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Laboratory Investigation

Extreme drug resistance in primary brain tumors: *in vitro* analysis of 64 resection specimens

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Summary

Understanding chemoresistance profiles of brain tumors may aid in more educated selection of chemotherapeutic regimens for clinical trials and patient treatment. Although the literature contains many reports of the application of drug resistance assays, little is known about extreme drug resistance (EDR) in primary brain tumors. We undertook this study to determine chemoresistance profiles for brain tumors. From September 1991 to February 1998, we collected 64 brain tumor specimens from patients admitted to the Johns Hopkins Hospital. Tumors were classified according to the revised World Health Organization system. Brain tumor specimens were tested against 13 different chemotherapeutic agents using an extreme drug resistance assay. Results were reported as percent cell inhibition (PCI) (compared to control cultures). A drug resistance profile (extreme, intermediate, or low) was determined based on statistical comparison to a historical database of tumor specimens tested against the same panel of chemotherapeutic agents. Brain tumor specimens were classified histologically as Grade IV astrocytoma (glioblastoma multiforme, $n = 35$), Grade II/III astrocytoma ($n = 11$), oligodendroglioma ($n = 6$), meningioma ($n = 9$), hemangiopericytoma ($n = 2$), and ependymoma ($n = 1$). A large percentage of glioblastomas displayed extreme drug resistance to paclitaxel (69%, $n = 35$), SN38 (75%, $n = 28$), and vincristine (38%, $n = 29$). The majority of Grade II/III astrocytomas displayed extreme drug resistance to carboplatin (67%, $n = 6$), cisplatin (60%, $n = 10$), and paclitaxel (60%, $n = 10$). In a similar fashion, oligodendrogliomas displayed extreme drug resistance to vincristine (60%, $n = 5$) and paclitaxel (50% $n = 6$). Most meningiomas displayed extreme drug resistance to vincristine (75%, $n = 8$), dacarbazine (63%, $n = 8$), and 4-HC (50%, $n = 8$). Through the continued analysis of brain tumor specimens and compilation of data from multiple institutions, chemoresistance profiles could assist in the development of rationale clinical trials and treatment regimens for patients with brain tumors.

Introduction

Despite many advances in elucidating the molecular mechanisms responsible for cancer, present chemotherapy for primary malignant brain tumors is limited, and the prognosis of patients with these tumors remains poor. Chemotherapy of malignant brain tumors has evolved more slowly than such treatment for other solid tumors, largely given the limitations posed by the blood–brain barrier. Although many chemotherapeutic agents might prove effective in treating primary brain tumors, systemic toxicity and limited central nervous system penetration have proven to be large obstacles in the practical treatment of patients. In addition, the biological heterogeneity of malignancies implies that the optimal chemotherapeutic agent for a given histologic tumor type may vary from one patient to the next. Designing effective therapies for primary brain tumors then requires an understanding of the selective vulnerabilities of their constituent cells.

Chemosensitivity and chemoresistance testing have been controversial as adjuncts to the treatment of cancer [1]. *In vitro* chemosensitivity tests are poor predictors of clinical response for many reasons, including *in vivo* treatment barriers such as the blood–brain barrier,

alteration and inactivation of drugs, and host-dependent resistance mechanisms [2,3]. Bayes' theorem relates the predictive accuracy of a test to the characteristics of the test and the expected response rate of the patient population [4,5]. This theorem predicts the poor accuracy of chemosensitivity tests. However, it also predicts that extreme drug resistance (EDR) tests are accurate. This finding has been confirmed in several clinical trials, in which extreme drug resistance assays were more than 99% accurate in predicting poor clinical response (independent of cancer type studied) [6–8].

Understanding the chemoresistance profile of a specific tumor could help clinicians avoid ineffective drugs and prevent related side effects. Understanding general resistance profiles of a given histologic tumor type may also aid in more educated selection of chemotherapeutic regimens for clinical trials. Although the literature contains many reports of the application of extreme drug resistance assays, almost nothing is known about extreme drug resistance in primary brain tumors. We report here an *in vitro* analysis of extreme drug resistance in specimens from 64 primary brain tumors.

Material and methods

Tissue specimen collection

From September 1991 to February 1998, we collected 64 brain tumor specimens from patients at Johns Hopkins Hospital undergoing craniotomy. In the operating room, specimens were divided for histological classification and for extreme drug resistance testing. Each brain tumor specimen was reviewed by a pathologist (PCB) and classified according to the revised World Health Organization system [9]. A portion of each surgical specimen was placed aseptically into transport vials containing sterile transport medium (RPMI containing 15% fetal calf serum, 2 mM L-glutamine, 1.25 ng/ml fungizone, and penicillin/streptomycin (200 IU/ml pen. + 200 μg/ml strep.)). Specimens arrived by Federal Express at Oncotech Corporation in Irvine, California 24–48 h after resection. They were assigned a tracking number and then processed.

EDR assay

Specimens were mechanically disaggregated into suspensions of small clumps of cells. Viability was then determined using trypan blue exclusion. Culture was performed as described previously [6,10]. Briefly, viable malignant cells were suspended in soft agar in 24 well plates at an approximate density of 30,000 cells per well. Selected chemotherapeutic agents as listed in Table 1 were added individually to duplicate or triplicate wells at doses that approximated their *in vivo* peak plasma concentrations [6,10]. Tested cell suspensions were incubated for 72 h and then labeled with tritiated thymidine (^{3}H–TdR, Amersham). Cultures were pulsed with ^{3}H–TdR at 5 μCi per well for the last 48 h of the culture period. Culture plates were then heated to 90°C to liquefy the agarose, and cells were harvested onto glass fiber filters and placed into counting vials containing liquid scintillation fluid. The radioactivity trapped on the filters was then counted in a Beckman scintillation counter. Positive (lethal dose cisplatin exposed)

Table 1. Chemotherapeutic agents tested against brain tumors in the EDR assay

Drug name	Abbreviation	Concentration (μM)	Putative mechanism of action
4-Hydroxy-cyclophosphamide	4HC	4.35	Alkylating agent
Carmustine	BCNU	37.0	Cross-linking of DNA
Irinotecan	CPT-11 (SN38)[a]	0.01	Topoisomerase I (Topo I) inhibitor
Carboplatin	CARBO	10.26	Cross-linking of DNA
Cisplatin	CPLAT	1.67	Cross-linking of DNA
Doxorubicin	DOXO	0.017	Intercalates in DNA
Dacarbazine[b]	DTIC	54.95	Temozolomide analog, Topo I inhibitor
Paclitaxel	TAXOL	2.45	Blocks microtubule polymerization
Topotecan	TOPO	0.10	Topo I inhibitor
Vincristine	VCR	0.54	Blocks mitosis with metaphase arrest

[a]Active metabolite of CPT-11 used in the EDR assay. [b]Light-activated drug, cytotoxic in the EDR assay.

and negative (media-exposed) control cultures were performed with each assay to determine ^{3}H–TdR incorporation in treated and untreated control cells. Results were reported as percent cell inhibition (PCI) of media-exposed control cultures.

The performance characteristics for each drug, including the median PCI and standard deviation (SD), were determined prior to the study, employing Oncotech's historic database of over 60,000 test results. Generally, each suspension of brain tumor cells was tested against a panel of 3–7 or more single agents per assay, and individual PCI values for each drug were then compared to the historic median PCI and SD. *In vitro* response to individual drugs was categorized as either 'extreme drug resistance' (EDR) if the PCI was more than one SD below the median; 'intermediate drug resistance' (IDR) if the PCI was between the median and minus 1 SD; or 'low drug resistance' if the PCI was above the median.

The PCI data and extreme drug resistance data for each drug are presented regardless of sample size. However, to better characterize extreme drug resistance, we discuss only those drugs tested against at least half of the brain tumor specimens for each histological grade. We excluded tumors with small sample sizes ($n < 6$) from EDR analysis.

Results

Tumor histology

The 64 brain tumor specimens were classified histologically as Grade IV astrocytoma (glioblastoma multiforme, $n = 35$), Grade II/III astrocytoma ($n = 11$), oligodendroglioma ($n = 6$), meningioma ($n = 9$), hemangiopericytoma ($n = 2$), and ependymoma ($n = 1$). Thirty-five glioblastoma specimens were obtained from 31 patients. One patient had specimens collected at three time points and a second patient had specimens collected at two time points. Eleven specimens of Grade II/III astrocytoma were obtained from 10 patients (one patient with specimens collected at two time points). For all other tumor groups, each specimen corresponded to a single patient. The subset of Grade II/III astrocytomas ($n = 11$) contained eight high-grade (Grade III) and three low-grade specimens (Grade II). The subset of meningiomas ($n = 9$) contained one malignant (Grade III) and one atypical meningioma (Grade II).

Percent cell growth inhibition

In vitro drug responses of the 64 brain tumor specimens assayed against the 10 chemotherapeutic agents were profiled according to histologic type (Table 2). For Grade IV astrocytomas, agents with the lowest median PCI included paclitaxel (1%, SD: 16, $n = 35$), irinotecan (SN38) (15%, SD: 19, $n = 28$), and vincristine (55%, SD: 25, $n = 29$). Given the small sample size of Grade II/III astrocytomas, we pooled these two groups together despite the difference in prognosis. When analyzed separately (data not shown), we found that every drug tested against Grade II astrocytomas (except dacarbazine) had a slightly higher PCI compared to Grade III astrocytomas. For Grade II/III astrocytomas, agents with the lowest median PCI included paclitaxel (11%, SD: 18, $n = 10$), vincristine (35%, SD: 31, $n = 8$), and cisplatin (41%, SD: 35, $n = 10$).

For oligodendrogliomas, drugs with the lowest median PCI included paclitaxel (21%, SD: 20, $n = 6$) and vincristine (36%, SD: 19, $n = 5$). For meningiomas, drugs with the lowest median PCI included vincristine (18%, SD: 28, $n = 8$) and SN38 (42%, SD: 21, $n = 5$). For hemangiopericytomas ($n = 2$), agents with the lowest average PCI included vincristine (14%, $n = 2$), paclitaxel (42%, $n = 2$), and SN38 (59%, $n = 1$). For the ependymoma specimen ($n = 1$), agents with the lowest PCI included camptothecin (1%), paclitaxel (26%), and topotecan (28%).

Frequency of drug resistance

The frequency of *in vitro* drug resistance was determined as described previously, and profiled for 61 of the 64 brain tumor specimens (Table 3). A high percentage of tumors demonstrated either extreme or low drug resistance to standard agents. The GBM specimens displayed a high degree of extreme drug resistance to paclitaxel (69%, $n = 35$), SN38 (75%, $n = 28$), and vincristine (38%, $n = 29$). Only 18% of GBM specimens displayed extreme drug resistance to BCNU ($n = 33$).

Grade II/III astrocytomas displayed the highest degree of extreme drug resistance to carboplatin (67%, $n = 6$), cisplatin (60%, $n = 10$), and paclitaxel (60%, $n = 10$). Oligodendrogliomas displayed the highest degree of extreme drug resistance to vincristine (60%, $n = 5$) and paclitaxel (50%, $n = 6$). The meningioma specimens displayed the highest degree of extreme drug resistance to vincristine (75%, $n = 8$),

Table 2. In vitro drug resistance (percent cell growth inhibition; PCI) profiles for brain tumor patient cohort: comparison of tumor type ($n = 61$)[a]

Tumor grade (n)	4HC	BCNU	SN38[b]	CARBO	CPLAT	DOXO	DTIC	TAX	TOPO	VCR
Glioblastoma ($n = 35$)										
Median PCI	85	86	15	79	91	89	85	1	47	55
Standard deviation	22	30	19	22	23	28	25	16	26	25
(n)	(28)	(33)	(28)	(33)	(35)	(22)	(26)	(35)	(30)	(29)
Astrocytoma II/III ($n = 11$)										
Median PCI	69	87	25	47	41	65	85	11	26	35
Standard deviation	35	35	23	20	35	27	14	18	35	31
(n)	(8)	(8)	(4)	(6)	(10)	(4)	(8)	(10)	(6)	(8)
Oligodendroglioma ($n = 6$)										
Median PCI	65	69	9	80	87	49	74	21	48	36
Standard deviation	30	18	0	7	7	0	12	20	0	19
(n)	(5)	(6)	(1)	(6)	(6)	(1)	(4)	(6)	(1)	(5)
Meningioma ($n = 9$)										
Median PCI	63	58	42	82	91	66	44	46	54	18
Standard deviation	31	35	21	15	10	34	27	18	30	28
(n)	(8)	(8)	(5)	(9)	(9)	(6)	(8)	(9)	(5)	(8)
Cohort ($n = 64$)[a]										
Median PCI	80	85	19	79	88	81	77	18	46	39
Standard deviation	27	30	21	20	24	30	25	20	27	27
(n)	(52)	(59)	(41)	(58)	(64)	(35)	(49)	(64)	(45)	(54)

[a]Hemangiopericytoma and ependymoma discussed in text, bringing total of specimens to 64. [b]SN38 is the active metabolite of CPT-11.

dacarbazine (63%, $n = 8$), and 4-HC (50%, $n = 8$). Meningiomas ($n = 3$) displaying extreme drug resistance to BCNU were cross-resistant to dacarbazine and 4HC. In general, for this cohort of brain tumors, whether patients had prior therapy had no impact on *in vitro* drug resistance (data not shown).

Discussion

The intrinsic chemoresistance of brain tumors is one of the most challenging obstacles in their treatment. During the last thirty years a number of chemosensitivity and chemoresistance assays have been developed in the hope of optimizing the chemotherapeutic regimen of individual patients with cancer [10–14]. Unlike chemosensitivity assays that have an overall positive predictive value of only 69% (inadequate for selection of a chemotherapeutic regimen in clinical practice) [15], chemoresistance assays have an accuracy of greater than 99% in predicting what drugs will not affect a clinical response. This study to our knowledge is the first to examine extreme drug resistance in primary brain tumors. A full understanding of drug resistance profiles could help guide the selection of chemotherapeutic regimens for clinical trials and individual patient treatment.

Grade IV astrocytomas

Nitrosoureas, the most frequently used drug for the treatment of high-grade gliomas [16], had a response rate between 10% and 40% in studies performed during the pre-CT era [17–20]. More recent studies have shown an increase in median survival [21,22] and long-term survival [23,24] (12–24 months) in groups treated with nitrosoureas plus radiation therapy compared to radiation therapy alone. Based on these studies, nitrosoureas remain the gold standard for chemotherapeutic treatment of brain tumors. We found that only a small proportion (18%) of Grade IV astrocytomas displayed extreme drug resistance to BCNU. Agents displaying an even smaller percentage of extreme drug resistance to this histologic type included 2-chlorodeoxyadenosine, doxorubicin, and cisplatin. Although nitrosoureas are widely used for treatment of brain tumors, they produce a limited response in a minority of patients, which has prompted a search for more potent chemotherapeutic agents.

The use of vincristine for malignant gliomas arose from a study published in 1968 in patients with systemic and central nervous system tumors [25]. In that study, clinical improvement was most notable for patients with brain tumors. Although response rates of

Table 3. In vitro drug resistance frequency profile in brain tumor patient cohort: comparison of tumor type ($n = 61$)[a]

Tumor grade (n)	4HC	BCNU	SN38[b]	CARBO	CPLAT	DOXO	DTIC	TAX	TOPO	VCR
Glioblastoma ($n = 35$)										
% EDR	18	18	75	24	14	9	15	69	24	38
% IDR	21	15	21	9	17	5	27	26	43	24
% LDR	61	67	4	67	69	86	58	5	33	38
(n)	(28)	(33)	(28)	(33)	(35)	(22)	(26)	(35)	(30)	(29)
Astrocytoma II/III ($n = 11$)										
% EDR	25	38	25	67	60	25	12	60	50	63
% IDR	37	0	25	0	0	75	25	30	17	12
% LDR	38	62	50	33	40	0	63	10	33	25
(n)	(8)	(8)	(4)	(6)	(10)	(4)	(8)	(10)	(6)	(8)
Oligodendroglioma ($n = 6$)										
% EDR	20	17	100	0	0	0	25	50	0	60
% IDR	40	50	0	33	0	100	50	33	100	40
% LDR	40	33	0	67	100	0	25	17	0	0
(n)	(5)	(6)	(1)	(6)	(6)	(1)	(4)	(6)	(1)	(5)
Meningioma ($n = 9$)										
% EDR	50	37	20	11	0	33	63	11	20	75
% IDR	12	25	60	33	11	17	25	22	20	12
% LDR	38	38	20	56	89	50	12	67	60	13
(n)	(8)	(8)	(5)	(9)	(9)	(6)	(8)	(9)	(5)	(8)

[a]Hemangiopericytoma and ependymoma discussed in text, bringing total of specimens to 64. [b]SN38 is the active metabolite of Irinotecan or CPT-1.

20–50% are found in the literature, the true efficacy of vincristine as a single agent is controversial since these studies were conducted in the pre-CT era [26]. Unfortunately, very few modern studies evaluate the efficacy of vincristine as a single agent. Further doubt of vincristine's effectiveness arises from reports which suggest that vincristine does not cross the blood–brain barrier [27–29]. We found that although a high percentage of Grade IV astrocytomas displayed extreme drug resistance to vincristine, other histological tumor types (Grade II/III astrocytomas, oligodendrogliomas, and meningiomas) displayed an even higher percentage of extreme drug resistance to this agent. Perhaps the prior treatment histories of these patients might have contributed to their tumors' *in vitro* response to this and other chemotherapy drugs.

In clinical trials, paclitaxel displayed a partial response rate of 10–20% and an overall response rate of 35–55% in patients with recurrent primary brain tumors after radiation therapy and initial chemotherapy (predominantly nitrosoureas) [30,31]. However, in a more recent trial of intravenous paclitaxel, none of the 15 patients with glioblastoma multiforme who were assessed showed a radiographic response to the drug (although median survivals were comparable to standard therapy) [32]. Our data show that *in vitro* Grade IV astrocytomas are associated with a high level of extreme drug resistance to paclitaxel. Interestingly, of the brain tumors showing extreme drug resistance to BCNU ($n = 14$), 57% were cross-resistant to paclitaxel.

Grade II/III astrocytomas

Anaplastic astrocytomas have been shown to be more responsive to chemotherapy than glioblastomas. A meta-analysis of randomized trials between 1975 and 1989, has shown a statistically significant survival advantage for patients treated with chemotherapy and radiation therapy (a 10.1% increase in survival at one year and an 8.6% increase in survival at two years, $p = 0.002$) [20]. In this study, patients with anaplastic astrocytomas derived the most benefit.

Carboplatin [33,34] and cisplatin [35] have been used in the treatment of glioblastomas and Grade II/III astrocytomas with modest success. The relevance of these clinical trials has been limited, however, by the failure to stratify for histological grade, functional status of the patient, and prior type of chemotherapy [36]. Despite these encouraging results, Grade II/III astrocytomas displayed a higher percentage of extreme drug resistance to carboplatin and cisplatin than did all other tumor types (glioblastoma, oligodendroglioma, and meningioma).

Oligodendroglioma

PCV chemotherapy (procarbazine, CCNU, vincristine), introduced by Levin et al. [37] in 1980, has been used successfully in the treatment of oligodendrogliomas. Cairncross and Macdonald [38] were the first to demonstrate its benefit in a series of eight consecutive patients with recurrent malignant oligodendroglioma who unexpectedly responded to this regimen. In another study, 75% of patients with anaplastic oligodendrogliomas responded to PCV based on radiological assessment (CT, MRI) with a mean period of tumor control greater than 16 months [39]. PCV was also effective for mixed lesions (oligoastrocytomas) [40,41]. A genetic marker has been found to be predictive of a chemotherapeutic response to the PCV regimen. In that study, researchers found an association between radiographic response in patients with oligodendrogliomas and the loss of the short arm of chromosome 1, or combined loss involving 1p and 19q [42].

Although the PCV regimen is highly effective in the treatment of oligodendrogliomas, we found one of the agents (vincristine) to be associated with a high degree of extreme drug resistance, suggesting that it may be the least effective of the three agents. Analogs of the other two agents (BCNU, dacarbazine) had a significantly lower level of extreme drug resistance, raising the possibility that vincristine could be removed from the regimen without effecting the clinical response. At Johns Hopkins, we no longer administer vincristine for treatment of patients with oligodendrogliomas (Stuart Grossman, personal communication). This is supported by the associated toxicity of vincristine, i.e., peripheral neuropathies and myelosuppression. Eighty-five percent of patients receiving the PCV regimen experience myelosuppression [43].

Numerous other agents have been tested against oligodendrogliomas (melphalan, thiotepa, temazolamide, paclitaxel, BCNU, AZQ, cisplatinum, and carboplatin), but with only modest success [43]. In a recent clinical trial, paclitaxel displayed limited success as salvage chemotherapy in patients with recurrent oligodendrogliomas who were pretreated with radiation and PCV chemotherapy [44]. In our study, oligodendrogliomas displayed a high percentage of extreme drug resistance to paclitaxel.

Meningioma

The role of chemotherapy for meningiomas that have failed surgery and radiation therapy is also not well-defined. Several chemotherapeutic agents have shown modest success including hydroxyurea [45,46] and combination adriamycin/dacarbazine [47]. Immunotherapy with interferon alpha [48] has also shown some success. Other agents including tamoxifen [49] have been tested but have not demonstrated efficacy.

Although there is little in the literature regarding vincristine, dacarbazine, or 4HC for the treatment of recurrent meningiomas, we found at least half of the meningioma specimens to display extreme drug resistance to these agents. Of all the histological tumors that we tested against BCNU, meningiomas displayed the highest percentage of extreme drug resistance. One mechanism of resistance to alkylating agents is O6-alkylguanine-DNA alkyltransferase (AGAT). AGAT reverses alkylation of guanine at the O6 position thereby blocking cross-link formation. Interestingly, in a study of 27 different specimens, meningiomas displayed the highest AGAT activity in comparison to other tumors (sarcomas, glioblastomas, astrocytomas, oligodendrogliomas, and lymphomas) [50]. Glioma cells with high AGAT activity have been shown to be highly resistant to DNA alkylating agents like BCNU.

AGAT and drug resistance

Recent studies of AGAT in tumor samples from 47 glioma patients showed that a methylated form of the AGAT gene was a predictive marker for favorable response to chemotherapy with BCNU and increased survival [51]. All patients in this study received aggressive therapy that included intra-arterial cisplatin, whole-brain radiotherapy, and intravenous BCNU. Patients with methylated genes lived an average of 13 months longer.

A subset of tumor specimens from our 64-patients cohort were included in an immunohistochemical analysis of selected biomarkers including AGAT in paraffin-embedded specimens from a total of 320 malignant glioma patients. The frequency of AGAT protein expression in 190 specimens tested was 65% (19 of our 25 evaluable specimens stained positive for the protein). There was a significantly greater frequency of AGAT protein expression in tumors from previously treated patients compared to treatment naive patients. Further, when tested against BCNU in the drug resistance assay, AGAT-positive tumors exhibited increased *in vitro* resistance to BCNU compared to AGAT-negative tumors.

EDR and therapy for gliomas

Intrinsic and acquired drug resistance mechanisms generally account for the heterogeneity of drug response in cancer. Thus, brain tumors may be as varied as the individuals they afflict, both in their natural history and their response to chemotherapy. Anaplastic astrocytomas and glioblastoma multiforme are the most common primary brain tumors. The impact of resistance factors on drug response, along with drug availability and blood–brain barrier limitations make this disease difficult to treat. Perhaps the former accounted for both the variability and higher degree of *in vitro* drug resistance observed in the tumors from our 64-patient cohort. Most of the brain tumors were obtained from patients who had previous radiotherapy and/or chemotherapy for an already relatively resistant advanced-stage or recurrent disease, where poor outcomes were anticipated, given the impact of resistance factors on therapy. The extreme drug resistance assay has been shown to identify clinical non-responders to specific chemotherapeutic agents with more than 99% accuracy [6]. *In vitro* drug resistance testing is a viable strategy of identifying patients whose tumors are least likely to respond to various drugs and thus avoid use of interventions with serious morbidity and allow these patients to consider alternative treatments.

Local drug delivery and extreme drug resistance

The treatment of malignant brain tumors with chemotherapy is limited by systemic toxicity and the blood–brain barrier. To overcome these obstacles, implantable biodegradable polymers and microspheres were developed to release high concentrations of chemotherapeutic agents directly at the tumor site [52–55]. This strategy is especially relevant for patients with malignant brain tumors as most recurrences occur within 2 cm of the original resection field [56]. Although the use of BCNU-impregnated polymers has been shown to statistically improve survival of patients with malignant gliomas [54], limitations of this approach include resistance to BCNU or other chemotherapeutic agents.

Given the efficacy of interstitial chemotherapy in animal models, other drug-impregnated polymers are currently being developed for the treatment of malignant gliomas. We envision the neurosurgeon performing a stereotactic biopsy of the patient's tumor prior to definitive surgical resection. Information from an extreme drug resistance assay could guide the neuro-oncologist in selecting the appropriate interstitial chemotherapeutic regimen at the time of definitive surgical resection by excluding agents to which the tumor is highly resistant. Through the continued analysis of brain tumor specimens and compilation of data from multiple institutions, chemoresistance profiles could assist in the development of rationale clinical trials and individualized treatment regimens.

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