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Dosing to Rash: A Phase II Trial of the First-Line Erlotinib for Patients with Advanced Non-Small-Cell Lung Cancer an Eastern Cooperative Oncology Group Study (E3503)

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Abstract

Background—The development of a rash has been retrospectively associated with increased response and improved survival when treated with erlotinib at the standard dose of 150 mg per day. The objective of this trial was to evaluate the association of the activity of erlotinib in the first-line setting in patients with advanced non-small-cell lung cancer (NSCLC) with the development of a tolerable rash via dose escalation of erlotinib or tumor characteristics.

Methods—Patients, with advanced NSCLC without prior systemic therapy, were treated with erlotinib 150 mg orally per day. The dose was increased by 25 mg every two weeks until the development of grade 2/tolerable rash or other dose limiting toxicity. Tumor biopsy specimens were required for inclusion.

Results—The study enrolled 137 patients, 135 were evaluable for safety and 124 were eligible and evaluable for response. Only 73 tumor samples were available for analysis. Erlotinib dose escalation occurred in 69/124 patients. Erlotinib was well tolerated with 70% of patients developing a grade 1/2 rash and 10% developing grade 3 rash. Response rate and disease control rate were 6.5% and 41.1% respectively. Median overall survival was 7.7 months. Toxicity and tumor markers were not associated with response. Grade 2 or greater skin rash and low pMAPK were associated with improved survival.

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Conclusions—Overall survival was similar in this trial compared to first-line chemotherapy in this unselected patient population. Dose escalation to the development of grade 2 skin rash was associated with improved survival in this patient population.

INTRODUCTION

In 2003, gefitinib became the first oral epidermal growth factor inhibitor (EGFR) approved for use which revolutionized care for patients with non-small-cell lung cancer.[1] Erlotinib is currently the only EGFR tyrosine kinase inhibitor (TKI) approved for use in the United States based on the only trial to show a survival advantage of an oral EGFR TKI compared to placebo in the second and third-line treatment setting in advanced disease.[2] These two drugs are widely used throughout the world in patients with advanced NSCLC. After the discovery of the epidermal growth factor receptor (EGFR) mutation and its association with tumor response,[3,4] tumor EGFR mutation analysis has helped guide the use of EGFR TKIs in advanced NSCLC. Reports of improved progression-free survival (PFS) with EGFR tyrosine kinase inhibitors compared to chemotherapy in the first-line setting in patients with EGFR mutations has led to EGFR TKIs use restricted in the first-line setting to patients with EGFR mutation positive tumors.[5,6] Prior to these reports and the discovery of EGFR mutations, improved survival was linked retrospectively to clinical characteristics, EGFR signaling, and the development of toxicities such as skin.[2,7–9]

Many groups have attempted to unlock the answer why patients who do not have EGFR mutations benefit from erlotinib. EGFR amplification, as assessed by FISH has been implicated,[10] as well as other markers of the EGFR pathway or other linked pathways such as MAPK or AKT.[11,12] Investigators have also used protein expression patterns otherwise known as serum proteomics to predict benefit from EGFR TKIs. Carbone and colleagues previously published validation of VeriStrat ™ which is a proteomic signature that retrospectively was associated with benefit to EGFR TKIs.[13] The Veristrat signature is undergoing prospective studies.

The development of a rash caused by the EGFR TKIs has been retrospectively associated with improved response and survival.[9] The hypothesis of the current study was that by increasing the dose of erlotinib until the development of a grade 2 or tolerable skin rash, response and survival would be improved. This study of erlotinib in the first-line setting of advanced NSCLC evaluated prospectively if increasing the dose of erlotinib until the development of a tolerable skin rash was associated with improved outcome. Given that this trial was designed prior to the discovery of EGFR mutations, this trial also set out to prospectively identify downstream markers of EGFR linked signaling pathways that could be predictive of response or survival to erlotinib.

METHODS

ECOG 3503 was a phase II trial of first-line erlotinib treatment in patients with advanced non-small-cell lung cancer. The trial was designed to evaluate downstream markers of EGFR linked signaling pathways that might be predictive of clinical benefit to erlotinib, particularly the MAPK/Erk pathway. Because rash had been retrospectively associated with

increased response and survival in the past,[9] this trial was designed to prospectively see if the development of grade 2 rash was a predictor of response to erlotinib and of patient survival. Other exploratory analyses of correlative biological markers of EGFR activation and EGFR TKI metabolism in an attempt to broaden our understanding of the impact of erlotinib on our patients were explored.

This trial included patients with previously untreated stage IIIB (with a pleural effusion) and stage IV or recurrent NSCLC. Trial eligibility required submission of an available paraffin-embedded tumor block from the diagnostic specimen. Patients had to have measurable disease, adequate major organ function, and ECOG performance status (PS) of 0 to 2.[14] Patients were required to discontinue known CYP 3A4 inducers or inhibitors one week prior to starting erlotinib. Patients with active peptic ulcer disease, prior surgical procedures affecting absorption and non-healing wounds were not eligible.

All patients were treated with erlotinib starting at 150 mg once a day. The dose was escalated by 25 mg once every two weeks up to 250 mg unless a grade 2 rash or other dose limiting toxicity occurred. A grade 2 rash was defined as a symptomatic macular, papular or erythematous skin eruption covering less than 50% of body surface area. The dose of erlotinib was increased or decreased based on the development and tolerability of rash. The patients with a grade 2 (tolerable) rash were maintained at the current dose of erlotinib. If patients experienced intolerable rash or other adverse events felt to be due to the erlotinib, the dose of erlotinib was reduced by 25 mg increments. No subsequent dose re-escalation was allowed at any time during the study. Patients remained on treatment until disease progression, unacceptable toxicity, withdrawal of consent, treatment delay for more than 14 days, or inter-current co-morbidities. All patients were followed for response until progression and for survival for five years. Tumor assessment was evaluated every two cycles (i.e. 56 days).

Tumor response was defined by the standard Response Evaluation Criteria in Solid Tumors (RECIST 1.0).[15] The National Cancer Institute Common Terminology Criteria (CTCAE, version 3.0) was used to grade toxicities.[16] This study was carried out in accordance with the Declaration of Helsinki, current Food and Drug Administration Good Clinical Practices, and local institutional ethical and legal requirements.

Laboratory Correlates

Phosphorylated mitogen-activated protein kinase (pMAPK) measurement— Paraffin embedded tumor blocks obtained at the time of diagnosis were collected for the assessment of expression of mitogen-activated protein kinase (MAPK) and phosphorylated-MAPK (pMAPK). pMAPK by immunohistochemistry (IHC) was assayed using Dako (Carpantaria, CA) pMAPK kit. The H-score was generated by multiplying the intensity of staining (0=negative, 1=weak, 2=moderate, 3=strong) by the proportion of cell staining (0–100%) which gave scores ranging from 0–300.[17,18]

EGFR mutation—Polymerase chain reaction (PCR) for EGFR exons 19 and 21 were performed in the laboratory of David Carbone at Vanderbilt University.

E-Cadherin, and Vimentin—The protein expression of E-cadherin and vimentin was assessed by OSI Pharmaceuticals using IHC. E-cadherin was assessed by IHC with antibody H-108 (Santa Cruz Biotechnology No. 7870, Santa Cruz, CA). High expression was assessed if at least 40% of cells stained with intensity of 2 or 3. Vimentin assessment was performed by IHC with antibody V9 (Dako No. M0725). High expression of vimentin was defined as at least 10% of cells stained of any intensity.

Others—Gastrin Related Protein (GRP), GRPR, ERα and ERβ IHC assays were performed in the laboratory of Dr. Jill Siegfried at the University of Pittsburgh Cancer Center. Commercial antibodies were available for GRP, ERα and ERβ. The GRPR antibody used was developed within the laboratory of Dr. Siegfried.

Molecular assays performed on blood samples—Optional blood samples were requested at baseline for exploratory analyses. Polymorphisms of drug metabolizing enzymes, CYP 3A4 and 5, the major metabolic pathway for erlotinib, were performed in the lab of Jill Kolesar (University of Wisconsin). DNA was extracted by standard methods and the polymorphism in CYP3A4/5 was evaluated by pyrosequencing, a primer extension sequencing method.[19] Other exploratory analyses using blood samples, such as serum proteomics, have been published separately.[13]

Statistical Analysis

The objective response rate was defined as the proportion of patients with either a complete response or a partial response amongst all eligible and treated patients. Patients who were unevaluable for response were included in the denominator when computing this rate. The disease control rate was defined similarly as the objective response rate but with the numerator included patients with stable disease as well. Overall survival (OS) was defined as the time from registration to death from any cause. Patients who were alive at the time of this analysis or lost to follow-up were censored at the date last known alive. Time to progression (TTP) was defined as the time from registration to first documentation of disease progression (per RECIST). Patients without documented progression were censored at the time of last known free of progression. If such a date was not available, patients were censored at the time of registration.

Exact binomial 90% confidence intervals were computed for the objective response rate and the disease control rate. Descriptive statistics were used to characterize patient demographics, disease characteristics, and adverse events. Fisher's exact test[i] was used to examine the differences in response rate or disease control rate between groups. A landmark analysis[ii] was performed to compare the effects of rash (experienced before the landmark) on overall survival to minimize lead-time bias. Overall survival was computed forward from the landmark. A 2-month landmark analysis was performed on OS together with a 4-month landmark analysis serving as a sensitivity analysis. Patients who died before the landmark were excluded in the landmark analysis. Kaplan-Meier estimates[iii] were used for event-time

[i]Cox DR (1970). Analysis of binary data. London: Methuen and Co.
[ii]Anderson JR, Cain KC, Gelber RD, Gelman RS (1985). Analysis and interpretation of the comparison of survival by treatment outcome variables in cancer clinical trials. Cancer Treatment Reports, 69: 1139–1144.

distributions and the curves were compared using a logrank test[iv]. Hazard ratios were computed using Cox regression models.[v] All tests were performed using SAS 9. All p-values are two-sided. A level of 5% was considered statistically significant. Since analyses on correlative data were exploratory in nature, no statistical adjustment for multiple comparisons was performed.

RESULTS

Patients and Treatment

The study enrolled 137 patients. Nine patients were ineligible, one of which never started protocol therapy. Additional one patient never started protocol treatment. Three patients did not have confirmed eligibility status at the time of this analysis and were excluded from the main analyses. All analyses were based on 124 eligible and treated patients. The toxicity analysis included all 135 treated patients. The majority of patients was female (57.3%), white (91.1%), and had non-squamous cell carcinoma (87.9%). (Table 1)

Treatment with erlotinib was tolerable and most patients discontinued treatment due to disease progression (57.3%). The median number of cycles received was 2.5 (range, 1–17) with 21 (17.0%) of patients received more than six cycles of treatment. Table 2 presents the number of patients treated with the different maximum doses of erlotinib. Seventeen (13.7%) patients received erlotinib at the maximum dose of 250 mg.

Safety

Treatment with erlotinib was tolerable in the first line setting.(Table 3) A quarter of patients (24.2%) discontinued treatment due to toxicity and ten (8.1%) patients came off study due to treatment refusal. Two (1%) patients died due to treatment-related toxicities (pneumonitis/pulmonary infiltrates). The most common grade 1/2 adverse event was rash (70%). Even with dose escalation to a grade 2 rash, not all patients developed a rash. The most common grade 3 adverse events were rash, fatigue , and diarrhea (each with 10%).

Efficacy

Patient response rates and survival were consistent with other phase 2 trials of erlotinib.[8,20] Of the eligible and treated patients, eight (6.5%) patients had an objective response (90% CI 3.2–11.4%). Two patients (1.6%) experienced a complete response. Forty-three (34.7%) patients had stable disease as the best response. The disease control rate is 41.1% (90% CI 33.7–48.9%).

Response rate was not associated with a particular patient demographic. Response rate or disease control rate was not associated with the development of toxicities including a grade 2 or greater rash. One hundred patients eventually experienced disease progression. The median time to progression (TTP) was 3.3 months (95% CT 2.0–3.7).

[iii]Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Journal of American Statistical Association, 1958; 53: 457–481.

[iv]Peto R, Peto J (1972). Asymptotically efficient rank invariant test procedures. Journal of the Royal Statistical Society, 135: 185–206.

[v]Cox, DR (1972), Regression Models and Life Tables. Journal of the Royal Statistical Society, Series B, *34: 187 – 220.*

Of the 124 treated patients, 118 have died and one was lost to follow-up at the time of this analysis. The median follow-up time is 60 months (range 59–63) for the 5 patients still alive. The median overall survival was 7.7 months (95% CI of 5.5–11.7 months). The one year overall survival rate was 40% (95% CI, 32–49%). The two month landmark analysis indicated that patients experiencing grade 2 or greater rash had a significantly better overall survival than those who did not experience a grade 2 rash by 6.8 months (Table 4). The same conclusion was seen if a 4 month analysis was used (Table 4). The two month landmark analysis also indicated patients with a grade 2 rash who also received a maximum dose of greater than 150 mg had a significantly better overall survival than those who received the standard dose of erlotinib or lower doses (median 19.1 months versus 7.2 months respectively). However, at the four month analysis the difference was not statistically significant. (Table 5)

Tumor samples were mandatory on E3503. Only 73 tumor samples were received even though this was required for the eligibility for the trial. Three patients were found to have EGFR mutations. The pMAPK analysis was performed successfully on tumor samples from 60 of the 124 patients on study. The group of patients were dichotomized into two groups (low-expression versus high-expression) using the median of the pMAPK score (median 22.5, range: 0–200) and the pMAPK intensity (median 2, range: 0–10). Regardless of the pMAPK index (theh pMAPK score or intensity), no significant association was detected between the pMAPK expression group and response rate or disease control rate. Patients with low pMAPK expression tended to have a superior OS or TTP than their counterparts. Only overall survival was significantly improved in the low pMAPK groups (with respect to the pMAPK intensity, Table 6).

Other markers evaluated

No difference in response or survival was seen in patients for E-cadherin high (n=19) versus low (n=17) expression. Patients with high vimentin expression had a longer median TTP (3.6 vs. 1.7 mo, p=0.01) and longer median overall survival (12.4 vs. 5.6 mo, p=0.053). Only tumors from 36 patients were assessed for these biomarkers which limited its analysis.

EGFR ligand, ERα, ERβ, GRP, and GRPR, marker analysis was performed on 31 patient samples for this analysis. No difference in response rate, TTP, or OS was noted among or between groups for any markers.

Polymorphism analysis was performed on 65 blood samples for CYP3A4/5, enzymes involved in erlotinib metabolism.[21] No difference was observed in response rate. However, patients with variant (homozygous) polymorphism trended to an improved survival and TTP compared to their counterparts but this was not statistically significant for either CYP3A53B or CYP3A41B.

Discussion

Our results are the first to prospectively associate the development of a grade 2 rash by using the standard 150 mg dose or escalating the erlotinib dose until the development of a grade 2 rash with survival in patients treated with erlotinib in the first-line treatment setting.

Others have dosed to rash in the second-line setting but this maneuver was not associated with improved activity or survival.[22] Based on these results, patients with tumors with no known EGFR mutations could be started on the standard dose of erlotinib and dose escalated until a rash develops. However, a randomized trial comparing 150 mg per day fixed dose to dose escalation to rash in a population without known EGFR mutations would be needed to adequately test this hypothesis. Our analysis is hindered by a lack of baseline smoking history which was added to the protocol via an amendment one month before enrollment finished. Smoking is known to increase erlotinib metabolism.[23] In smokers, one would be more likely to need to increase the dose to develop a rash. Smoking history was collected only on 23% of eligible and treated patients in this trial.

The optimal biomarker of benefit in patients without EGFR mutations has yet to be found. Markers of EGFR linked pathways such as pMAPK have not been helpful to identify patients who both respond or develop disease stabilization and have prolonged survival with the treatment of EGFR TKIs. Genotyping patient's drug metabolizing enzymes may be helpful to identify patients who may require dose escalation of EGFR TKIs. However, this analysis does not take into account therapies that either induce or inhibitor enzyme activity and did not evaluate CYP1A2, a metabolic pathway for erlotinib, which is known to be induced by smoking[21] Our analysis was hindered significantly by the low numbers of available tissue. This remains a significant hurdle for all trials that require tissue for biomarker analysis. In the age of personalized medicine based on tumor evaluation, this is a crucial issue. Development of techniques that either can use smaller amounts of tissue or blood based testing is vital to the future of personalized cancer therapy.

Our results in response and survival indicate that erlotinib used as first-line treatment in an unselected population has similar results to those with first-line chemotherapy which is contradictory to data from IPASS,[5] but is consistent with other small phase 2 trials of first-line erlotinib in advanced NSCLC.[8,20] These results may be due to the fact that the patient's dose was increased in order to develop a rash, which is associated with improved survival.[9]

In conclusion, intrapatient dose escalation of erlotinib beyond 150 mg to develop a tolerable rash was feasible. The development of a rash was associated with improved survival. For patients without known EGFR mutations, tumor markers associated with response, disease stabilization, or survival remain unknown in patients with NSCLC. Availability of tumor tissue to prospectively test biomarkers of activity remains an ongoing issue and impacted the analysis of this trial. This issue remains outstanding in many trials and is one that needs to be resolved in order to make personalized cancer therapy a reality for the majority of our patients with NSCLC.

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Table 1

Patient Demographics and Disease Characteristics at Baseline (N=124)

	N	%
Age (Median, Range)	70	(41–93)
Sex Male Female	53 71	42.7 57.3
Race White Black Asian	113 9 2	91.1 7.3 1.6
PS 0 1 2	34 57 33	27.4 46.0 26.6
Disease Stage at Entry IIIB (not recurrent) IV (not recurrent) Recurrent	8 91 25	6.4 73.4 20.2
Histology Squamous Cell Carcinoma Adenocarcinoma Large Cell Carcinoma Bronchoalveolar Carcinoma (BAC) Non-Small Cell Lung Cancer, NOS Combined/Mixed Other	15 74 2 2 23 3 5	12.1 59.7 1.6 1.6 18.6 2.4 4.0

Table 2

Number of Patients Receiving Various Maximum Dose (N=124)

Dose (mg)	N	%
150	55	44.4
175	24	19.4
200	22	17.7
225	6	4.8
250	17	13.7

Table 3

Treatment-Related Toxicity

Toxicity Type	Treatment Arm A (n=135) Grade				
	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)
Hemoglobin	27	4	-	-	-
Fatigue	30	25	10	1	-
Weight loss	19	7	1	-	-
Dry skin	27	12	2	-	-
Alopecia	18	2	-	-	-
Pruritus/itching	27	13	1	-	-
Rash/desquamation	3	5	1	-	-
Rash: acne/acneiform	28	39	9	-	-
Erythema multiforme	-	1	-	-	-
Hand-foot reaction	1	2	1	-	-
Diarrhea w/o prior colostomy	38	20	10	-	-
Dry mouth	16	1	-	-	-
Dysphagia	1	1	-	-	-
Muco-stomatitis (symptom) oral cavity	16	7	1	-	-
Nausea	25	11	4	-	-
Vomiting	14	3	3	-	-
Alkaline phosphatase	9	2	-	-	-
ALT, SGPT	9	2	1	1	-
AST, SGOT	8	2	2	-	-
Bilirubin	12	9	-	-	-
Hyperglycemia	19	3	1	-	-
Hyponatremia	12	-	2	-	-
Dry eye syndrome	7	1	1	-	-
Pneumonitis/pulmonary infiltrates	-	-	1	-	1

Table 4

Response and Survival by Rash

							P	
Grade	**Complete Response**		**Partial Response**	**Stable Disease**	**Progression**	**Unevaluable**	**ORR**	**DCR**
Grade <2	N	0	2	16	25	14	0.68	0.14
	%	0.0	3.5	28.1	43.9	24.5		
Grade ≥2	N	2	2	24	23	11		
	%	3.2	3.2	38.7	37.1	17.8		
Efficacy	Landmark		Skin Rash	# of Events/N	Median (months)	95% CI	P	
OS	2-Month		Grade <2	41/43	3.9	(2.8, 6.6)	0.02	
			Grade ≥2	54/58	10.7	(6.5, 19.6)		
	4-Month		Grade <2	33/35	3.9	(1.6, 9.3)	0.01	
			Grade ≥2	48/52	15.7	(8.4, 21.2)		

Table 5

Overall Survival by Maximum Dose Level for Patients Developing Grade≥2 Rash

	2-Month Landmark		4-Month Landmark	
	# of Events/N	**Median & 95% CI**	**# of Events/N**	**Median & 95% CI**
Maximum Dose				
≤150	30/30	7.2 (2.7, 16.2)	23/23	8.6 (2.5, 21.2)
>150	29/32	19/1 (9.6, 26.6)	27/30	18.3 (11.5, 25.0)
P	0.047		0.19	

Table 6

Response and Survival by pMAPK Expression Group

Response	**Index**		**Group**	**Yes (N)**	**No (N)**	**p**
CR+PR	pMAPK Score		Low	2	28	1.00
			High	1	29	
	pMAPK Intensity		Low	3	26	0.11
			High	0	31	
Survival	Index	Group	# of Events/N	Median (months)	HR (95% CI) (High vs Low)	p
OS	pMAPK Score	Low	28/30	7.3	1.61 (0.95, 2.74)	0.08
		High	29/30	5.4		
	pMAPK	Low	27/29	8.5	2.09 (1.22, 3.59)	0.01
	Intensity	High	30/31	4.5		