exposure seemed to be minimal following the first dose. There was no difference in dose-normalized C_{max} and only ~10% decrease in dose-normalized AUC. The metabolite to parent drug AUC ratio showed ~3-fold increase in the presence of EIAEDs. At steady state, the dose-normalized C_{min} decreased by 79% for imatinib and by 40% for CGP74588 in the presence of EIAEDs. Unfortunately, no AUC and C_{max} exposure data were available at steady state. The metabolite to parent drug C_{min} ratio increased by 2.8-fold when compared with imatinib taken alone.

Table 1. Patient characteristics in phase I component

Patient characteristics	Patients, *n* (%)
No. eligible patients	50
Anticonvulsants	
EIAED	27 (54)
Non-EIAED	23 (46)
Sex	
Male	30 (60)
Female	20 (40)
Age (y)	
Median	47
Range	18-73
Performance status	
Median	90
100	8 (16)
90	18 (36)
80	13 (26)
70	8 (16)
60	3 (6)
Histology	
Glioblastoma multiforme	35 (70)
Anaplastic glioma	15 (30)
Anaplastic astrocytoma	4 (8)
Anaplastic oligodendroglioma	7 (14)
Anaplastic oligoastrocytoma	3 (6)
Meningioma	1 (2)
Prior chemotherapy regimens	
Median	1
0	6 (12)
1	21 (42)
2	22 (44)
3	1 (2)

Phase II component

Patient characteristics. Fifty-five eligible group A (non-EIAED) patients were enrolled into the phase II component. Six group A patients in the phase I component who received the MTD used in the phase II component and fulfilled all other phase II eligibility criteria were included in the phase II analysis. The study closed before the MTD was determined for group B (EIAED) patients. As a consequence, no group B patients were enrolled into the phase II component of the study. There were 30 men and 25 women with a median age of 51 years (range, 27-73 years). There were 34 glioblastoma multiforme and 21 anaplastic glioma patients (14 anaplastic astrocytoma, 5 anaplastic oligodendroglioma, and 2 anaplastic oligoastrocytoma). Median Karnofsky performance score was 80 (range, 60-100). The patients had a median of 1 prior chemotherapy regimen (range, 0-4; Table 5). All glioblastoma multiforme patients and 6 anaplastic glioma patients received 800 mg/d imatinib; 15 anaplastic glioma patients received 600 mg/d imatinib.

Toxicity data. Five patients (4 glioblastoma multiforme and 1 anaplastic glioma) treated with 800 mg/d imatinib developed intratumoral hemorrhages all in the setting of progressive disease. One patient had a prior history of hemorrhage and one had grade 3 thrombocytopenia at the time of the hemorrhage. The other patients had normal platelet counts and no evidence of a coagulopathy at the time of the hemorrhages. No hemorrhages were observed in the 15 anaplastic glioma patients treated with 600 mg/d imatinib. Imatinib was otherwise generally well tolerated (Table 6). Four patients required dose reduction (one each for thrombocytopenia, fatigue, granulocytopenia, and hypophosphatemia).

Table 2. Cycle 1 adverse events related to imatinib in phase I component

Adverse events	Group A (non-EIAED; *n* = 23)				Group B (EIAED; *n* = 27)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic								
Anemia	8	0	0	0	10	0	0	0
Leukopenia	9	0	0	0	10	0	0	0
Granulocytopenia	2	1	0	1	4	0	0	1
Lymphopenia	0	3	1	0	0	1	0	0
Thrombocytopenia	8	0	0	0	7	0	0	0
Nonhematologic								
Abdominal pain	4	0	0	0	2	0	0	0
Alkaline phosphatase	3	0	0	0	2	0	0	0
Anorexia	0	0	0	0	1	0	0	0
Arthralgia	0	0	0	0	0	0	1	0
Bicarbonate (low)	1	0	0	0	0	0	0	0
Bilirubin (elevated)	0	0	0	1	0	0	0	0
Drowsiness	0	0	0	0	1	0	0	0
Diarrhea	3	0	0	0	0	0	0	0
Dizziness	4	2	0	0	0	1	0	0
Dyspnea	0	0	0	0	0	1	0	0
Edema	6	0	0	0	3	2	0	1
Elevated liver function test	7	0	1	0	1	1	0	0
Fatigue	6	0	0	0	9	1	0	0
Headaches	3	1	0	0	3	0	0	0
Heartburn	2	0	0	0	2	0	0	0
Hypocalcemia	2	0	0	0	3	0	0	0
Hypophosphatemia	0	1	0	0	0	1	0	
Nausea	4	0	0	0	10	0	0	0
Proteinuria	2	0	0	0	0	0	0	0
Rash	1	1	0	0	0	1	0	0
Tremor	2	0	0	0	1	0	0	0
Vomiting	2	0	0	0	1	0	0	0

Efficacy data. Of the 34 glioblastoma multiforme patients, there were 0 complete response, 2 partial response, and 6 stable disease. One patient was removed from the study for toxicity and was not evaluable for efficacy. The 6M-PFS was 3% (1 of 33). Among the 21 anaplastic glioma patients, there were 0 complete response, 0 partial response, and 5 stable disease. One patient was not evaluable for efficacy because of early withdrawal for toxicity. The 6M-PFS was 10%.

Results of genotyping studies. Tumor specimens were available from 27 phase II patients, but reliable results were obtained from only 20 tumor samples. The frequency of *PTEN* mutations was lower than that reported (15% versus 30-40%; ref. 25). We identified 6 *PTEN* sequence variants, of which only 3 are likely to be of pathogenic significance. The average number of *EGFR* copies in cases with amplification was 62.5 (range, 4-477) copies per cell. The EGFRvIII variant was detected only in tumors with amplified *EGFR* gene, with a single exception. No tumors with *EGFR* amplification had p53 mutations (26, 27). *PTEN* mutations were detected in both tumors without other detectable lesions ($n = 2$) and those with concurrent p53 mutations ($n = 3$) or *EGFR* amplification ($n = 1$). No pathogenic mutations were detected in the kinase domain of *PDGFRA* and *PDGFRB* genes. Two synonymous single nucleotide polymorphisms, P567P in PDGFRA and L867L in PDGFRB, were found to have a high prevalence of the reported minor allele (93% and 47%, respectively). There are no reports on the frequency of the PDGFRA single nucleotide polymorphism, and the PDGFRB single nucleotide polymorphism has a frequency similar to that of other cancers.[13] The tumor from one of the responders had mutations in both *p53* and *PTEN* genes. Amplification of *EGFR* without accompanying EGFRvIII variant was detected in the tumor of a second responder. The small number of samples and responders did not allow for correlation of genotype with response.

Discussion

In this study, the MTD of imatinib in malignant glioma patients not receiving EIAED was 800 mg/d. EIAED patients were able to receive up to 1,200 mg/d imatinib without developing DLTs. Pharmacokinetic studies show that the mean plasma exposure of imatinib was significantly reduced in EIAED patients compared with patients not on EIAED. In EIAED patients, the imatinib plasma exposure decreased by ~70% following the first dose and 79% based on trough level at steady state. The metabolite CGP74588, which has similar activity in inhibiting PDGFR as the parent drug, showed little change (only ~10%) in AUC following the first dose but 40% decrease based on the trough level at steady state. The difference in the decrease in levels between imatinib and CGP74588 and between single dose and steady-state C_{min} may be due to differences in elimination pathways between imatinib and CGP74588. In addition, the decrease in exposure may be overestimated by C_{min} compared

[13] Sellers and Meyerson, personal communication.

Table 3. Pharmacokinetic variables of imatinib and its metabolite CGP74588 [mean ± SD (geometric mean)] following the first dose without EIAED (group A) and with EIAED (group B)

	Group A (non-EIAED; n = 14)	Group B (EIAED; n = 11)	Change with EIAEDs*
Imatinib			
Dose-normalized C_{max} (ng/mg)	4.8 ± 2.9 (4.1)	1.8 ± 0.77 (1.6)	61.0% decrease†
T_{max} (h)‡	4 (1-24)	4 (2-10)	—
Dose-normalized AUC_{last} (ng·h/mL/mg)	71.6 ± 42.6 (61.5)	20.6 ± 7.3 (19.4)	68.5% decrease†
Dose-normalized AUC_{inf} (ng·h/mL/mg)§	86.5 ± 37.3 (78.3)	22.8 ± 8.2 (21.5)	72.5% decrease†
CL/F (L/h)	14.4 ± 8.1 (12.8)	49.3 ± 17.5 (46.5)	3.6-fold increase†
$t_{1/2}$ (h)	13.7 ± 6.7 (12.5)	8.2 ± 1.7 (8.1)	35.6% decrease†
CGP74588			
Dose-normalized C_{max} (ng/mg)	0.69 ± 0.45 (0.58)	0.67 ± 0.31 (0.60)	No difference
T_{max} (h)‡	6 (3-32)	9 (2-24)	—
Dose-normalized AUC_{last} (ng·h/mL/mg)	11.3 ± 7.4 (9.2)	10.5 ± 5.7 (9.2)	No difference
Dose-normalized AUC_{inf} (ng·h/mL/mg)	16.4 ± 10.8 (13.3)	13.5 ± 6.9 (12.0)	9.8% decrease
CGP74588/imatinib AUC_{last} ratio	0.16 ± 0.05 (0.15)	0.44 ± 0.09 (0.43)	2.9-fold increase†
CGP74588/imatinib AUC_{inf} ratio	0.17 ± 0.06 (0.16)	0.50 ± 0.11 (0.49)	3.1-fold increase†

*Comparison using geometric mean.
†$P < 0.05$, significant difference between groups A and B.
‡Median (range).
§Four patients in group A and two patients in group B were excluded for AUC_{inf}, CL/F, and $t_{1/2}$ calculations because the extrapolated AUCs were >40%.

with AUC and C_{max}. Nonetheless, the overall AUC exposure of imatinib and CGP74588 was decreased in the presence of EIAED (by 63% or 2.7-fold) from a total 91.6 ng h/mL/mg dose of imatinib in group A (non-EIAED; 78.3 ± 13.3 ng h/mL/mg) to 33.5 ng h/mL/mg dose of imatinib in group B (EIAED; 21.5 ± 12.0 ng h/mL/mg). Thus, to achieve comparable total plasma exposure for both imatinib and CGP74588 between the two groups, the imatinib dose for patients on EIAEDs would have to be ~2.7-fold higher than the imatinib dose for non-EIAED patients. These results underscore the significance of avoiding medications that induce CYP3A4 metabolism in patients receiving imatinib for other malignancies. Given the limited efficacy of imatinib in the phase II component in non-EIAED patients and possible toxicity from intratumoral hemorrhage, the study was closed before the MTD in EIAED patients could be determined.

In the phase II component, the 6M-PFS for glioblastoma multiforme patients was 3%, whereas that for anaplastic glioma was 10%. In comparison, a retrospective review of negative phase II trials in recurrent malignant gliomas from the M.D. Anderson Cancer Center found a 6M-PFS of 15% for glioblastoma multiforme and 31% for anaplastic glioma (2). The results are especially disappointing for anaplastic gliomas where the relative importance of PDGF raised the possibility of potential benefit from imatinib.

The European Organization for Research and Treatment of Cancer and the North Central Cancer Treatment Group are also conducting phase II studies of imatinib in recurrent gliomas. In the European Organization for Research and Treatment of Cancer study, glioblastoma multiforme and anaplastic glioma patients were initially treated with imatinib at a dose of 300 mg twice daily, increasing after 8 weeks to 400 mg twice daily if no grade II toxicity was observed. Subsequently, the protocol was amended to treat patients initially with 400 mg imatinib twice daily, increasing to 500 mg twice daily if no toxicity was observed after 8 weeks. The majority of these patients were on EIAED, and there was no attempt to adjust the dose according to the type of AED. Preliminary results of the European Organization for Research and Treatment of Cancer phase II study in glioblastoma multiforme patients showed 3 partial response and 5 stable disease over 6 months in 51 patients, with a 6M-PFS of 15.7% (28, 29). In anaplastic glioma patients, there was only 1 partial response in 36 anaplastic oligodendroglioma/anaplastic oligoastrocytoma patients and 1 partial response in 25 anaplastic astrocytoma patients (30). These results are consistent with our findings and suggest that

Table 4. Dose-normalized trough plasma concentrations [mean ± SD (geometric mean)] of imatinib and its metabolite CGP74588 at steady state without EIAED (group A) and with EIAED (group B)

Dose-normalized C_{min} (ng/mL/mg) at steady state	Group A (non-EIAED; n = 6)	Group B (EIAED; n = 9)	Change with EIAEDs
Imatinib	3.0 ± 1.4 (2.8)	0.72 ± 0.53 (0.58)	79.3% decrease*
CGP74588	0.81 ± 0.46 (0.70)	0.48 ± 0.26 (0.42)	40.0% decrease†
CGP74588/imatinib ratio	0.26 ± 0.07 (0.25)	0.83 ± 0.49 (0.71)	2.8-fold increase*

*$P < 0.05$, significant difference between groups A and B.
†$P = 0.051$, nonsignificant difference between groups A and B.

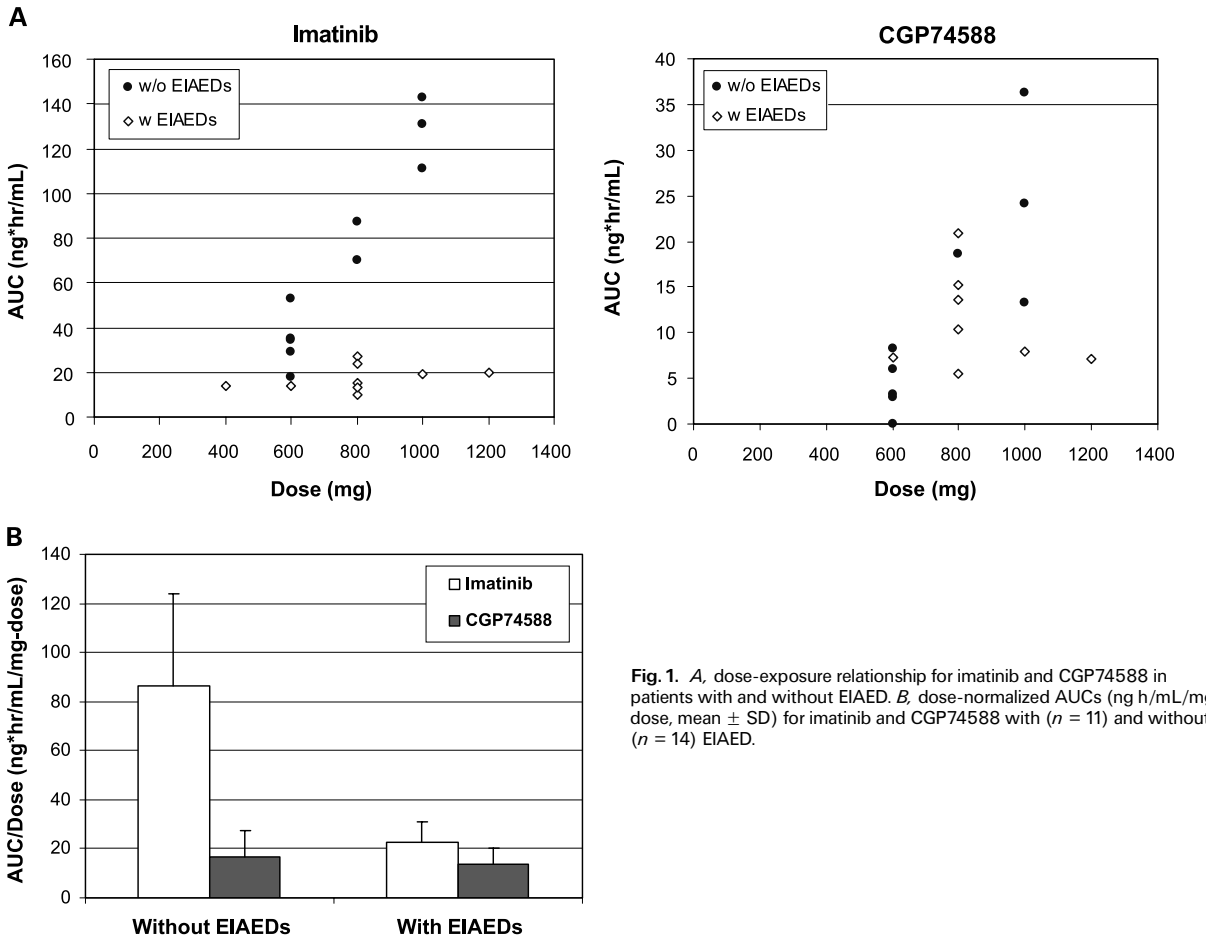

Fig. 1. *A,* dose-exposure relationship for imatinib and CGP74588 in patients with and without EIAED. *B,* dose-normalized AUCs (ng h/mL/mg dose, mean ± SD) for imatinib and CGP74588 with (n = 11) and without (n = 14) EIAED.

imatinib has minimal single-agent activity in malignant gliomas.

There are several potential reasons for the disappointing results with single-agent imatinib in malignant gliomas. The penetration of the drug across the blood-brain barrier is likely to be limited by P-glycoprotein and other efflux pumps, reducing tumor concentrations of the drug (31–34). In chronic myelogenous leukemia patients with an intact blood-brain barrier, the total imatinib concentrations in the cerebrospinal fluid are ~1.3% of that in plasma (0.044 μg/mL; 0.088 ± 0.029 μmol/L) compared with 3.27 μg/mL (6.54 ± 0.93 μmol/L; refs. 32, 33), which is 3.8-fold below the free concentration in plasma (~5%; ref. 35), suggesting involvement of an active transporter for the efflux of imatinib from cerebrospinal fluid to the systemic circulation. Although the imatinib concentrations in malignant gliomas may be increased as a result of a partially disrupted blood-brain barrier, the generally lower concentrations of imatinib in the central nervous system probably contribute to its limited efficacy. Of note, the one phase I patient who had a partial response in group A (non-EIAED) received 1,000 mg imatinib, a dose that ultimately turned out to be above the MTD. Unfortunately, a full pharmacokinetic profile was not available for this patient. The trough plasma concentration on day 8 following the first 1,000 mg dose reached 1,900 ng/mL (~3.8 μmol/L, imatinib molecular weight, 494 Da; i.e., 0.2 μmol/L free plasma concentration assuming a 5% free fraction in plasma). This free plasma level is ~2 times the IC_{50} (0.1 μmol/L) of imatinib for inhibition of PDGFR. However, if the presence of P-glycoprotein transporter at the blood-brain barrier is taken into consideration, the concentration of imatinib, even when combined with CGP74588, may be slightly below the IC_{50}. The use of PDGFR inhibitors with improved central nervous system penetration or the combination of imatinib with drugs that inhibit P-glycoprotein may potentially result in higher central nervous system concentrations and greater efficacy.

A second reason for the limited activity of imatinib may be that inhibition of PDGFR alone is insufficient to prevent growth of malignant gliomas. Signaling through the Ras/mitogen-activated protein kinase and Akt pathways as a result of EGFR amplification and mutations and deletion of PTEN, respectively, may result in tumor growth even in the presence of PDGFR inhibition. In addition, the importance of PDGF signaling in tumor maintenance in malignant gliomas is unclear. Although there is evidence that PDGFR autocrine loops contributes to both initiation of the transformation process and tumor maintenance (4, 10, 36–38), it is possible that other growth factors and signaling pathways play a greater role in maintaining the transformed phenotype. An attempt was made to correlate

Table 5. Patient characteristics in phase II component

Patient characteristics	Patients, *n* (%)
No. eligible patients	55
Anticonvulsants	
Non-EIAED	55 (100)
Sex	
Male	30 (55)
Female	25 (45)
Age (y)	
Median	52
Range	27-73
Performance status	
Median	80
100	6 (11)
90	18 (32.5)
80	18 (32.5)
70	11 (20)
60	2 (4)
Histology	
Glioblastoma multiforme	34 (62)
Anaplastic glioma	21 (38)
Anaplastic astrocytoma	14 (25)
Anaplastic oligodendroglioma	5 (9)
Anaplastic oligoastrocytoma	2 (4)
Prior chemotherapy regimens	
Median	1
0	2 (4)
1	27 (49)
2	21 (38)
3	5 (9)

tumor genotype with response. However, no conclusions could be reached as a result of the limited number of tumor specimens available and the very small number of responders. No activating mutations were detected in the kinase domain of PDGFRA and PDGFRB genes in the tumor specimens analyzed.

In the phase II study, imatinib was generally well tolerated. However, 5 of the 55 patients developed intratumoral hemorrhage in the setting of progressive disease. Although spontaneous hemorrhages can occur in malignant gliomas with a prevalence of up to 3.5% (39, 40), the rate observed in this study is higher than expected. A review of three NABTC recurrent malignant glioma trials conducted at the same time as this study (NABTC 99-01: phase I/II study of R115777, NABTC 99-05: phase II study of fenretinide, and NABTC 99-07: phase I/II study of temozolomide and CPT-11) showed 4 hemorrhages in 184 patients (2.2%). The precise mechanism for the increased rate of hemorrhage is unclear but may be partly related to the inhibition of PDGFRβ on pericytes. Hemorrhages have also been observed in the Pediatric Brain Tumor Consortium study of imatinib with radiotherapy in brainstem gliomas but only in small numbers in other studies of imatinib in malignant gliomas in adults (28–30, 41, 42).

There are several studies evaluating the therapeutic efficacy of imatinib in combination with other agents in malignant gliomas. Dresemann combined imatinib (400 mg/d) with hydroxyurea (1,000 mg/d) in an attempt to improve central nervous system penetration of imatinib in patients with malignant gliomas (41). In a preliminary study of 30 patients with recurrent glioblastoma multiforme treated with this regimen, there was encouraging activity with 20% partial response and a 6M-PFS of 32%. Reardon et al. treated 33 recurrent glioblastoma multiforme patients with the same regimen for non-EIAED patients and imatinib (1,000 mg/d) and hydroxyurea (1,000 mg/d) for EIAED patients (42). Three (9%) patients achieved a partial response and 14 (42%) had stable disease; 6M-PFS was 27%. The reason for the increased activity of the combination of imatinib with hydroxyurea is unclear but may include complementary antiangiogenic activity, reduction of tumor interstitial pressure by imatinib resulting in enhanced chemotherapy delivery, or enhanced drug delivery as a result of modulation of ATP-dependent transporter proteins (42). The ultimate value of these and other combinations and the precise mechanisms await further studies.

Conclusions

The MTD of imatinib in malignant glioma patients not receiving EIAED was 800 mg/d. DLTs were neutropenia, rash, and elevated alanine aminotransferase. Patients on EIAED were able to receive up to 1,200 mg/d imatinib without developing DLT. The mean plasma exposures of imatinib in EIAED patients were reduced by as much as 70% compared with patients not on EIAED. CYP3A4 inducers, such as EIAEDs, should be avoided in patients receiving imatinib for other indications, such as chronic myelogenous leukemia and gastrointestinal stromal tumor. Single-agent imatinib seems to have only minimal activity in malignant gliomas and may be associated with a slightly increased risk of intratumoral hemorrhage. The evaluation of the activity of combination regimens incorporating imatinib is under way in several trials.

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Table 6. Adverse events related to imatinib in phase II component

Adverse events	Group A (non-EIAED; *n* = 55)	
	Grade 3	Grade 4
Hematologic		
Leukopenia	3	0
Neutropenia	2	0
Lymphopenia	2	0
Thrombocytopenia	1	0
Nonhematologic		
Central nervous system hemorrhage	3	2
Constipation	1	0
Diarrhea	2	0
Edema	3	0
Elevated lactate dehydrogenase	1	0
Fatigue	3	0
Hypokalemia	1	0
Hyponatremia	1	0
Hypophosphatemia	4	0
Infection without neutropenia	1	0
Ischemia	1	0
Pruritis	1	0
Rash	3	0

Appendix A. NABTC Investigators Prime Award CA62399

Institution	Investigators	NABTC grant	General Clinical Research Center grant
University of California-San Francisco	Michael Prados, M.D.,* Susan Chang, M.D.	CA62422	M01-RR00079
University of Texas M. D. Anderson	W.K.A. Yung, M.D.,* Kurt Jaeckle, M.D.	CA62412	—
University of Texas Southwestern	Karen Fink, M.D., Ph.D.*	CA62455	M01-RR00633
Dana-Farber Cancer Center	Patrick Wen, M.D.	CA62407	—
University of Pittsburgh	Frank Lieberman, M.D.*	CA62404	M01-RR00056
University of Texas San Antonio	John Kuhn, PharmD*	CA62426	M01-RR0134
University of California-Los Angeles	Timothy Cloughsey, M.D.*	CA62399	M01-RR0865
University of Michigan	Larry Junck, M.D.*	CA62399	M01-RR00042
University of Wisconsin	Minesh Mehta, M.D.,* I.H. Robbins, M.D., Ph.D.	CA62421	M01-RR03186

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References

1. Levin VA, Leibel SA, Gutin PH. Neoplasms of the central nervous system. Cancer: principles and practice of oncology. In: DeVita VT, Jr., Hellman S, Rosenberg SA, editors. Philadelphia (PA): Lippincott-Raven Publishers; 1997. p. 2022–73.
2. Wong ET, Hess KR, Gleason MJ. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. J Clin Oncol 1999; 17:2572–8.
3. Pietras K, Sjoblom T, Rubin K, Heldin C-H, Ostman A. PDGF receptors as cancer targets. Cancer Cell 2003; 3:439–43.
4. Maher EA, Furnari FB, Bachoo RM, et al. Malignant glioma: genetics and biology of a grave matter. Genes Dev 2001;15:1311–33.
5. Guha A, Dashner K, Black PM, et al. *In vivo* expression of PDGF and PDGF receptors in human astrocytomas. Int J Cancer 1995;60:168–73.
6. Nister ML, Claesson-Welcsh L, Eriksson A, et al. Differential expression of platelet-derived growth factor receptors in human malignant glioma cell lines. J Biol Chem 1991;266:16755–63.
7. Hermanson M, Funa K, Hartman L, et al. Platelet-derived growth factor and its receptors in human glioma tissue: expression of messenger RNA and protein suggests the presence of autocrine and paracrine loops. Cancer Res 1992;52:3213–9.
8. Maxwell M, Naber SP, Wolfe HJ, et al. Coexpression of platelet-derived growth factor (PDGF) and PDGF-receptor genes by primary human astrocytomas may contribute to their development and maintenance. J Clin Invest 1990;86:131–40.
9. Feldkamp MM, Lau N, Guha A. Signal transduction pathways and their relevance in human astrocytomas. J Neuro-Oncol 1997;35:223–48.
10. Shamah SM, Stiles CD, Guha A. Dominant-negative mutants of a platelet-derived growth factor revert the transformed phenotype of human astrocytoma cells. Mol Cell Biol 1993;13:7203–12.
11. Buchdunger E, Cioffi CL, Law N, et al. Abl protein-tyrosine kinase inhibitor STI571 inhibits *in vitro* signal transduction mediated by c-kit and platelet-derived growth factor receptors. J Pharmacol Exp Ther 2000; 295:139–45.
12. Capdeville R, Buchdunger E, Zimmerman J, Matter A. Glivec (STI571, imatinib), a rationally developed targeted anticancer drug. Nat Rev Drug Discov 2002;1: 493–502.
13. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 2001;344:1031–7.
14. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347: 472–80.
15. Kilic T, Alberta J, Zdunek PR, et al. Intracranial inhibition of platelet-derived growth factor-mediated glioblastoma cell growth by an orally active kinase inhibitor of the 2-phenylaminopyrimidine class. Cancer Res 2000;60:5143–50.
16. Guo P, Hu B, Gu W, et al. Platelet derived growth factor-B enhances glioma angiogenesis by stimulating vascular endothelial growth factor expression in tumor endothelia and by promoting pericyte recruitment. Am J Pathol 2003;162:1083–93.
17. Prados MD, Yung WK, Jaeckle KA, et al. Phase 1 trial of irinotecan (CPT-11) in patients with recurrent malignant glioma: a North American Brain Tumor Consortium study. Neuro-oncol 2004;6:44–54.
18. Vecht CJ, Wagner GL, Wilms EB. Treating seizures in patients with brain tumors: drug interactions between antiepileptic and chemotherapeutic agents. Semin Oncol 2003;30:49–52.
19. Black PM, Carroll R, Glowacka D, et al. Platelet-derived growth factor expression and stimulation in human meningiomas. J Neurosurg 1994;81:388–93.
20. Maxwell M, Galanopoulos T, Hedley-Whyte ET, et al. Human meningiomas co-express platelet-derived growth factor (PDGF) and PDGF-receptor genes and their protein products. Int J Cancer 1990;46:16–21.
21. Macdonald DR, Cascino TL, Schold SC, Jr., Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 1990; 8:1277–80.
22. Parise RA, Ramanathan RK, Hayes MJ, et al. Liquid chromatographic-mass spectrometric assay for quantitation of imatinib and its main metabolite (CGP 74588) in plasma. J Chromatogr B Analyt Technol Biomed Life Sci 2003;791:39–44.
23. Goff LK, Neat MJ, Crawley CR, et al. The use of real-time quantitative polymerase chain reaction and comparative genomic hybridization to identify amplification of the REL gene in follicular lymphoma. Br J Haematol 2000;111:618–25.
24. Bolton AE, Peng B, Hubert M, et al. Effect of rifampicin on the pharmacokinetics of imatinib mesylate (Gleevec, STI571) in healthy subjects. Cancer Chemother Pharmacol 2004;53:102–6.
25. Rasheed BK, Wiltshire RN, Bigner SH, Bigner DD. Molecular pathogenesis of malignant gliomas. Curr Opin Oncol 1999;11:162–7.
26. Bigner SH, Vogelstein B. Cytogenetics and molecular genetics of malignant gliomas and medulloblastoma. Brain Pathol 1990;1:12–8.
27. Cavenee WK, Scrable HJ, James CD. Molecular genetics of human cancer predisposition and progression. Mutat Res 1991;247:199–202.
28. van den Bent M, Brandes AA, Van Oosterom A, et al. Multicentre phase II study of imatinib mesylate (Gleevec®) in patients with recurrent glioblastoma: an EORTC: NDDG/BTG Intergroup Study. Society for Neuro-Oncology Ninth Annual Meeting; 2004; Toronto, Ontario, Canada.
29. Raymond E, Brandes A, Van Oosterom A, et al. Multicentre phase II study of imatinib mesylate in patients with recurrent glioblastoma: an EORTC: NDDG/BTG Intergroup Study [abstract 1501]. J Clin Oncol 2004;22:107S.
30. van den Bent M, Brandes AA, Van Oosterom A, et al. Multicentre phase II study of imatinib mesylate in patients with recurrent anaplastic oligodendroglioma (AOD)/mixed oligoastrocytoma (MOA) and anaplastic astrocytoma (AA)/low grade astrocytoma (LGA): an EORTC New Drug Development Group (NDDG) and Brain Tumor Group (BTG) study [abstract 1517]. J Clin Oncol 2005;23:118S.
31. Dai H, Marbach P, Lemaire M, et al. Distribution of STI-571 to the brain is limited by P-glycoprotein-mediated efflux. J Pharmacol Exp Ther 2003;304: 1085–92.
32. Leis JF, Stepan DE, Curtin PT, et al. Central nervous system failure in patients with chronic myelogenous leukemia lymphoid blast crisis and Philadelphia chromosome positive acute lymphoblastic leukemia treated with imatinib (STI-571). Leuk Lymphoma 2004;45: 695–8.
33. Neville K, Parise RA, Thompson P, et al. Plasma and cerebrospinal fluid pharmacokinetics of imatinib after administration to nonhuman primates. Clin Cancer Res 2004;10:2525–9.
34. Loscher W, Potschka H. Drug resistance in brain diseases and the role of drug efflux transporter. Nat Rev Neurosci 2005;6:591–602.
35. Peng B, Lloyd P, Schran H. Clinical pharmacokinetics of imatinib. Clin Pharmacokinet 2005;44: 879–94.
36. Strawn LM, Mann E, Elliger SS, et al. Inhibition of glioma cell growth by a truncated platelet-derived growth factor-β receptor. J Biol Chem 1994;269: 21215–22.
37. Uhrbom L, Hesselager G, Nister M, Westermark B. Induction of brain tumors in mice using a recombinant platelet-derived growth factor B-chain retrovirus. Cancer Res 1998;58:5275–9.
38. Vassbotn F, Ostman SA, Langeland N, et al. Activated platelet-derived growth factor autocrine pathway drives the transformed phenotype of a human glioblastoma cell line. J Cell Physiol 1994;158:381–9.
39. Licata B, Turazzi S. Bleeding cerebral neoplasms with symptomatic hematoma. J Neurosurg Sci 2003; 47:201–10.
40. Lieu AS, Hwang SL, Howng SL, Chai CY. Brain tumors with hemorrhage. J Formos Med Assoc 1999;98:365–7.
41. Dresemann G. Imatinib and hydroxyurea in pretreated progressive glioblastoma multiforme: a patient series. Ann Oncol 2005;16:1702–8.
42. Reardon DA, Egorin MJ, Quinn J, et al. Phase II study of imatinib mesylate plus hydroxyurea is adults with recurrent glioblastoma multiforme. J Clin Oncol 2005;23:9359–68.