Correlation between Development of Rash and Efficacy in Patients Treated with the Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Erlotinib in Two Large Phase III Studies

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Abstract

Purpose: Data from two large phase III studies were analyzed to characterize the correlation between the occurrence of rash during treatment with the epidermal growth factor receptor inhibitor erlotinib and improved clinical outcomes.

Experimental Design: Overall survival, progression-free survival (PFS), and tumor response were compared between patients in a rash-evaluable subset who did or did not develop rash in National Cancer Institute of Canada Clinical Trials Group Studies BR.21 (single agent in non–small-cell lung cancer, $n = 444$ in erlotinib group and $n = 229$ in placebo group) and PA.3 (combination with gemcitabine in pancreatic cancer, $n = 254$ in erlotinib plus gemcitabine group and $n = 245$ in placebo plus gemcitabine group).

Results: Presence of rash strongly correlated with overall survival in both studies. In Study BR.21, these correlations increased with rash severity grade: grade 1 versus no rash [hazard ratio (HR), 0.41, $P < 0.001$] and grade ≥ 2 versus no rash (HR, 0.29, $P < 0.001$). Similar results were observed for PFS. Disease control (complete response + partial response + stable disease) seemed to increase with the presence and severity of rash. In Study PA.3, grade ≥ 2 rash (but not grade 1) strongly correlated with overall survival improvement: grade ≥ 2 versus no rash (HR, 0.47, $P < 0.001$). Similarly, grade ≥ 2 rash was strongly correlated with improvements in PFS and disease control.

Conclusions: Physicians and patients should view rash development as a positive event indicative of greater likelihood of clinical benefit. Further studies are required to identify patients most likely to develop rash and to determine if dose escalation to induce rash can improve efficacy.

Patients treated with epidermal growth factor receptor (EGFR) inhibitors frequently develop a rash characterized by inflammatory papules and pustules on the scalp, face, neck, and upper trunk. The incidence of rash ranges from 50% to 100%, depending on the agent and cancer type, and the median onset is typically within 1 to 2 weeks of start of therapy (1). Previous studies have suggested that development of rash is associated with improved outcomes in several different tumor types, including non–small-cell lung cancer (2–8), head and neck cancer (2, 3, 9, 10), ovarian cancer (2, 11), colorectal cancer (3, 12), and pancreatic cancer (3, 13).

The most studied area has been lung cancer. In this setting, the initial work with gefitinib, an EGFR tyrosine kinase inhibitor, showed no relationship between either dose or development of skin toxicity or its degree and outcome. In the single-agent studies (IDEAL 1 and 2) testing two doses of gefitinib, the incidence of grade 1, 2, and 3 rash was 26%, 19%, and 1%, respectively, in the 500 mg cohort and 49%, 13%, and 0%, respectively, in the 250 mg cohort. Similar rates were reported in the combination studies: INTACT 1 and 2 (14, 15). Association between degree of skin toxicity and gefitinib efficacy were not reported in these studies. More recently, in two single-agent studies with gefitinib, in bronchioloalveolar and in head and neck carcinomas, an association between occurrence of skin toxicity and efficacy was found (4, 9).

In contrast, analyses from several phase II and III studies with erlotinib in patients with non–small-cell lung cancer (2, 5–8), head and neck cancer (2, 10), ovarian cancer (2, 11), and pancreatic cancer (13) found associations between survival and occurrence and severity of rash. An overview of all phase II erlotinib studies by Perez-Soler showed a correlation between rash severity and response and survival (5).

A similar relationship between rash and clinical outcomes was noted in studies of cetuximab, an EGFR monoclonal antibody. In an analysis by Saltz et al. of multiple phase II studies, there was an association between rash and response rate (3). With panitumumab, another EGFR monoclonal antibody, an association between rash and survival was observed (12).

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These observations have lead to the hypothesis that rash may be a surrogate marker of favorable outcome. As noted elsewhere, however, additional analyses are needed to characterize the relationship between the occurrence of rash and clinical outcomes (16).

Studies showing correlation between development of rash and clinical outcomes of tumor response, progression-free and overall survival typically have been in patients with late-stage disease and short life expectancy. Patients who die within the first month of therapy may not have sufficient time to develop rash, and there would seem to be a greater likelihood of underreporting rash in this group of very ill patients. This underreporting may result in a potential bias against the group of "no rash" patients when correlating outcome to rash.

Two large, multicenter, randomized, phase III studies have shown increased survival with the use of erlotinib: one study was conducted in patients with non–small-cell lung cancer [National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) Study BR.21] and one in patients with pancreatic cancer (NCIC CTG Study PA.3). This report includes further analyses using data from these studies to assess the relationships between the observed efficacy of these therapies and the development of the characteristic EGFR inhibitor–related rash. To avoid the potential bias of early deaths, landmark analyses were done to correlate rash with outcome, excluding patients who died within the first 28 days on study.

Materials and Methods

NCIC CTG Study BR.21. Study BR.21 evaluated single-agent erlotinib 150 mg daily compared with placebo in 731 patients (2:1 randomization) with stage IIIB/IV non–small-cell lung cancer who had failed at least one prior chemotherapy regimen. The protocol was approved by local Institutional Review Boards/Ethics Committees, and all patients provided written informed consent for participation in the study. Results have been reported previously (6). In the intent-to-treat analysis (n = 731), the hazard ratio (HR) for death in the erlotinib group relative to the placebo group was 0.70 [95% confidence ratio (95% CI), 0.58-0.85, $P < 0.001$]. Tumor response, progression-free survival (PFS), and time to symptom deterioration were also improved.

NCIC CTG Study PA.3. Study PA.3 evaluated erlotinib (either 100 or 150 mg daily) compared with placebo given in combination with standard gemcitabine therapy for the treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer. The protocol was approved by local Institutional Review Boards/Ethics Committees, and all patients provided written informed consent for participation in the study. Results have been reported previously (13). In the intent-to-treat analysis (n = 569), the HR for death in the erlotinib group relative to the placebo group was 0.81 (95% CI, 0.67-0.97; P = 0.025).

Rash definition. In both studies, rash was reported, and severity was graded according to NCI CTC version 2.0, using the following criteria: grade 1, macular or papular eruption or erythema without associated symptoms; grade 2, macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface; grade 3, symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥50% of body surface; grade 4, generalized exfoliative dermatitis or ulcerative dermatitis.

Statistical methods. A "rash-evaluable" population was defined for this analysis by including a guarantee time of 28 days of survival to minimize potential reporting bias in occurrence of rash in the group of patients who died early. A landmark of 28 days was selected because in both studies, there was a large difference in the incidence of rash in erlotinib-treated patients who died within 4 weeks (<20%) compared with those patients who survived beyond 4 weeks (>70%). Patients were classified by the treatment that was actually received. Patients who did not receive study drug or who died within 28 days of study start were excluded from the analysis. For Study PA.3, only patients who were in the 100 mg daily erlotinib or placebo plus gemcitabine cohort were included in the analyses because this is the approved dose and schedule in the United States. Survival data (Study PA.3) were updated in June 2005, and these results are used for this report.

Patients on each treatment arm were categorized into one of three groups by worst grade of rash experienced on treatment: no rash (i.e., grade 0), grade 1, and grade ≥2. All reported cases of rash were included in the analyses regardless of the causality assessment. In Study PA.3, analysis of the correlation of rash with outcome was potentially confounded because rash is an adverse event associated with both erlotinib and gemcitabine treatment. The case report forms did not permit the investigator to distinguish between rash attributable to erlotinib therapy versus rash attributable to gemcitabine therapy. Therefore, it was not feasible to distinguish rash that was possibly related to gemcitabine treatment from rash possibly related to erlotinib in these analyses.

Overall survival was measured from time of randomization to death. PFS was measured from time of randomization to progression or death for any cause. Kaplan-Meier methods were used to estimate medians. Disease response was evaluated by the Response Evaluation Criteria in Solid Tumors every 8 weeks. Only patients with evaluable disease at baseline were included in the disease response analyses. Response rates were estimated using a best response of either complete response (CR) or partial response (PR). Disease control was defined as a best response of CR, PR, or stable disease (SD).

A significance level of 0.05 was used for statistical testing. Univariate Cox models were used to examine the association of rash grade with overall survival and PFS in both the overall population and by subgroups. Logistic regression was used to examine the association of rash grade with disease response and disease control by grade of rash. Multivariate Cox models for survival and PFS were constructed with rash and numerous baseline characteristics to see if the rash effect might be explained by these other factors. Factors of particular importance included gender, race, performance status, smoking status, histology, extent of disease, EGFR protein expression as determined by immunohistochemistry, *EGFR* gene amplification or polysomy determined by fluorescence *in situ* hybridization (FISH), and EGFR mutations and kRAS mutations determined by direct sequencing. The results of these assays and the corresponding methods have been previously published (17, 18). In these Cox models, grade of rash was included as if it were a baseline factor instead of as a time-dependent covariate because it seems likely that the occurrence of rash is related to an underlying, but as of yet unidentified, predisposition of the patient. The clinical benefit from erlotinib in patients who develop rash would be expected to start with initiation of therapy rather than at the onset of rash. In addition, because rash usually occurs very early in treatment, there is little difference in the results whether or not rash is included in the model in a time-dependent fashion.

In the following presentation of results, emphasis is given to analyses of the erlotinib-treated patients in these placebo-controlled studies. Rash in the placebo arm occurred much less frequently and likely had a different etiology and, therefore, is not generally comparable to the erlotinib-induced rash.

Results

Study BR.21. Of the 731 randomized patients, 58 who were either not treated or died within 28 days on study (44 erlotinib, 14 placebo) were excluded from the analysis. Rash was reported in only 8 of the 44 erlotinib-treated patients and in none of the 14 placebo patients who were excluded. With these exclusions,

444 patients in the erlotinib group and 229 patients in the placebo group were included in the rash-evaluable population.

Eighty-one percent of the 444 erlotinib-treated patients experienced rash: 30% grade 1, 41% grade 2, 9% grade 3, and 1% grade 4. Eighteen percent of the placebo-treated patients experienced rash: 14% grade 1 and 5% grade 2. Among the patients who experienced rash in the erlotinib group, the median time to onset of maximum grade rash was 8 days, and 90% experienced rash within 25 days. Subgroups of patients who had a notably higher incidence of grade ≥2 rash included patients with baseline Eastern Cooperative Oncology Group performance status (PS) 0 or 1 (55% versus 40% for PS 2 or 3) and patients who did not currently smoke (never/former smokers: 59%/56% versus current smokers: 26%; Table 1). Although the number of patients with biomarker data was relatively small, the presence of a FISH-positive tumor also seemed to result in higher incidence of grade ≥2 rash. Mutations in the *EGFR* or *kRAS* gene did not seem to be associated with the presence of rash.

In univariate analyses, the presence of any rash strongly correlated with overall and PFS, and these correlations increased with the grade of rash (Fig. 1). Patients who developed grade 1 rash survived 144% longer than patients who did not develop rash (HR, 0.41; 95% CI, 0.31-0.55; $P < 0.001$), and patients with grade ≥2 rash survived 245% longer than patients who did not develop rash (HR, 0.29; 95% CI, 0.22-0.38; $P < 0.001$). The difference in survival between patients with grade 1 rash and grade 2 rash was also statistically significant ($P = 0.005$). Multivariate analyses using Cox models were also conducted to adjust for the potential influence of baseline factors. Factors considered for the model included PS, smoking status, prior weight loss, best response to prior therapy, time from initial diagnosis, prior platinum exposure, prior taxane exposure, number of prior therapies, geographic region, gender, age, histology, and EGFR protein status by immunohistochemistry. Factors in the final model were PS, smoking status, prior weight loss, and time from initial diagnosis, using stepwise regression. There remained a strong correlation between rash grade and survival (HR, 0.51 for grade 1: grade 0, $P < 0.001$; HR, 0.34 for grade ≥2: grade 0, $P < 0.001$). In similar multivariate analyses, PFS also remained strongly correlated with rash grade (HR, 0.51 for grade 1: grade 0, $P < 0.001$; HR, 0.35 for grade ≥2: grade 0, $P < 0.001$). Analyses were also done within subgroups classified by gender, age, race, histology, PS, smoking status, and EGFR status as measured by protein expression by immunohistochemistry, gene copy number by FISH, or mutational status for EGFR or kRAS. Higher grade of rash correlated with improved survival

Table 1. Study BR.21 baseline characteristics and tumor biomarkers by rash: erlotinib arm (% patients)

	N	No rash (*n* = 86)	Grade 1 (*n* = 135)	Grade ≥2 (*n* = 223)	*P*
Gender					
Female	162	22	30	49	0.66
Male	282	18	31	51	
Age (y)					
<65	272	21	31	48	0.39
≥65	172	17	29	54	
PS					
0 or 1	303	15	30	55	<0.01
2 or 3	141	28	31	40	
Race					
Asian/Oriental	60	15	42	43	0.12
Non-Asian/Oriental	384	20	29	51	
Smoking status					
Never smoked	101	8	33	59	<0.01
Former Smoker	237	17	27	56	
Current Smoker	65	38	35	26	
Histology					
Adenocarcinoma	226	18	29	53	0.47
Non-Adenocarcinoma	218	21	32	47	
Stage					
Stage < IV at diagnosis	239	19	29	52	0.71
Stage IV at diagnosis	205	20	32	48	
Time from initial diagnosis					
<12 mo from diagnosis	192	25	27	48	0.05
≥12 mo from diagnosis	252	15	33	52	
EGFR protein status by immunohistochemistry					
EGFR positive	107	11	30	59	0.34
EGFR negative	80	19	29	53	
Gene copy number					
FISH positive	33	3	15	82	0.01
FISH negative	55	18	31	51	
EGFR mutational status					
EGFR mutation	20	15	15	70	0.38
EGFR wild type	85	9	29	61	
KRAS mutational status					
kRAS mutation	17	12	47	41	0.20
kRAS wild type	101	16	26	58	

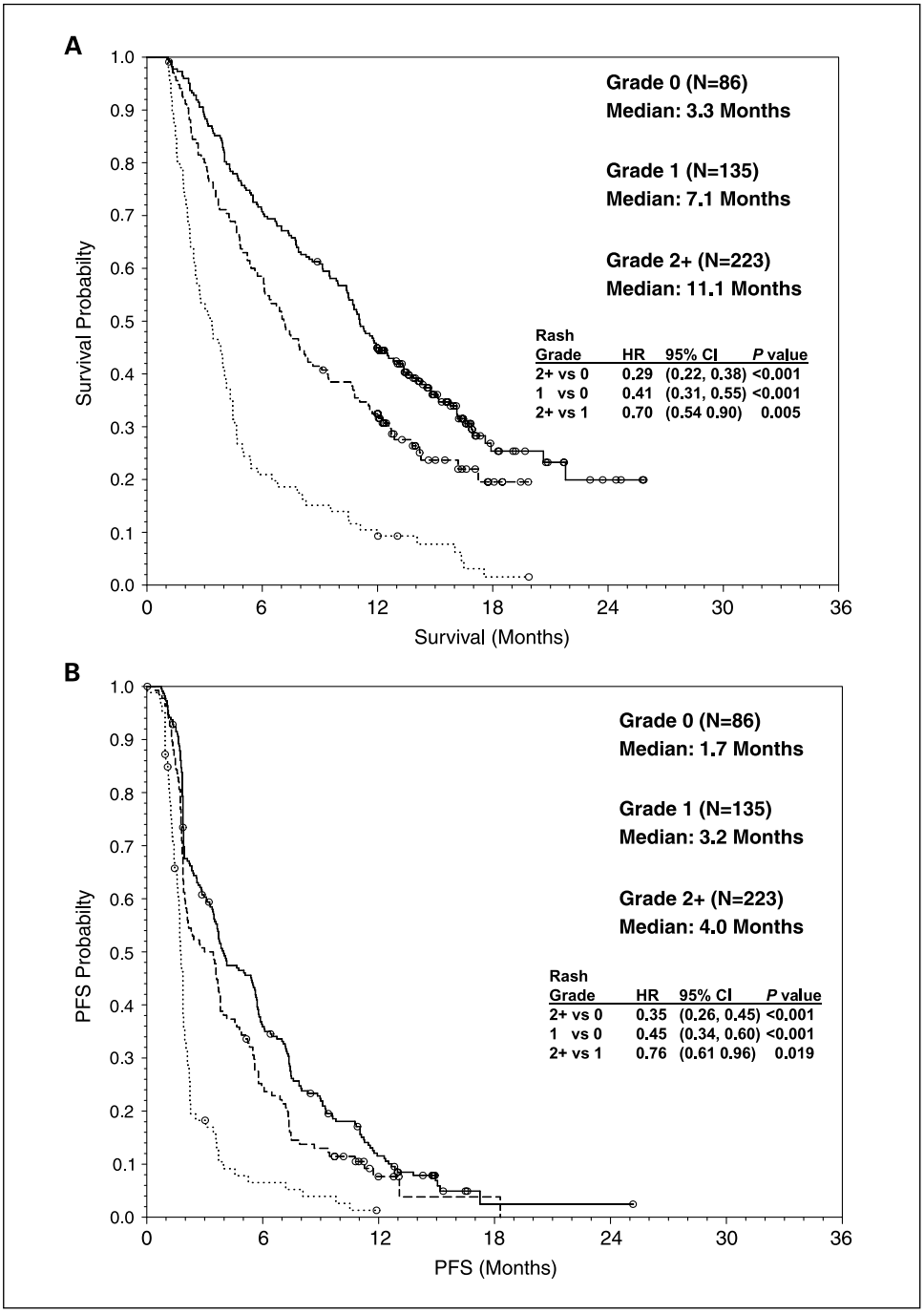

Fig. 1. Survival and PFS by rash grade in erlotinib arm of Study BR.21. There was a significant increase in the probability of survival and PFS associated with increased severity of rash.

and PFS regardless of baseline and biomarker characteristics (data not shown).

Overall survival was also longer in the 18% of placebo patients who developed rash (HR, 0.67; 95% CI, 0.46-0.98; P = 0.039). This improvement did not correlate with the severity of rash with median survival of 4.7 months in patients without rash compared with 8.2 months for patients with grade 1 rash and 7.4 months for patients with grade ≥2 rash.

Disease response (CR + PR) in the erlotinib-treated group was higher by grade of rash. Among the 77 patients in the erlotinib-treated group who did not develop rash, the response rate (CR + PR) was 1% compared with 10% of the 115 patients who developed grade 1 rash and 13% of the 197 patients who developed grade ≥2 rash (grade 1 versus grade 0, P = 0.048; grade 2 versus grade 0, P = 0.017). Only 1% of placebo patients had a response. Disease control (CR + PR + SD) increased with the presence and severity of rash. The disease control rate in the erlotinib-treated group was 16% in patients with no rash compared with 50% in patients with grade 1 rash and 60% in patients with grade ≥2 rash (grade 1 versus grade 0, $P < 0.001$; grade 2 versus grade 0, $P < 0.001$). Twenty-nine percent of the 199 patients in the placebo group had disease control, with disease control rates of 27%/41%/40% for rash grade 0/1/≥2, respectively. These differences were not statistically significant.

In the erlotinib group, dose reductions due to rash occurred in 11% of the erlotinib-treated patients, and 21% were dose reduced for any cause. Dose was interrupted for more than 7 days due to rash in 8% of the patients, and 3% of patients were permanently discontinued due to rash. Overall survival was not associated with dose reductions, interruptions, or discontinuations due to rash.

Diarrhea, anorexia, and fatigue were the most common adverse events associated with erlotinib, other than rash. Among patients in the erlotinib-treated group, there seemed to be a trend for an increase in the incidence of diarrhea with the grade of rash: no rash, 41%; grade 1 rash, 54%; grade ≥2 rash, 66% (Table 2). Other adverse events that had notably higher incidences among patients with rash compared with patients who did not develop rash include cough (no rash, 23%; grade 1 rash, 36%; grade ≥2 rash, 34%), nausea (no rash, 24%; grade 1 rash, 33%; grade ≥2 rash, 39%), and infection (no rash, 15%; grade 1 rash, 27%; grade ≥2 rash, 30%). Patients with rash had longer time on treatment and, therefore, had a longer observation period for adverse events.

Study PA.3. Of the 521 patients randomized within the 100 mg cohort of Study PA.3, 22 were excluded from the analysis because they were either not treated or died within 28 days on study (7 in the erlotinib plus gemcitabine group and 15 in the placebo plus gemcitabine group). Rash was reported in only 1 of the 7 excluded patients on the erlotinib arm, and 2 cases of rash were reported among the 15 excluded patients in the placebo group. The resulting rash-evaluable population for Study PA.3 comprised 254 patients in the erlotinib plus gemcitabine group and 245 patients in the placebo plus gemcitabine group.

The incidence of rash was 71% among the 254 patients in the erlotinib plus gemcitabine group: 36% grade 1, 30% grade 2, and 5% grade 3. The incidence of rash was 30% among the 245 patients in the placebo plus gemcitabine group: 20% grade 1, 9% grade 2, and 1% grade 3. Among the patients who experienced rash in the erlotinib plus gemcitabine group, the median time to onset of maximum grade rash was 10 days, and 90% experienced rash within 44 days. Patients with baseline PS 0 or 1 had a notably higher incidence of grade ≥2 rash (39%) compared with PS 2 patients (16%; Table 3). Although the number of patients with available data was relatively small, there was no apparent relationship between EGFR protein status and the development of rash.

Table 2. Incidence of adverse events occurring in ≥20% of patients in study BR.21 by rash (% patients)

	Erlotinib			Placebo, all (*n* = 229)
	No rash (*n* = 86)	Grade 1 (*n* = 135)	Grade ≥2 (*n* = 223)	
Diarrhea	41	54	66	19
Anorexia	47	55	57	40
Fatigue	56	49	55	45
Dyspnea	45	35	39	33
Cough	23	36	34	30
Nausea	24	33	39	25
Infection	15	27	30	16
Vomiting	21	17	30	20
Headache	12	18	23	17
Chest pain	16	18	19	23
Hemoptysis	12	10	21	14

In univariate analyses, there were no statistically significant differences in overall survival or PFS between patients who did not develop rash and those who did develop grade 1 rash ($P \geq 0.507$), although grade ≥2 rash strongly correlated with improved survival and PFS (Fig. 2). Patients with grade ≥2 rash survived 113% longer than patients who did not develop rash (HR, 0.47; 95% CI, 0.34-0.64; $P < 0.001$) and survived 92% longer than patients with grade 1 rash (HR, 0.52; 95% CI, 0.38-0.71; $P < 0.001$). Multivariate analyses using Cox models were conducted to adjust for the potential influence of baseline factors. Factors considered for the model included PS, any prior chemotherapy, region, gender, age, race, extent of disease, baseline pain score, and baseline albumin. Factors in the final model were extent of disease and baseline pain score, using stepwise regression. There remained a strong correlation between rash grade ≥2 and survival (HR, 0.46 for grade ≥2: grade 0, $P < 0.001$) but not for rash grade 1 and survival (HR, 0.93 for grade 1: grade 0, $P = 0.66$). In similar multivariate analyses, PFS also remained strongly correlated with rash grade ≥2 (HR, 0.43 for grade ≥2: grade 0, $P < 0.001$) but not rash grade 1 (HR, 0.98 for grade 1: grade 0, $P = 0.881$). Analyses were also done within subgroups. The correlation of grade ≥2 rash with improved survival and PFS was maintained across a number patient groups classified by baseline and biomarker characteristics, including gender, age, race, PS 0 or 1, and EGFR protein status (data not shown). The notable exception was the subgroup of patients with PS of 2 who had median overall survival of 4.5/4.7/4.1 months for rash grades 0/1/≥2, respectively.

Survival was not significantly longer in the 30% of placebo plus gemcitabine patients who developed rash (HR, 0.90; 95% CI, 0.68-1.18; $P = 0.435$). Median survival was 6.0 months in patients without rash compared with 6.3 months for patients with grade 1 rash and 7.2 months for patients with grade ≥2 rash.

Disease response (CR + PR) in the erlotinib-treated group was higher in grade ≥2 rash, but the improvement was not statistically significant (response rates of 6% for no rash patients, 7% for grade 1, and 15% for grade ≥2). There were no statistically significant differences in response by rash grade in the placebo plus gemcitabine group. Disease control (CR + PR + SD) increased with the occurrence and severity of rash in the erlotinib plus gemcitabine group: no rash, 49%; grade 1 rash, 58%; and grade ≥2 rash, 74% (grade 1 versus grade 0, $P = 0.210$; grade 2 versus grade 0, $P = 0.002$). Fifty-two percent of the 228 patients in the placebo plus gemcitabine group had disease control, with disease control rates of 49%/61%/59% for rash grade 0/1/≥2, respectively. These differences were not statistically significant.

In the erlotinib plus gemcitabine group, erlotinib dose reductions due to rash occurred in 2% of the erlotinib-treated patients, and 13% were dose reduced for any cause. Erlotinib dose was interrupted for more than 7 days due to rash in 5% of the patients, and 2% of the patients were permanently discontinued due to rash. Overall survival was not associated with erlotinib dose reductions, interruptions, or discontinuations due to rash.

The most common adverse event was fatigue, likely due to concomitant gemcitabine therapy (Table 4). There was a small

Table 3. Study PA.3 baseline characteristics and tumor EGFR protein expression by rash: erlotinib + gemcitabine arm (% patients)

	N	No rash (*n* = 74)	Grade 1 (*n* = 92)	Grade 2+ (*n* = 88)	*P*
Gender					
Female	129	28	36	36	0.90
Male	125	30	36	34	
Age (y)					
<65	135	25	33	41	0.05
>65	119	34	40	27	
PS					
0 or 1	210	26	36	39	0.01
2	43	47	37	16	
Race					
Oriental	20	15	55	30	0.15
Non-Oriental	234	30	35	35	
Histology					
Locally advanced	57	32	40	28	0.49
Distant metastases	197	28	35	37	
Time from initial diagnosis					
<6 mo from diagnosis	236	28	36	36	0.46
≥6 mo from diagnosis	18	39	39	22	
Baseline AAG (α1-acid glycoprotein)					
Normal	97	25	36	39	0.30
Abnormal	116	31	40	29	
EGFR protein status by immunohistochemistry					
EGFR positive	49	27	41	33	0.45
EGFR negative	36	17	53	31	

increase in the incidence of fatigue with the occurrence of rash: no rash, 69%; grade 1 rash, 72%; and grade ≥2 rash, 78%. In the placebo plus gemcitabine group, irrespective of rash, the incidence of fatigue was 71%. There was a higher incidence of diarrhea among patients with grade 1 rash compared with patients with no rash (grade 1 rash, 58% versus no rash, 34%), but this did not seem to be related to the severity of the rash (grade 2 rash, 52%). There was also a higher incidence of alopecia among patients who developed rash: no rash, 5%; grade 1 rash, 13%; and grade ≥2 rash, 24%. Almost twice as many patients with grade ≥2 rash experienced bone pain compared with patients without rash, and more than thrice with grade ≥2 rash had myalgia.

Discussion

These analyses show a relationship between the development of rash during erlotinib therapy and improvements in survival, PFS, and disease control. It is intriguing that in one study, there was also a weak but statistically significant correlation between rash and survival in the placebo group (P = 0.039, Study BR.21). There is no obvious explanation for this observation. The relatively few patients in the placebo group who developed rash in Study BR.21 compared with those on erlotinib, the lack of correlation of clinical outcomes with the severity of the rash, as well as the distinctive nature of an erlotinib-induced rash suggest that this is probably a different phenomenon from the rash observed in erlotinib patients. However, the nature of the rash, other than severity, was not reported in this study; therefore, it is not possible to determine differences in types of rashes experienced between patients treated with erlotinib and those treated with placebo.

In Study BR.21, rash of any severity (grades 1-4) strongly correlated with better outcome compared with no rash in the erlotinib arm. Outcome also improved with increasing severity of rash. In Study PA.3, however, only rash of grade ≥2 correlated with better outcome. These different results may be associated with the addition of gemcitabine with erlotinib in Study PA.3, a lower dose of erlotinib in this study, or with intrinsic patient factors; however, it is difficult to draw any conclusions.

The incidence of some adverse events also increased with increasing severity of rash in patients treated with erlotinib. Longer time on treatment is a possible explanation for this difference. In each study, patients with rash of grade ≥2 had median PFS more than twice as long as that for patients with no rash. Another possible explanation is drug exposure. It is not known whether severity of rash is associated with the patient's level of drug exposure, but if this is the case, then higher incidences of other adverse events may also be related to exposure.

Because rash and severity of rash are strongly associated with improved outcome with erlotinib treatment, it may be useful to be able to predict before initiating therapy that patients would likely develop or not develop rash. To date, attempts to identify patients who will develop rash on EGFR inhibitors have been unsuccessful. Comparisons of the baseline characteristics of patients who developed rash with those who did not failed to identify which patients were most likely to develop a rash. The only baseline characteristic that was associated with increase incidence of rash in both studies was PS, with patients with PS 0 or 1 more likely to develop rash. However, some PS 2 patients in both studies developed grade ≥2 rash, and in Study BR.21, these patients benefited from treatment. A similar benefit in Study PA.3 was not seen for PS 2 patients with grade ≥2 rash. Erlotinib exposure is known to be less in current smokers (19). In Study BR.21, current smokers were less likely to develop rash than never or former smokers, but grade of rash was still

associated with longer survival for current smokers. Smoking status data were not available from Study PA.3. Rash was predictive of better outcome regardless of a positive or negative EGFR status, whether measured as protein expression by immunohistochemistry, gene copy number by FISH, or mutational status.

To clearly show the magnitude of benefit with erlotinib by grade of rash relative to placebo, a control group within the placebo arm was needed. Identifying placebo patients who would get a rash if exposed to erlotinib is desirable. However, there was no reliable way using baseline characteristics in either study to identify a proper placebo control group that could be used to estimate the treatment differences between erlotinib and placebo in subgroups defined by occurrence of rash or by grade of rash. Therefore, it is not possible to provide precise estimates of the benefit that erlotinib confers to the patients with rash relative to a placebo control. However, one can conclude that the associated benefit in patients who develop a rash with erlotinib therapy is substantial. Generally, baseline factors were similar between rash/no rash erlotinib-treated patients and between rash erlotinib-treated patients and placebo patients. The prognostic significance of dissimilarities in baseline factors, where they did exist (PS in Study BR.21 and Study PA.3, never smokers in Study BR.21, FISH positive in

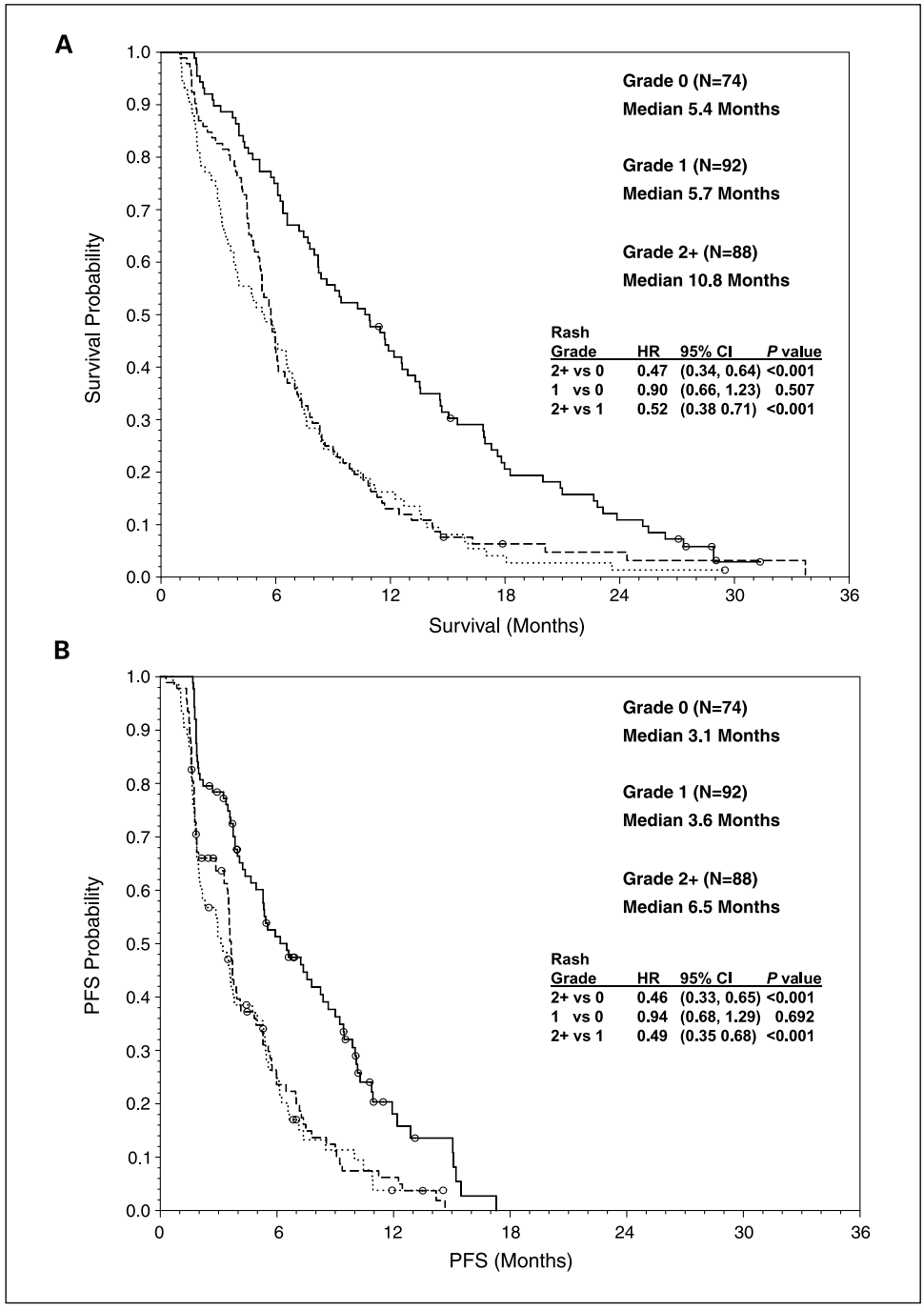

Fig. 2. Survival and PFS by rash grade in erlotinib plus gemcitabine arm of Study PA.3. There was a significant increase in the probability of survival and PFS associated with grade 2 rash compared with grade 1 rash or no rash.

Table 4. Incidence of adverse events occurring in ≥20% of patients in study PA.3 by rash (% patients)

	Erlotinib + gemcitabine arm			Placebo + gemcitabine arm, all (*N* = 245)
	No rash (*n* = 74)	Grade 1 (*n* = 92)	Grade 2+ (*n* = 88)	
Fatigue	69	72	78	71
Nausea	62	45	75	58
Anorexia	45	58	55	52
Abdominal Pain	46	36	57	47
Diarrhea	34	58	52	36
Vomiting	38	39	50	41
Pyrexia	20	43	40	31
Weight Decrease	38	41	40	29
Constipation	20	32	41	34
Edema	38	35	40	36
Infection	20	34	36	24
Bone pain	18	24	34	24
Myalgia	8	23	31	20
Dyspnea	18	23	31	24
Stomatitis	15	24	25	12
Depression	14	18	25	15
Dyspepsia	12	14	24	13
Alopecia	5	13	24	12
Headache	11	11	23	11
Cough	11	20	17	12

Study BR.21, and age in Study PA.3), was in favor of the patients with rash. However, these dissimilarities were relatively small in comparison with the observed magnitude of survival, PFS, and disease control benefit. The differences in baseline characteristics were unlikely to be large enough to account for either the benefit in the rash group or the lack of benefit in the no-rash group relative to placebo. In addition, rash remained a highly significant factor in multivariate survival and PFS analyses, suggesting that it is an important biomarker in its own right. Furthermore, correlations of rash and severity of rash with improved survival and PFS were consistent across virtually all patient subgroups (Study BR.21).

Possible explanations for why some patients develop rash and others do not include individual differences in drug exposure or perhaps the integrity of the immune system or EGFR polymorphisms (20, 21). As stated, rash usually occurs within 2 weeks of start of therapy. In the absence of a reliable predictive factor or diagnostic method, future studies to address the importance of rash as a biomarker for improved outcome may need to require a 2- to 3-week lead-in period on erlotinib to establish which patients develop rash and should assess overall survival or PFS, not response. After the lead-in period, patients could be stratified by whether rash occurred and randomized to different therapies or doses of erlotinib.

One important question is whether increasing the dose of erlotinib can induce rash or increase the severity of rash in those patients who do not develop rash at the initial prescribed dose. It is notable that in Study PA.3 with 100 mg/d erlotinib dosing, most adverse events occurred at a similar lower rate in erlotinib plus gemcitabine patients without rash compared with placebo plus gemcitabine patients. In Study BR.21, a higher erlotinib dose was administered (150 mg/d), and the rate of adverse events in erlotinib patients who did not develop rash tended to be higher than placebo patients. More important than merely inducing rash, it would need to be shown that inducing rash with higher erlotinib doses translates to improved clinical outcome in overall survival or PFS without excessive toxicities. One study has shown the feasibility of escalating erlotinib to doses of 200 to 450 mg/d in most patients without a concomitant increase in non-rash toxicities (22). However, that study was not designed to show improvements in outcome.

Because clinical benefit in patients on erlotinib who develop rash is often substantial, developing effective strategies to manage rash while continuing erlotinib therapy is important. Optimal management of rash in patients on EGFR inhibitors remains somewhat controversial, but aggressive treatment of the side effects may allow patients to continue receiving therapy without dose interruption or drug discontinuation (16, 23). Patients should be counseled regarding the positive aspects of developing rash on erlotinib as part of clinical management of this side effect.

The analyses presented here suggest physicians and patients should view the development of rash as a desirable outcome, perhaps as a sign of erlotinib-induced biological effect. The patient who does not develop a characteristic rash within 2 to 4 weeks is less likely to benefit from erlotinib. There is a need to develop methods for managing the rash without interfering with improvement in outcomes associated with the rash. Further studies are needed to identify which patients are more likely to develop rash and whether increasing the dose of erlotinib can induce rash in patients without rash at the standard dose and improve outcome.

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