

Small molecule kinase inhibitors in glioblastoma: a systematic review of clinical studies

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The efficacy of small-molecule kinase inhibitors has recently changed standard clinical practice for several solid cancers. Glioblastoma is a solid cancer that universally recurs and unrelentingly results in death despite maximal surgery and radiotherapy with concomitant and adjuvant temozolomide. Several clinical studies using kinase inhibitors in glioblastoma have been reported. The present study systematically reviews the efficacy, toxicity, and tissue analysis of small-molecule kinase inhibitors in adult patients with glioblastoma as reported in published clinical studies and determines which kinases have been targeted by the inhibitors used in these studies. Publications were retrieved using a MEDLINE search and by screening meeting abstracts. A total of 60 studies qualified for inclusion, of which 25 were original reports. A total of 2385 glioblastoma patients receiving kinase inhibitors could be evaluated. The study designs included 2 phase III studies and 37 phase II studies. Extracted data included radiological response, progression-free survival, overall survival, toxicity, and biomarker analysis. The main findings were that (i) efficacy of small-molecule kinase inhibitors in clinical studies with glioblastoma patients does not yet warrant a change in standard clinical practice and (ii) 6 main kinase targets for inhibitors have been evaluated in these studies: EGFR, mTOR, KDR, FLT1, PKC β , and PDGFR.

Keywords: clinical trial, glioblastoma, kinases, review, small-molecule inhibitors.

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Small-molecule compounds that inhibit the kinase domain of specific kinase targets have recently changed clinical practice for several advanced solid cancers, such as lapatinib, which inhibits HER2 and EGFR in HER2-positive metastatic breast cancer;¹ sunitinib, which inhibits VEGFR and PDGFR in metastatic renal-cell carcinoma;² and sorafenib, which inhibits RAF, PDGFR, VEGFR, and KIT in advanced hepatocellular carcinoma³ and also in advanced renal-cell carcinoma.⁴ These advances followed the seminal contribution to cancer therapy by gefitinib for chronic myeloid leukemia by inhibiting the ABL/CBR fusion protein⁵ and for gastrointestinal stroma tumor by inhibition of the activating KIT mutation.⁶

Glioblastoma is one of the most aggressive solid cancers and the most common primary brain tumor. Because this tumor is inherently resistant to conventional therapy, the median patient survival is approximately 14 months. Although standard treatment with surgery, irradiation, and temozolomide postpones progression and extends survival to some extent, these tumors universally recur and unrelentingly result in death.⁷ Therefore, improvement of treatment options for patients with glioblastoma is imperative. For this purpose, inhibition of kinase targets that drive glioblastoma growth seems a reasonable treatment strategy to be further explored.

Several clinical studies have reported the efficacy of kinase inhibitors in glioblastoma. The outcome of these clinical studies has not been systematically reviewed, although a number of reviews highlight in their discussions a selection of studies using kinase inhibitors for glioblastoma.^{8–15} The aim of the present study was to review the efficacy of small-molecule kinase inhibitors in adult patients with glioblastoma based on published clinical study results and to determine which kinases are targeted by the inhibitors used in these clinical studies.

Search Strategy and Data Extraction

Results of clinical studies were obtained from 2 sources. A systematic search was performed in PubMed MEDLINE with the MeSH term “glioma” limited by publication type “clinical trial” and “adults”, with publication after January 1, 2002. Furthermore, the abstracts of the annual meetings of the American Society for Clinical Oncology from 2002 to 2008, of the European Association of Neuro-Oncology from 2005 to 2008, of the Society for Neuro-Oncology from 2003 to 2008, and of the World Federation of Neuro-Oncology in 2001 and 2005 were systematically searched for preliminary outcome data of clinical studies.

To compare the data obtained from studies without control patient groups, the results from published studies in patients with newly diagnosed and progressive glioblastoma receiving conventional therapy were included as historical controls.

The data extracted from these sources were the total number of patients in the study, the number of evaluated patients in the population used for data extraction, histopathological diagnosis, study design, type of inhibitor and dosage, inhibitor target, percentage of radiologically complete responses and partial responses, median progression-free survival (mPFS), PFS at 6 months (PFS6), median overall survival (mOS), OS at 12 months (OS12), the number of adverse events of grade 3, 4, or 5 according to the National Cancer Institute Common Toxicity Criteria, and the tissue analysis in relation to response. Data on the effect of kinase inhibitors on the functional status of patients were unavailable from the vast majority of evaluable studies. As far as possible, the data were extracted for the glioblastoma subgroup. When exact percentages and survival times were not provided, these were estimated from the time to progression and survival curves.

Publications and abstracts were screened for efficacy data. Audiovisual material at the ASCO website (<http://www.asco.org/ASCOv2/Meetings/Abstracts>) was available for some of the meeting presentations and was scanned for additional data not included in the meeting abstract. If no outcome data (ie, radiological response, PFS, or OS) were provided, the publication or abstract was excluded from the analysis.

Meta-analysis of the efficacy data was not performed because of the small sample sizes and the highly selected populations with inhomogeneity of inclusion criteria, histopathological diagnosis, stages of disease, drug schedules, and definitions of outcome and efficacy. Therefore, analysis of data is descriptive and qualitative.

Results

A total of 60 studies qualified for inclusion, of which 25 were published as original reports in peer-reviewed journals and 35 as meeting abstracts. Study designs included 2 phase III studies, 1 randomized phase II study, 28 single-arm phase II studies, 8 single-arm phase I/II

studies, 16 phase I studies, 4 retrospective observational series, and 1 pharmacodynamic study. The sum of evaluated patients receiving kinase inhibitors was 2385. The average number of evaluable patients per study was 40, ranging from 6 to 178.

The efficacy, toxicity, and tissue analysis results are listed in Table 1.

Radiological Response

Radiological response rates (ORs) were evaluable in 51 studies.

The reported objective radiological ORs were approximately double the baseline rates after inhibition of EGFR using erlotinib or gefitinib in 6 of 12 evaluable single-inhibitor studies, in 2 of 7 studies combining inhibition of EGFR and mTOR, and in none of 4 evaluable studies combining EGFR inhibition with conventional therapy. In 1 study combining EGFR inhibition by erlotinib with VEGF inhibition by bevacizumab, an OR of 48% was observed,¹⁶ which was comparable with the results for pan-VEGFR inhibition with cediranib.¹⁷ The ORs after inhibition of mTOR were comparable with the baseline results in 4 single-agent studies. Inhibition of PKC β by enzastaurin increased the OR compared with baseline in 1 of 3 studies. Two of 6 single-agent studies using PDGFR/KIT/ABL inhibition by imatinib and 3 of 5 combination therapy studies with imatinib and hydroxyurea showed an increased OR. The combination of imatinib, hydroxyurea, and KDR inhibition by vatalanib resulted in increased ORs in 2 of 2 studies.

Progression-Free Survival

The PFS was evaluable as mPFS in 36 studies and as PFS6 in 34 studies.

The mPFS approximately doubled in progressive glioblastoma compared with baseline in 1 of 8 evaluable studies with EGFR inhibition by gefitinib or erlotinib¹⁸ and in 1 of 6 evaluable studies with combined EGFR and mTOR inhibition using gefitinib at high dose.¹⁹ Seven evaluable studies combining EGFR inhibition with conventional therapy had PFS comparable with baseline values. The mPFS was comparable with baseline in 3 evaluable studies with single-agent mTOR inhibition. The remarkable OR of VEGFR inhibition by cediranib was substantiated by a slightly increased mPFS of 4 months.¹⁷ The mPFS was increased in 2 of 4 evaluable studies with imatinib as single-agent therapy, although a relevant number of anaplastic gliomas were included in these 2 studies.^{20,21} One of 3 evaluable studies using combined imatinib and hydroxyurea showed a small increase in mPFS of 3.6 months compared with baseline.²²

The PFS6 was comparable with baseline in all 8 evaluable studies with EGFR inhibitors as single-agent therapy, was possibly increased in 2 of 5 evaluable studies with combined EGFR and mTOR inhibition including 1 study with a number of anaplastic

Table 1. A summary of efficacy, toxicity, and tissue analysis in clinical studies with small molecule kinase inhibitors in adult patients with newly diagnosed and progressive glioblastoma.

Kinase target	First author	Year	Reference(s)	Total no. of patients in the study	No. of patients in evaluated population				Study design	Therapy	CR (%)	PR (%)	OR (%)	mPFS	PFS6 (%)	mOS	OS12 (%)	Toxicity as no. of grade 3, 4, or 5 events in no. of evaluable patients	Tissue analysis to predict response ^e	
					Newly diagnosed		Progressive													
					GB	AG	GB	AG												
Baseline studies																				
	Stupp	2005	7	573	286				III	rth	—	—	—	5	9	12.1	51	—	NA	
	Stupp	2005	7	573	287				III	rth + tmz	—	—	—	6.9	27	14.6	61	75 in 284	NA	
	Athanassiou	2005	60	130	57				r II	rth	—	—	—	5.2	45	7.7	16	—	NA	
	Athanassiou	2005	60	130	53				r II	rth + tmz	—	—	—	10.8	67	13.4	56	6 in 110	NA	
	Brada	2001	61	138	138				II	tmz	2	6	8	2.1	18	5.4	15	60 in 138	NA	
	Yung	2000	62	225	112				r II	tmz	0	5	5	3	21	7.1	22	26 in 110	NA	
	Yung	2000	62	225	113				r II	Procarbazine	0	5	5	2.1	8	5.6	18	26 in 110	NA	
	Wong	1999	63	375	225				^d	Various salvage treatments without tmz, without kinase inhibitors	—	—	6	2.3	15	6.3	21	—	NA	
Single target small molecule inhibitors																				
<i>EGFR</i>																				
	Van den Bent	2009	45,64,65	54	54				r II	Erlotinib 150–500 mg pod vs tmz or carmustine	0	4	4	1.8	11	7.7	22	13 in 54	ihc: EGFR EGFRvIII* PTEN pAKT; fish: EGFR; mut: EGFR	
	Preusser	2008	44	21	14				7	RObs	Erlotinib 100–150 mg pod or Gefitinib 250 mg pod	0	14	14	3.1	19	5.1	5	1 in 21	ihc: EGFR EGFRvIII PTEN pAKT
	Franceschi	2007	42	16	16				II	Gefitinib 250 mg pod	0	0	0	2.1	13	6.2	14	5 in 28	ihc: EGFR pAKT; fish: EGFR	
	Buie	2007	66	6	6				I	Erlotinib 450–900 mg every 3 days	0	17	17	—	—	—	—	0 in 6	None	
	Mellinghoff	2006	46	49	49				II	Erlotinib 150–500 mg pod or Gefitinib 250–1000 mg pod	0	18 ^a	18	—	—	—	—	—	ihc: EGFRvIII* PTEN*; fish: EGFR; mut: EGFR, HER2, PTEN; pcr: EGFR EGFRvIII	
	Haas-Kogan	2005	43	52	29				I	Erlotinib dosage unavailable	0	17	17	—	—	—	—	—	ihc: EGFR* EGFRvIII pAKT*; fish: EGFR*; mut: EGFR PTEN	
	Cloughesy	2005	67,68	48	48				II	Erlotinib 150–300 mg pod	2	6	8	—	17	—	—	—	ihc: EGFR EGFRvIII PTEN; fish: EGFR	
	Rich	2004	31,69	57	57				II	Gefitinib 500–1000 mg pod	0	0	0	2	13	9.9	36	27 in 55	ihc: EGFR EHGRvIII; pcr: EGFR	
	Uhm	2004	70	96	96				II	Gefitinib 500–1000 mg pod	—	—	—	6.8	62	12.8	54	21 in 63	ihc: EGFR EGFRvIII; fish: EGFR	
	Raizer	2004	71	45	31				II	Erlotinib 150 mg pod	0	0	0	2.3	0	—	—	—	None	
	Lieberman	2004	72	65	38				I/II	Gefitinib 250–1000 mg pod	0	13	13	2	9	—	—	—	None	
	Vogelbaum	2004	18,73,74	31	16				II	Erlotinib 150 mg pod	0	25	25	5.2	—	—	—	—	fish: EGFR	
	Peery	2003	75	57	52				II	Gefitinib 500–1000 mg pod	0	2	2	—	—	—	—	10 in 52	ihc: EGFR EGFRvIII; pcr: EGFR	
<i>mTOR</i>																				
	Cloughesy	2008	39	15	15				I	Rapamycin 2–10 mg pod	0	7	7	3.6	—	—	—	7 in 15	ihc: pS6K pAKT pPRAS40*	
	Galanis	2005	27	65	65				II	Temsirolimus 250 mg ivw	0	0	0	2.3	8	4.4	—	40 in 65	ihc: PTEN S6K pS6K* AKT pAKT; fish: EGFR PTEN; act: S6K	

	Chang	2005	26,76	43		43		II	Temsirolimus 170–250 mg ivw	0	5	5	2.3	2	—	—	49 in 43	None	
	Chang	2004	77	12		9		I	Temsirolimus 250–330 mg ivw	0	0	0	—	—	—	—	4 in 12	None	
<i>VEGFR</i>																			
	Batchelor	2007	17	16		16		II	Cediranib 45 mg pod	0	56	56	4	30	7.5	—	9 in 16	ihc: VEGFR1 VEGFR2 VEGFR3 PDGFR α PDGFR β ; plasma: VEGF PIGF* sVEGFR2* bFGF* SDF1 α *	
<i>KDR</i>																			
	Conrad	2004	28,78–80	55		55		I/II	Vatalanib 150–2000 mg pod	0	4	4	2.5	25	—	—	10 in 45	None	
<i>PKCβ</i>																			
	Kreisl	2009	81	26		17	9	I	Enzastaurine 500–1000 mg pod	4	4	8	1.4	—	5.7	—	9 in 22	Plasma: Pgsk3 β	
	Fine	2008	34,82–84	266		174		III	Enzastaurine 500 mg pod vs lomustine	0	3	3	1.5	11	6.6	15	14 in 167	None	
	Fine	2005	85,86	85		57		II	Enzastaurine 500 mg pod	0	18	18	—	—	—	—	3 in 85	None	
<i>Multitarget small molecule inhibitors</i>																			
<i>PDGFR/KIT/ABL</i>																			
	Raymond	2008	87–89	112		51		II	Imatinib 600–1000 mg pod	0	6	6	1.8	16	5.9	—	34 in 112	mut: KIT PDGFR α PDGFR β ABCG2	
	Razis	2007	90	20	19	1		PD	Imatinib 800 mg pod	0	0	0	—	—	6.2	—	—	ihc: AKT MAPK p27 EGFR PDGFR	
	Viola	2007	21	20		18	2	II	Imatinib 800 mg pod	0	0	0	7.8	52	—	—	0 in 20	ihc: PDGFR α PDGFR β	
	Wen	2006	41,91,92	55		34		I/II	Imatinib 800 mg pod	0	6	6	—	3	—	—	35 in 55	pcr: EGFR EGFRVIII; mut: PTEN PDGFR α PDGFR β	
	Marosi	2006	20	34		23	11	II	Imatinib 400 mg pod	0	18	18	9.5	33	12.3	45	0 in 34	ihc: PDGFR α PDGFR β KIT ABL	
	Franceschi	2005	93	28		16		II	Imatinib 250 mg pod	0	0	0	2	13	6.1	14	5 in 28	None	
<i>KIT/PDGFR/KDR/FLT3/RET</i>																			
	Chaskis	2008	94	12		7	5 ^b	II	Sunitinib 37.5 mg pod	0	8	8	—	—	—	—	5 in 12	None	
<i>EGFR/VEGFR</i>																			
	Kreisl	2008	95	32		32		II	Vandetanib 300 mg pod	0	16	16	—	—	—	—	11 in 32	None	
<i>KDR/FLT1/PDGFR/FLT3/RET/KIT</i>																			
	Reardon	2008	96	16		16		II	Sorafenib 400 mg pod + tmz	0	0	0	—	—	—	—	7 in 16	None	
<i>Combination therapy</i>																			
<i>EGFR + mTOR</i>																			
	Kreisl	2009	36	22		22		I/II	Gefitinib 250 mg pod + everolimus 70 mg ivw	0	14	14	2.6	5	—	—	21 in 22	ihc: EGFR PTEN pAKT pS6K EGFRVIII	
	Friedman	2008	97	27		27		II	Erlotinib 150–500 mg pod + Rapamycin 5–10 mg pod	0	0	0	—	—	—	—	6 in 27	None	
	Phuphanich	2008	19	18		18		I	Gefitinib 250–1000 mg pod + rapamycin 2–6 mg pod	0	0	0	5	—	9.4	—	6 in 18	None	
	Reardon	2006	24	34		29	5	I	Gefitinib 500–750 mg pod + rapamycin 5–10 mg pod	0	6	6	2.1	24	—	—	36 in 32	ihc: pMAPK pS6K pAKT PTEN EGFR; fish: EGFR PTEN	

Continued

Table 1. Continued

Kinase target	First author	Year	Reference(s)	Total no. of patients in the study	No. of patients in evaluated population				Study design	Therapy	CR (%)	PR (%)	OR (%)	mPFS	PFS6 (%)	mOS	OS12 (%)	Toxicity as no. of grade 3, 4, or 5 events in no. of evaluable patients	Tissue analysis to predict response ^e
					Newly diagnosed		Progressive												
					GB	AG	GB	AG											
	Doherty	2006	23	28			22	RObs	Gefitinib 500 mg pod + rapamycin 4 mg pod	0	18	18	3	25	—	—	3 in 28	None	
	Badruddoja	2006	98	21			18	I/II	Gefitinib 500–1500 mg pod + rapamycin 2 mg pod	0	0	0	3	17	—	—	8 in 18	None	
	Nguyen	2006	99	19			19	I/II	Gefitinib 250 mg pod + everolimus 30–70 mg ivw	0	11	11	2.6	5	6.5	—	—	None	
<i>EGFR + conventional therapy</i>																			
	Prados	2009	32,100	65	65			II	Erlotinib 100–300 mg pod + tmz	—	—	—	8.2	72	19.3	68	48 in 65	ihc: EGFR EGFRvIII PTEN*; fish: EGFR; pcr: MGMT*	
	Schwer	2009	25	15			11	I	Gefitinib 250 mg pod + radiosurgery	—	—	—	—	53	10	—	—	None	
	Brown	2008	101	97	97			II	Erlotinib 150 mg pod + tmz + rth	—	—	—	7.2	—	15.3	61	—	ihc: EGFR EGFRvIII PTEN p53; fish: EGFR	
	De Groot	2008	37,102	44			43	II	Erlotinib 150–200 mg pod + carboplatin	0	2	2	2	13	7.5	—	82 in 43	ihc: EGFR EGFRvIII pAKT PTEN	
	Chakravarti	2006	103–106	178	178			I/II	Gefitinib 500 mg pod + rth	—	—	—	5.1	—	11	—	—	ihc: EGFRvIII PTEN	
	Prados	2006	107,108	83			60	I	Erlotinib 100–500 mg pod + tmz	0	8	8	2	7	—	—	36 in 83	None	
	Krishnan	2006	109	19	19			I	Erlotinib 100–200 mg pod + rth	0	0	0	6	—	13.8	—	5 in 20	None	
	Brewer	2006	33,38,110	28	28			II	Erlotinib 50–150 mg pod + tmz + rth	0	0	0	3.6	—	—	—	40 in 27	Fish: EGFR	
<i>PDGFR/KIT/ABL + hydroxyurea</i>																			
	Shah	2007	33	16			11	RObs	Imatinib 400–500 mg pod + hydroxyurea	0	21	21	—	—	10	—	8 in 16	None	
	Dresemann	2008	111,112	240			120	III	Imatinib 600 mg pod + hydroxyurea vs hydroxyurea	0	2	2	1.6	5	—	—	—	None	
	Dresemann	2008	35,113	30	30			II	Imatinib 600 mg pod + hydroxyurea	0	13	13	—	60	—	67	4 in 30	None	
	Dresemann	2006	29	30			30	RObs	Imatinib 400–600 mg pod + hydroxyurea	3	17	20	2.5	32	4.8	25	0 in 30	None	
	Reardon	2005	22,114–116	33			33	II	Imatinib 400–500 mg pod + hydroxyurea	3	6	9	3.6	27	12.2	—	14 in 33	None	

Others

KDR + PDGFR/KIT/ ABL	Kirkpatrick	2008	30	37	34	3	I	Vatalanib 2000 mg pod + imatinib 'standard dose' + hydroxyurea	0	22	22	—	27	—	—	—	None
EGFR + VEGF	Sathornsumetee	2008	16,117,118	25	25		II	Erlotinib 200–650 mg pod + bevacizumab	—	—	48	—	24	—	—	—	None
EGFR + SRC	Reardon	2008	119	15	13	2	I	Erlotinib 150–450 mg pod + dasatinib 100 mg pod	0	0	0	—	—	—	—	1 in 15	None
KIT/PDGFR/KDR/ FLT/RET	Wuthrick	2008	120	10	10		I	Sunitinib 37.5 mg pod + rth	0	10	10	—	—	—	—	1 in 10	None
KDR + PDGFR/KIT/ ABL	Sathornsumetee	2007	121	35	35		I	Vatalanib 500–1000 mg pod + imatinib 400–500 mg pod + hydroxyurea	0	29	29	—	—	—	—	4 in 35	None
KDR/FLT1/ PDGFR + EGFR/ HER2	Reardon	2007	122	32	32		II	Pazopanib 400 mg pod + lapatinib 1000 mg pod	0	0	0	—	—	—	—	10 in 75	ihc: PTEN EGFRvIII
PDGFR/KIT/ABL	Sathornsumetee	2006	123	56	46	10 ^c	I	Imatinib unavailable dose + tmz	0	7	7	—	—	—	—	5 in 56	None
PDGFR/KIT/ ABL + mTOR	Desjardins	2006	124	28	28		I	Imatinib 400 mg pod + hydroxyurea + everolimus 2.5 mg ivd	0	4	4	—	—	—	—	1 in 5	None
KDR	Reardon	2004	125,126	60	60		I/II	Vatalanib 500–1500 mg pod + tmz or lomustine	0	7	7	3.5	15	—	—	3 in 60	None

Abbreviations: rII, randomized phase II study; RObS, retrospective observational study; PD:, pharmacodynamic study; tmz, temozolomide 150–200 mg/m² po 5 days/28 days; rth, radiotherapy; pod, per os daily; iwv, intravenous weekly; ivd, intravenous daily; CR, complete response; PR, partial response; mPFS, median progression-free survival; PFS6: progression-free survival at 6 months; mOS, median overall survival; OS12, overall survival at 12 months; ihc, immunohistochemistry to determine protein expression; fish, fluorescence in situ hybridization to determine gene amplification; mut, sequencing analysis to determine gene mutation; pcr, PCR to determine gene copy number or gene expression; act, kinase activity assay to determine protein activity; plasma, plasma protein concentration analysis; na, not applicable. For comparison, baseline studies with conventional therapies are listed. Studies are categorized by single-target inhibitors, multitarget inhibitors, and combination therapies; subcategorized by kinase drug target; and sorted by year of publication and number of patients.

^aPartial response defined as > 25% decrease of bidirectional area.

^bIncluding 4 progressive low-grade gliomas.

^cIncluding 1 pleiomorph xanthoastrocytoma.

^dPrognosis study with data from 8 phase II trials.

^eTissue analysis results that are significantly correlated with efficacy are marked with an asterisk.

gliomas,^{23,24} and was increased in 1 of 4 evaluable studies with EGFR inhibition combined with conventional therapy, which included a relevant number of anaplastic gliomas.²⁵ When EGFR inhibition was combined with VEGFR ligand binding by bevacuzimab, the PFS6 was 24%.¹⁶ The PFS6 was comparable with baseline using both evaluable single-agent mTOR inhibitors.^{26,27} In both studies with single-agent VEGFR inhibitors, the PFS6 was increased, including a PFS6 of 30% after cediranib in concordance with the increased OR and mPFS.^{17,28} The PFS6 was comparable with baseline in 1 evaluable study with PKC β inhibition. The same 2 studies with single-agent imatinib that had an increased mPFS also had an increase in PFS6.^{20,21} Again, the number of anaplastic gliomas included in the study populations likely contributed to this finding. A slight increase in PFS6 was observed in 2 of 4 evaluable studies with combination therapy using imatinib and hydroxyurea, while 1 of these 2 studies was a retrospective observational series.^{22,29} Furthermore, the study with combined imatinib, hydroxyurea, and KDR inhibition by vatalanib had a PFS6 of 27%, although a number of anaplastic gliomas were included.³⁰

Overall Survival

The OS was evaluable as mOS in 23 studies and as OS12 in 12 studies.

The mOS increased to 9.9 months in 1 of 5 evaluable studies with single-agent EGFR inhibition.³¹ In the 1 evaluable study with combined EGFR and mTOR inhibition, the mOS was also increased.¹⁹ The mOS was remarkably increased to 19.3 months in 1 of 6 evaluable studies with the combination of EGFR inhibition and conventional therapy, erlotinib, and temozolomide in this study with newly diagnosed glioblastomas.³² Another study with combination therapy using EGFR inhibition by gefitinib and radiosurgery showed an increased mOS; however, anaplastic gliomas were included.²⁵ The one evaluable study with single-agent mTOR inhibition had an mOS comparable with baseline. The 1 evaluable study with VEGFR inhibition by cediranib, with encouraging OR, mPFS, and PFS6, barely presented an increase in mOS.¹⁷ The mOS was comparable with baseline in 2 evaluable studies with PKC β inhibition by enzastaurin. In 1 of 4 evaluable studies with imatinib as single-agent therapy, the mOS was increased, although a substantial number of anaplastic gliomas were included.²⁰ The mOS was increased in 2 of 3 evaluable studies with imatinib in combination with hydroxyurea; of these 2 studies, 1 included a number of anaplastic gliomas³³ and the other showed an mOS of 12.2 months in progressive glioblastoma.²²

The OS12 was increased to 36% in 1 of 5 evaluable studies with EGFR inhibition.²⁶ In 1 of 2 evaluable studies with EGFR inhibition by erlotinib combined with temozolomide, the OS12 was increased to 68%.³² In 1 evaluable study with PKC β inhibition by enzastaurin, the OS12 was comparable with baseline.³⁴ The OS12 was increased to 45% in 1 of 2 evaluable studies

with imatinib as single-agent therapy, which included a large number of anaplastic gliomas. Combination therapy using imatinib and hydroxyurea increased the OS12 in both evaluable studies.^{29,35}

Toxicity

Toxicity data were evaluable in 26 studies.

The toxicity increased to 27 events in 55 patients in 1 of 7 evaluable studies with EGFR inhibition by gefitinib compared with baseline.³¹ The toxicity of therapy combining EGFR and mTOR inhibition was increased up to 36 events in 32 patients in 2 of 6 evaluable studies.^{24,36} Toxic events associated with therapy combining EGFR inhibition by erlotinib with conventional therapy, such as temozolomide,³² carboplatin,³⁷ or temozolomide, and radiotherapy³⁸ were considerably increased, with 48 events in 65 patients, 82 in 43 patients, and 40 in 27 patients, respectively. In 3 of 4 evaluable studies with mTOR inhibition by rapamycin or temsirolimus, toxicity was increased up to 49 events in 43 patients.^{26,27,39} The toxicity was increased in 1 of 2 studies with VEGFR inhibition by cediranib¹⁷ and was not increased with PKC β inhibition. Imatinib was associated with increased toxicity (35 events in 55 patients) in 1 of 5 evaluable studies.⁴⁰ The combination therapy of imatinib and hydroxyurea showed increased toxicity (up to 8 events in 16 patients) in 2 of 4 evaluable studies.^{22,41}

Tissue Analysis

Patient tissue was analyzed in relation to response in 27 studies. The activation status of a substrate downstream of the kinase target was verified in 4 studies after EGFR inhibition^{42–45} and in 2 studies after mTOR inhibition,^{27,39} of which 3 provided an indication of target inactivation after kinase inhibition.^{27,39,43} Several molecular markers have been found to predict response, sometimes with conflicting results.

An association between tissue analysis and response to EGFR inhibition was identified in 3 of 10 studies that analyzed tissue. In one of these studies, the presence of the EGFRvIII mutant correlated with poor PFS after erlotinib.⁴⁵ In the second study, the presence of the EGFRvIII mutant coinciding with PTEN protein expression was associated with radiological response after erlotinib or gefitinib.⁴⁶ In the third study, high EGFR protein expression, EGFR amplification, and low phosphorylated AKT protein expression, as a downstream target of EGFR, each correlated with radiological response, and in addition, high phosphorylated AKT protein expression was associated with poor PFS.⁴³

A response correlation was found in 2 studies describing tissue analysis after mTOR inhibition. In one study, high protein expression of phosphorylated PRAS40, as a downstream target of AKT, correlated with poor PFS after rapamycin.³⁹ In the other study, high protein expression of phosphorylated S6K, as a downstream

target of mTOR, was associated with radiological response after temsirolimus.²⁷

After VEGFR inhibition by cediranib, radiological tumor progression was associated with a decrease in the plasma protein level of PIGF and an increase in plasma protein levels of sVEGFR2, bFGF, and SDF1 α .¹⁷

A survival benefit was identified in patients with both a methylated MGMT promotor status and positive PTEN protein expression after combination therapy of EGFR inhibition by erlotinib and temozolomide during and after radiotherapy.³²

Kinase Drug Targets

The targets of small-molecule kinase inhibitors in clinical studies with glioblastoma patients have mainly been 6 kinases: EGFR, mTOR, KDR, FLT1, PKC β , and PDGFR. In addition, 3 evaluated multitargeted agents also inactivate other kinase targets nonspecifically: imatinib also inhibits KIT and ABL, sunitinib also inhibits FLT3 and RET, and lapatinib also inhibits HER2.

Discussion

The main findings of the present study are that (i) the efficacy of small-molecule kinase inhibitors in clinical studies with adult glioblastoma patients does not yet warrant a change in standard clinical practice, and (ii) the main kinase targets of the inhibitors evaluated in these studies are EGFR, mTOR, KDR, FLT1, PKC β , and PDGFR.

The evaluated studies have several limitations that should be considered in interpreting these results. First, many of the studies were not designed to determine the efficacy of therapy and consequently no control group was included for comparison of results in the intervention group. Included in this analysis were outcome results from 4 retrospective observational, 1 pharmacodynamic, 16 phase I, and 8 phase I/II studies. Control group data were available from 1 randomized phase II and 2 phase III studies. Second, sample sizes were small. For instance, the average number of patients in the phase II studies was 39 (range: 12–65). Third, the study populations predominantly consisted of patients with progressive glioblastoma or anaplastic glioma, except for 9 studies of patients with newly diagnosed glioblastoma. Fourth, drug activity was usually unknown, as the inactivation of downstream targets was seldom verified in tissue samples. Fifth, the classical study endpoints of radiological response, PFS, and OS were evaluated, each with their limitations. Beneficial effects for individual patients, for instance in terms of improved quality of life or alleviation of symptoms, cannot be excluded by evaluation of these classical endpoints. As an example of the limitations of the classical endpoints, the radiological response criteria rely on enhancement due to blood-brain barrier disruption. Causes other than tumor progression can induce enhancement, such as postoperative gliosis, infection,

or radiation necrosis, and enhancement can be reduced by stabilization of the blood-brain barrier rather than by a decrease of the tumor burden. Furthermore, limitations to the PFS as an endpoint are inherent to the radiological definition of progression, its dependence on timing of radiological follow-up, and the fact that radiological progression is not necessarily equal to cessation of clinical benefit. Evaluation of the OS is hampered by bias from subsequent salvage therapies after the trial intervention and does not reflect the quality of the prolonged lifetime.

The lack of efficacy in these clinical studies can have several causes. First, results that have been obtained in preclinical glioma models and that have motivated further clinical evaluation may not adequately represent the pathobiology of glioblastoma in patients. Second, the inhibitor may have failed to inactivate the target in glioblastoma cells, for instance due to low concentrations in tumor tissue or agent inactivation mechanisms. Third, the pursued kinase target may be active only in a subpopulation of patients. The efficacy of kinase inhibition in this subpopulation may have been diluted by unselected glioblastoma patients. Fourth, alternative kinase signaling pathways may be active in parallel with the inhibited target, so that a single target's inactivation does not reduce downstream oncogenic signaling. Fifth, beneficial effects from these kinase inhibitors are perhaps not portrayed by the classical endpoints as evaluated.

Several strategies may help overcome these issues. First, the best kinase drug targets need to be identified for glioblastoma. Second, the preclinical efficacy from inhibition of these drug targets needs to be rigorously verified in several glioblastoma models to complement each single model's limitations. Third, kinase inhibitors need to be developed and optimized further, for instance by directing toward downstream targets or toward multiple kinase targets or by using a combination of inhibitors. However, the toxicity of the evaluated kinase inhibitors was significant, and hence improved safety of new inhibitors remains important. Fourth, the inactivation of the target and its downstream substrate should be verified in early studies with glioblastoma tissue obtained from patients. An elegant proof-of-concept of this biological activity endpoint was recently demonstrated.³⁹ Fifth, the study populations need to be enriched by including patients likely to respond, by determining the activation status of the aimed drug target. Sixth, other clinical trial endpoints, such as quality of life and cognitive status, can be considered in addition to the classical trial endpoints.^{47,48} The radiological response is a useful surrogate endpoint for glioma therapy in general, because objective results are provided shortly after therapy. From the presented data, it is clear that reduction in enhancement can also be observed after kinase inhibition. The PFS6 suitably predicts OS and therefore is considered a meaningful endpoint for evaluation of progressive glioblastoma. Perhaps the ideal endpoint for assessment of clinical benefit by targeted therapy would be a multidimensional construct of imaging, symptoms, quality, progression, and survival.

A more fundamental question is whether glioblastoma is in fact a kinase-driven cancer. Undoubtedly, oncogenic kinase signaling is involved in glioblastoma, but whether kinases are crucial for the oncogenic signaling network of glioblastoma and are thereby amenable to therapeutic inhibition, remains to be determined. Kinase drug targets that have changed clinical practice in the treatment of solid cancers are dysregulated in 1 of 3 ways: by mutation, gene overexpression, or protein fusion.⁴⁹ All three relevant mechanisms of kinase dysregulation have been identified in glioblastoma, for example, mutation of PIK3CA lipid kinase,⁵⁰ overexpression of the AURKA gene,⁵¹ and fusion of FIG to ROS kinase.⁵² Details on kinase involvement in glioblastoma can be found in dedicated reviews.^{9,10,14,53,54} The protein kinase gene family consists of 518 members.⁵⁵ The status of the vast majority of these kinases remains to be determined in glioblastoma, and it is unclear which kinases are best for targeting with small molecule inhibitors. Therefore, it may prove worthwhile to evaluate kinase targets other than those currently utilized for small molecule inhibition in glioblastoma.⁵⁶

Another fundamental question, if glioblastoma turns out to be kinase driven, is which strategy is best for kinase inhibition. For example, one of the more favorable responses in the clinical studies reviewed here has been observed using the FLT1/KDR inhibitor cediranib.¹⁷ A strategy alternative for inhibition of kinase signaling other than using a small-molecule inhibitor is

binding of the ligand of receptor tyrosine kinases with monoclonal antibodies. This strategy has recently been shown to hold promise as a cancer therapy for glioblastoma.^{57–59}

In conclusion, this review of published clinical studies demonstrates small-molecule kinase inhibitors for adult patients with glioblastoma to be not effective enough yet to warrant a change in clinical practice, whereas the evaluated drug targets have been generally limited to EGFR, mTOR, KDR, FLT1, PKC β , and PDGFR.

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