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RTOG 0211: A Phase I/II Study of Radiation Therapy with Concurrent Gefitinib for Newly Diagnosed Glioblastoma Patients

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Abstract

Purpose—To determine the safety and efficacy of gefitinib, an EGFR tyrosine kinase inhibitor, in combination with radiation for newly diagnosed glioblastoma (GBM) patients.

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Methods and Materials—Between 3/21/2002 and 5/03/2004 RTOG 0211 enrolled 31 and 147 GBM patients in the phase I and II arms respectively. Treatment consisted of daily oral gefinitnib started at the time of conventional cranial radiotherapy (RT) and continued post RT for 18 months or until progression. Tissue microarrays from 68 cases were analyzed for EGFR expression.

Results—The maximum tolerated dose (MTD) of gefitinib was determined to be 500 mg in patients on non enzyme-inducing anticonvulsant drugs (non-EIAEDs). All patients in the phase II component were treated at a gefitinib dose of 500mg; patients receiving EIADSs could be escalated to 750mg. The most common side-effects of gefitinib in combination with radiation were dermatologic and gastrointestinal. Median survival was 11.5 months for patients treated per protocol. There was no overall survival benefit for patients treated with gefitinib + RT when compared to a historical cohort of patients treated with RT alone, matched by RTOG RPA class distribution. Younger age was significantly associated with better outcome. Per protocol stratification, EGFR expression was not found to be of prognostic value for gefitinib + RT treated patients.

Conclusions—The addition of gefitinib to RT is well tolerated. Median survival of RTOG 0211 patients treated with radiation therapy with concurrent and adjuvant gefitinib was similar to a historical control cohort treated with radiation alone.

Introduction

Glioblastoma remains among the most aggressive of all human malignancies, with median survival times just over one year [1-3]. As radiation therapy (RT) remains one of the primary therapeutic modalities for these tumors and has been found to significantly increase survival compared to surgical resection alone [4, 5], there has been much interest in identifying mechanisms of radiation resistance to enhance radiation efficacy [6-10]. One putative resistance mechanism involves epidermal growth factor receptor (EGFR) signaling. It is well-known that EGFR gene amplification is a common event in GBMs and many GBMs express a mutant variant of EGFR called EGFRvIII, which lacks the extracellular binding domain and is constitutively active [7, 11-14]. EGFR tyrosine kinase inhibitors have been demonstrated to enhance sensitivity to radiation in pre-clinical models [15-17]. Targeting EGFR with the antibody cetuximab in postoperative head and neck cancer patients on RTOG 0234 produced clinical evidence of radiosensitization [18]. In humans, patients with tumors harboring a specific and rare molecular profile appear to benefit from EGFR TKIs, whereas most patients do not [11, 19-21]. Therefore, identifying molecular profiles associated with EGFR TKI sensitivity is a useful goal.

In this context, the Radiation Therapy Oncology Group (RTOG) initiated a single arm Phase I/II study, RTOG 0211, to examine the safety and efficacy of gefitinib, an EGFR tyrosine kinase inhibitor, in combination with radiation (without planned concomitant or adjuvant temozolomide) for newly-diagnosed GBM patients, with integrated tissue collection and correlative endpoints.

To enable improved quantification of expression levels of EGFR a molecular microscopy-based approach using AQUA® (HistoRx, New Haven, CT) was undertaken in lieu of traditional immunohistochemistry.

Methods and Materials

Selection Criteria

Eligibility criteria were: 18 years or older, Zubrod Performance Scale 0-1, histopathologically confirmed newly diagnosed unifocal supratentorial GBM, estimated survival of at least 8 weeks, no prior chemotherapy or RT to the head or neck area (except T1 glottic tumors), no active inflammatory disorders, no major medical/psychiatric illnesses, no malignancy (within three years) except non-melanomatous skin cancer or carcinoma in situ of cervix or bladder, no pregnancy or lactation. Radiotherapy must have been initiated within five weeks after surgery, with gefitinib initiated one week prior to radiotherapy.

Patient Treatment

RTOG 0211 was a Phase I/II study combining gefitinib with RT. RT was delivered using 3D-conformal radiation (60Gy in 30 fractions of 2Gy each). An initial target representing the T2/Axial FLAIR volume plus a tailored 2 cm margin was treated to 46 Gy in 23 fractions of 2 Gy each, followed by a 14 Gy boost (in 7 fractions of 2 Gy each) to the contrast-enhancing tumor plus 2.5 cm margin. To determine the maximum tolerated dose (MTD) in phase I, dose was escalated from 250mg QD to 750mg QD in 250mg increments in patients on enzyme-inducing drugs (EIAEDs, group I) and from 250mg to 500mg QD in patients not on EIAED (group II). Post-radiotherapy maintenance was gefitinib alone for 18 months or until disease progression or intolerable toxicity. No patient received concomitant or adjuvant temozolomide as the trial was designed and launched prior to the approval of temozolomide for newly diagnosed GBM.

Immunohistochemistry

Tissue microarrays [22] were deparaffinized and rehydrated using xylenes and ethanol rinses. Antigen retrieval was carried out in Tris-EDTA pH 9.0 using a LabVision PT Module (Labvision, Fremont, CA) programmed to heat, without boiling, for 25 minutes at 102 C. Slide staining was performed on a LabVision 720 Autostainer (Labvision, Fremont, CA) using Peroxidazed blocking reagent (Biocare Medical, Concord, CA) and Background Sniper (Biocare Medical). Mouse monoclonal EGFR (DAKO-M3563, Clone-H11, final conc. 5.9 ug/ml) primary antibody was incubated for one hour at room temperature (triplicate sections). Primary antibodies were included with rabbit anti-GFAP (Dako, Z0334, 1:200). Subsequently slides were rinsed and incubated with a cocktail of mouse EnvisionPlus (Dako) and Alexa555 conjugated anti-rabbit (Invitrogen, A21428, 1:200). Target signal was amplified using the Cy5 tyramide amplification system (Perkin Elmer, SAT705A, 1:50 dilution in amplification buffer) and slides were mounted with Prolong anti-fade with DAPI (Invitrogen, P36931). AQUA (HistoRx, New Haven, CT) scores [23] were calculated as previously described [24, 25].

Statistical Methodology

Dose limiting toxicities (DLT) for phase I were: any grade 3 or 4 nonhematologic toxicity excluding grade 3 nausea/vomiting, fatigue, and skin toxicity – unless there is evidence of erythema multiforme, or toxicity requiring i.v. dehydration, hospitalization, or an

interruption of greater than a total of 7 days during RT. If none of the first three patients for a dose, or one of the first three and none of the last three, experiences a DLT, then the next dose will be opened. The highest dose achieved will be considered the MTD.

The phase II study was designed to test whether the addition of gefitinib to RT prolonged survival. Using the Dixon-Simon method of calculating sample size for the comparison of survival against a historical control, a sample size of 140 was calculated (80% probability of detecting a 50% improvement in median survival time at a significance level of 0.05 (one-sided) in patients with high EGFR AQUA scores).

The Kaplan-Meier method was used to estimate overall survival (OS) and progression-free survival (PFS), and the log-rank test was used to compare the different treatment arms. An event for OS was death due to any cause, for PFS the first reported occurrence of progression or death.

Statistical analyses were done using SAS version 9 and R [26]. AQUA scores were log-base-2 transformed. Age was grouped into ten year increments.

Results

Phase I Results

The Phase I component consisted of 31 patients (Supplementary Material 1): 18 patients in Group I (on EIAEDs) and 13 patients in Group II (on non-EIAEDs). The MTD of gefitinib was determined to be 500 mg in Group II patients and 750 mg in Group I patients. The most common side-effects of gefitinib in combination with radiation were dermatologic, gastrointestinal, and fatigue (Table 1 and Supplementary Material 2). In the non-EIAED group at dose level one (250mg) there were two dermatologic (rashes), one hepatic (SGPT elevation), and one metabolic/laboratory (hypokalemia) grade 3 toxicities and no grade 4 toxicities. There were six patients enrolled at dose level 1. On dose level 2 (500mg) there were six patients enrolled in the non-EIAED group and there was one grade 3 skin toxicity, one grade 3 cardiovascular event (DVT), one grade 3 (SGOT/SGPT) and one grade 4 hepatic (SGPT) events. Dose level 2 therefore had more than one dose limiting toxicity and met specifications for maximum tolerated dose. Per protocol for patients not on EIAED gefitinib was dose escalated from 250mg to 500 mg QD and for patients on EIAED gefitinib was dose escalated from 250 mg to 750 mg QD in 250 mg increments. The MTD for patients on EIAED was determined to be 750 mg QD and for patients not on EIAED was determined to be 500 mg QD.

Phase II Results

The Phase II component (Table 2) consisted exclusively of group II patients treated by RT +gefitinib at 500 mg QD. There were 147 patients enrolled in the phase II component and 136 of the combined phase I/II cohort not receiving EIAED and receiving 500mg gefitinib were eligible for analysis. 119 patients were identified to have been treated per protocol or with acceptable deviation. The progression free survival at 6 months was 40 % (Fig. 1). Median progression free survival was 4.9 months. The median OS for patients treated on RTOG 0211 per protocol or with acceptable deviation was 11.5 months versus 11.0 months

for historical controls treated by RT alone (HR (0211 v. historical control) = 1.14; 95%CI: 0.94 – 1.37; p (one-sided) = 0.91), Table 3, Fig. 2). Median OS for all eligible patients was 11.1 months.

Toxicities observed during the phase II portion of the study are summarized in Table 1 (N=136). The incidence of grade 1 / 2 and 3 / 4 rash was 75 and 13% respectively. Grade 3/4 cardiovascular complications related to thromboembolic disease (8.8%), (which is an expected incidence for this patient population). Grade 3 /4 liver function tests abnormalities were observed in 21% of patients. Seventy two percent of the observed Grade 3 / 4 GI toxicity (15%) were due to diarrhea; grade 1 /2 diarrhea was ~51%.

Correlative results

Stratified by the RTOG recursive partitioning analysis (RPA) criteria, there did not appear to be a clinical group of patients who benefited from the addition of gefitinib to RT (Supplementary Material 3-5). Only younger age was significantly associated with improved clinical outcome in RTOG 0211-treated patients [HR (50+ v. <50) = 1.86 (95%CI: 1.22 – 2.83; p = 0.0037]. Therefore correlative analysis of EGFR expression was adjusted for age. Tissues were obtained from 68 out of 136 eligible patients in the Phase II component of RTOG 0211. There were no significant differences in pretreatment demographics or patient outcomes between patients with or without tissue submission.

EGFR over expression was not found to be of prognostic significance for patients treated with radiation therapy with concurrent and adjuvant gefitinib (HR 0.99). Additional correlative analysis will be reported separately.

Discussion

The biological significance of EGFR signaling in GBMs has galvanized much interest in investigating EGFR tyrosine kinase inhibitors by themselves or in combination with radiotherapy or chemotherapy. In the recurrent setting, it has become clear that only a relatively modest subset of GBM patients demonstrate an objective response to EGFR TKIs. RTOG 0211 was a single arm phase I/II study which demonstrated safety but no efficacy of gefitinib therapy when combined with radiation therapy. Per protocol analysis of EGFR expression did not identify a patient subset that benefited from radiation therapy with concurrent and adjuvant gefitinib. This is consistent with results from N0177, a NCCTG phase I/II trial of concurrent and adjuvant erlotinib and temozolomide and radiation therapy for newly diagnosed GBM. There was no survival benefit on N0177 when compared to RT/TMZ treated patients and EGFR gene amplification was not of prognostic value [27].

Limited and somewhat controversial previous data have suggested that patients that respond to EGFR RTK inhibition harbor the EGFRvIII gene and express wild-type PTEN implying that the proliferation drive was predominantly through the EGFR pathway, and hence shutting it off could be therapeutically useful [11]. At the time of protocol development this data was not available, and therefore no stratification based on EGFRvIII was undertaken. For that reason only EGFR expression was prespecified as a stratification variable. Outside of the protocol specified analysis we will report additional correlative analysis including

EGFRvIII and PTEN status separately. The recent discovery that oncogenic FGFR-TACC fusions are present in a small percentage of GBM patients is very interesting [28] and hopefully will result in development of an appropriate therapy for this patient subpopulation. At this time is remains to be determined if this or other molecular alteration can predict response to EGFR-TKi such as gefitinib.

Also, at the time of protocol development the standard of care for newly diagnosed glioblastoma patients did not include temozolomide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Conflict of Interest Statements

Arnab Chakravarti has no conflict to declare.

Meihua Wang has no conflict of interest to declare.

H. Ian Robins has served as a consultant to Genentech, Abbott, and Novocure.

Tim Lautenschlaeger has not conflict of interest to declare.

Walter Curran has no conflict of interest to declare.

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Paul Mischel has no conflict of interest to declare.

Adam Dicker has no conflict of interest to declare.

Markus Bredel has no conflict of interest to declare

Minesh Mehta has prior or current consulting and/or speaking relationships with Abbott, Adnexus, Bristol-Meyers, Elekta, Genentech, Merck, Novartis, Novocure, Schering Plough, and Tomotherapy; served on the DSMB for Apogenix; is on the Medical Advisory Board for Colby, and Stemina; is on the Board of Directors of Pharmacyclics; and has stock options in Colby, Pharmacyclics and Stemina, and previously in Tomotherapy.

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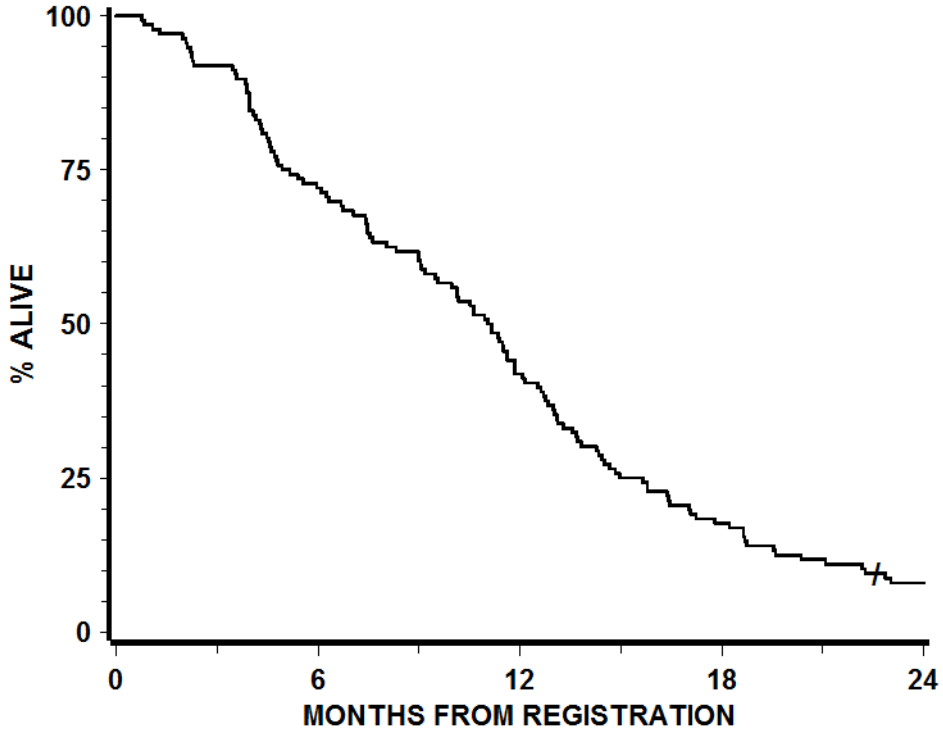

Figure 1. Progression-Free Survival

119 patients were identified to have been treated per protocol or with acceptable deviation. The progression free survival at 6 months was 40 %.

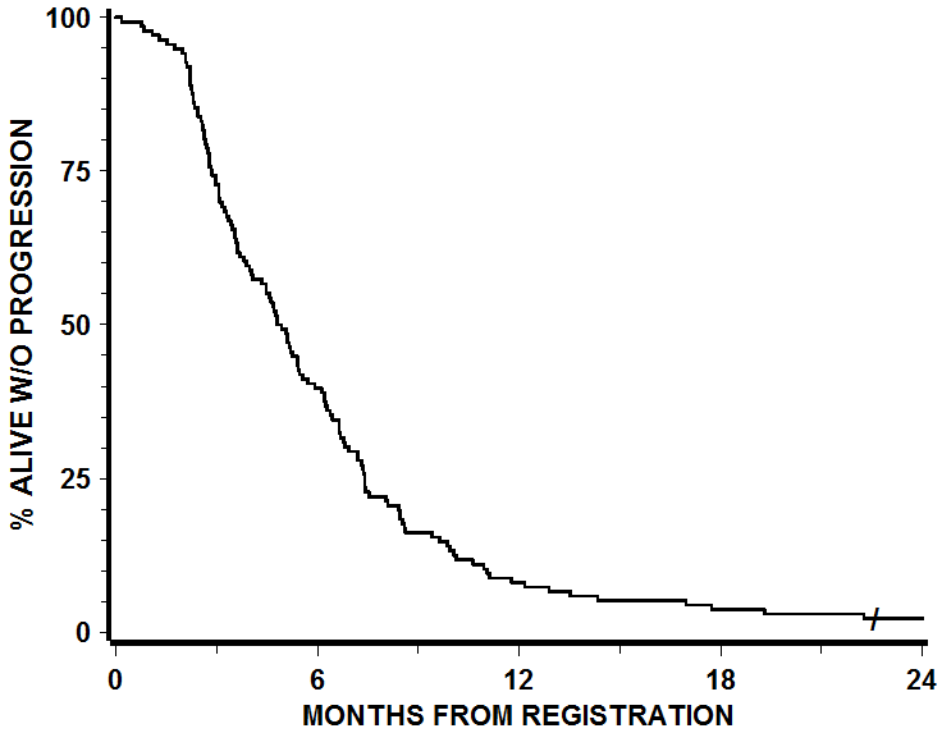

Figure 2. Overall survival

The median OS for patients treated on RTOG 0211 per protocol or with acceptable deviation was 11.5 months versus 11.0 months for historical controls treated by RT alone (HR (0211 v. historical control) = 1.14; 95%CI: 0.94 – 1.37; p (one-sided) = 0.91).

Table 1

Group 2 (non-EIACD). Iressa and Acute RT Toxicity. Reported as Definitely, Probably, or Possibly Related to Treatment

The most common side-effects of gefitinib in combination with radiation were dermatologic, gastrointestinal, and fatigue.

	250 mg (n=6) Grade				500 mg (n=136) Grade				
	1	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**5**
Allergy/Immunology	0	0	0	0	2	1	0	0	0
Auditory/Hearing	0	0	0	0	3	5	0	0	0
Blood/Bone marrow	4	1	0	0	48	17	7	1	0
Cardiovascular (arrhythmia)	0	0	0	0	2	3	0	0	0
Cardiovascular (general)	1	0	0	0	8	9	10	2	0
Coagulation	0	0	0	0	1	0	1	0	0
Constitutional symptoms	3	1	0	0	49	48	7	5	0
Dermatology/Skin	2	0	2	0	40	62	17	2	0
Gastrointestinal	0	3	0	0	40	48	17	4	1
Hemorrhage	0	0	0	0	7	3	2	2	0
Hepatic	1	3	1	0	17	19	23	5	0
Infection/Febrile Neutropenia	0	0	0	0	6	3	5	1	0
Metabolic/Laboratory	2	0	1	0	19	7	9	1	0
Musculoskeletal	0	0	0	0	1	3	3	0	0
Neurology	0	0	0	1	11	13	12	5	0
Ocular/Visual	0	1	0	0	6	7	0	0	0
Pain	0	0	0	0	19	16	1	0	0
Pulmonary	0	0	0	0	4	4	6	2	0
Renal/Genitourinary	0	1	0	0	19	2	2	1	0
Worst Non Hematological	1 (17%)	2 (33%)	2 (33%)	1 (17%)	7 (5%)	41 (30%)	63 (46%)	23 (17%)	1 (1%)
Worst Overall	1 (17%)	2 (33%)	2 (33%)	1 (17%)	6 (4%)	41 (30%)	63 (46%)	24 (18%)	1 (1%)

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Table 2

Pretreatment characteristics by 0211 and historical data set (7401, 7918, 8302, 9006, 9411)

There appear to be no differences in overall survival, neither in the group of all patients nor in patient groups stratified by.RPA class.

	RTOG 0211		Historical control	
	n	**%**	**n**	**%**
Age				
<50	30	22	487	33
>= 50	106	78	970	67
Zubrod				
0	57	42	629	43
1	79	58	684	47
2,3	0	0	143	10
unknown/missing	0	0	1	<1
Surgery				
biopsy	31	22	241	17
part.resect	68	51	878	60
tot.resect	36	26	328	23
other	1	1	8	1
unknown/missing	0	0	2	<1
Neurologic Function				
none/minor	107	79	794	54
moderate	27	20	582	40
hospital	0	0	77	5
unknown/missing	2	1	4	<1
RPA Class				
III	12	9	250	17
IV	83	61	652	45
V	41	30	555	38

Table 3

Overall Survival by 0211 (per protocol/acceptable) vs. historical control

The median OS for patients treated on RTOG 0211 per protocol or with acceptable deviation was 11.5 months versus 11.0 months for historical controls treated by RT alone (HR (0211 v. historical control) = 1.14; 95%CI: 0.94 – 1.37; p (one-sided) = 0.91). Median OS for all eligible patients was 11.1 months.

	0211 Per protocol/Acceptable		Historical control	
Months	**Survival**	**# at Risk**	**Survival**	**# at Risk**
0	100%	119	100%	1457
3	97%	115	90%	1315
6	78%	93	77%	1115
9	65%	77	61%	890
12	45%	54	44%	640
15	26%	31	32%	458
18	19%	23	23%	328
24	9%	10	13%	188
Median Survival Time (MST)		11.5 months		11.0 months
Dead/Total		117/119		1405/1457
Hazard ratio ($\lambda_{0211}/\lambda_{historical}$) (95% CI)		1.14 (0.94 to 1.37)		
p-value(one-sided log rank)		0.91		