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Factors Associated with Clinical Benefit from Epidermal Growth Factor Receptor Inhibitors in Recurrent and Metastatic Squamous Cell Carcinoma of the Head and Neck

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Abstract

Single agent epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) have demonstrated reproducible response rates of 5–15% in treatment of squamous cell carcinomas of the head and neck (SCCHN). The subset of patients that benefits most from these agents remains unknown. We reviewed individual patient data from 5 clinical trials of erlotinib, lapatinib, or gefitinib to determine if there are clinical characteristics that are associated with clinical benefit defined as complete response (CR), partial response (PR), and stable disease (SD) >4 months. Secondary endpoints included progression-free survival (PFS) and overall survival (OS). 319 subjects were included. Observed responses were: 1% CR, 6% PR, 24% SD >4mo, 18% SD < 4mo, 45% progressive disease (PD), 7% not evaluable (NE). The median OS was 6.4 months and the median PFS was 2.7 months. The most common toxicities observed were rash (grade 1 in 37%, grade 2 in 33%, grade 3+ in 6%) and diarrhea (grade 1 in 30%, grade 2 in 10%, grade 3+ in 5%). Performance status (PS) ($p=0.04$), older age ($p=0.02$), and development of rash ($p<0.01$), diarrhea ($p=0.03$), or oral side effects ($p=0.02$) were independently associated with clinical benefit. Older age, better PS, and development of rash were associated with longer PFS and OS. Clinical parameters that appear to predict response to EGFR TKI include PS and age. EGFR mechanistic toxicities that develop during therapy are also highly associated with benefit and suggest a relationship between drug exposure and outcome.

Keywords

Epidermal Growth Factor Receptor; Tyrosine Kinase Inhibitor; Head and Neck Squamous Cell Carcinoma; Meta-analysis

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Conflict of interest statement

The authors have no conflicts of interest to declare.

Introduction

A significant proportion of patients with squamous cell carcinoma of the head and neck (SCCHN) present with either metastatic disease or develop local or distant recurrence ¹. Patients with recurrent or metastatic (R/M) SCCHN are usually treated with palliative intent with a median survival of 6 months. Therefore, an interest in molecularly-targeted therapies has been pursued including those directed at the epidermal growth factor receptor (EGFR)². Different modalities have been used to inhibit EGFR signaling including small molecule tyrosine kinase inhibitors (TKI), monoclonal antibodies, anti-sense therapy, and immunotoxin conjugates. Clinical trials thus far have demonstrated response rates of 5–11% using EGFR TKI as single agents, making it clear that only a subset of patients with R/M SCCHN benefit from this type of treatment ³.

In SCCHN, predictors of benefit from EGFR TKI remain elusive, although development of an acneiform rash has been consistently correlated with clinical benefit. In non-small cell lung cancer (NSCLC) patients, specific phenotypes appear to confer a higher likelihood of response including history of never smoking, female sex, Asian ethnicity, and adenocarcinoma histology ⁴. Interestingly, these clinical characteristics have been associated with the presence of EGFR TKI mutations which do not appear to be present in SCCHN ⁵.

In the past 7 years, the University of Chicago has led or participated in five phase II clinical trials of EGFR TKI in patients with R/M SCCHN. Data from all subjects in the studies were combined to determine if clinical parameters were associated with response to, or benefit from, EGFR TKI.

Materials and Methods

Patient Selection

Between 1999 and 2005, 336 subjects with recurrent or metastatic SCCHN were treated in five multi-institutional phase II trials with erlotinib, lapatinib, or gefitinib ^{6–10}. The protocols for each trial were reviewed and approved by the Institutional Review Boards of all institutions and informed consent was obtained from all patients. Eligibility and patient characteristics from the individual trials are reported elsewhere ^{6–10}. Briefly, all patients were required to be 18 years or older with ECOG performance status < 2, recurrent or metastatic SCCHN, and normal organ function.

Treatment Protocols

The details of the five treatment protocols have been published previously ^{6–10} and the treatment plans of each are detailed in Table 1. To determine response to treatment, patients in each study were evaluated clinically and radiologically at baseline, and then clinically every 4 weeks and radiologically every 8 weeks. The Response Evaluation Criteria in Solid Tumors (RECIST) was used for objective tumor response assessment and Common Terminology Criteria for Adverse Events Version 2.0 was used for toxicity assessment.

Methods and Database

In total, 336 patients were treated on the five protocols, and 319 were ultimately included in the analysis. The UC 13394 trial allowed patients who had had prior EGFR palliative therapy in its “B” arm, a total of fifteen patients, so those patients were excluded from the current analysis. One patient from UC 10869 and one from UC 13394 were excluded due to insufficient data for the variables of interest.

All original data from each trial were recorded and managed at treating sites, and then sent centrally to the University of Chicago to form five databases. The data for this retrospective study were then extracted from the University of Chicago Hematology/Oncology Databases, individual patient charts, and OSI Pharmaceutical databases (with permission). Demographic and clinical data were collected including sex, race, age, nicotine and alcohol history, prior therapies, disease status, performance status, and toxicities (worst grade of rash, diarrhea, nausea, oral/stomatitis, and respiratory symptoms). Responses to the therapy were coded as complete response (CR), partial response (PR), stable disease (SD) >4 months, SD <4 months, and progressive disease (PD). All baseline characteristics, demographic variables, toxicities, and outcome measures were subsequently reconfirmed by individual chart review when available, and then condensed into a single database.

Statistical Analysis

The primary endpoint was clinical benefit defined to include CR, PR, and SD >4 months. Secondary endpoints assessed were progression-free survival (PFS) and overall survival (OS). PFS was defined as date from study entry to date of disease progression or death. Overall survival was defined as date from study entry to death. Both univariate and multivariate analyses were conducted using either logistic regression (clinical benefit) or Cox proportional hazard regression (OS and PFS)¹¹, and Kaplan-Meier curves were used to describe OS and PFS¹². For the multivariate analyses, variables with $p < 0.10$ in the univariate models were included in the full model. Then, a backward elimination procedure was employed to arrive at the final model. Factors analyzed included demographic data (sex, race, age, nicotine and alcohol history, prior therapies, disease status, and performance status) and toxicities (grades of rash, diarrhea, nausea, oral stomatitis, and respiratory). All analyses controlled for individual trial by including dummy variables in each model to indicate treatment received. With respect to tobacco use, sufficient data were not available to differentiate between current and former users. Statistical significance was set at $p < .05$. All analyses were conducted using Stata, Version 10 (StataCorp., College Station, TX).

Results

Treatment Response, Survival, and Toxicity

Three-hundred and nineteen subjects were included in the analysis (Table 2). Across all five studies, 3 patients (1%) showed a complete response, 19 (6%) showed a partial response, 75 (24%) had stable disease for longer than 4 months, 57 (18%) had stable disease for less than 4 months, 142 (45%) had progressive disease, and 23 (7%) were not evaluable (Table 2). Therefore, as defined above, there were 97 patients [31%, 95% CI (25% - 36%)] that showed clinical benefit from EGFR TKI. The median OS for all patients was 6.4 months [95% CI (5.6–7.3), Figure 1A] and the median PFS was 2.7 months [95% CI (2.0–3.1)]. Table 2 displays the most common drug-related toxicities encountered in the five trials. Rash and diarrhea were the most common and were noted in 235 (76%) and 138 (45%) patients, respectively.

Prognostic Factor Analysis

Associations between various prognostic factors and clinical benefit are shown in Table 3. The clinical parameters that appear to predict clinical benefit from EGFR TKI in multivariate analysis include performance status and age. Based on the multivariate analysis, patients older than 70 were 2.33 times more likely to benefit than younger patients [95% CI (1.18 – 4.59), $p=0.02$]. Those with a performance status of 0 or 1 were each approximately 3.6 times more likely to benefit than those with a performance status of 2 (overall $p=0.04$). Additionally, EGFR mechanistic toxicities, including development of rash, diarrhea, and oral stomatitis, were highly associated with clinical benefit. As in previous studies, development of a rash was a robust predictor of benefit, with rash of any grade associated with a 3.52 times greater likelihood of

benefit than no rash development [95% CI (1.58 – 7.84), $p < 0.01$]. There was also evidence for a relationship between rash severity and clinical benefit with rates of benefit of 16%, 33%, and 43% for no rash, grade 1, and grade 2+ respectively ($p < 0.01$ for trend).

A number of factors were associated with better overall survival and progression-free survival (Table 4). Better performance status, older age (Figure 1B and C), nonwhite race, and less advanced disease were associated with longer OS. Those subjects who were older than 70 years had a hazard ratio of death of 0.62 compared to those younger than 70 [95% CI (0.45 – 0.85), $p < 0.01$]. Predictably, those with a performance status of 2 had a hazard of death 3.73 times greater than for those with a performance status of 0 [95% CI (2.38 – 5.85)], and there was also an increased risk for PS 1 versus 0 [HR=1.93, 95% CI (1.41 – 2.64)]. Those with metastatic and local disease fared worse than those with only local disease [HR=1.42, 95% CI (1.04 – 1.92)] and those with metastatic disease only. Finally, as with clinical benefit, development of rash (Figure 1D) and diarrhea were clearly associated with more favorable overall survival.

As with OS, older age, better PS, and development of rash were associated with longer progression-free survival (See Table 4). Those subjects over 70 years were 0.67 times as likely to have disease progression as those under 70 [95% CI (0.50 – 0.92), $p = 0.01$]. Those with PS of 2 were 1.69 times more likely to progress than those with PS of 0 [95% CI (1.11 – 2.58)]. Those who developed any grade of rash were half as likely to progress as those who did not [HR=0.52, 95% CI (0.39, 0.69), $p < 0.01$]. Unlike OS, development of oral stomatitis [HR=0.70, 95% CI (0.52, 0.94), $p = 0.02$] had a significant protective effect and race did not appear to be associated with PFS ($p = 0.30$). Of note, gender, prior palliative chemotherapy, and alcohol or tobacco use had no statistically significant effect on either overall survival or progression-free survival.

Discussion

The present study was undertaken to determine whether benefit in patients receiving EGFR TKI was associated with a specific clinical phenotype. Although individual trials found correlations between certain patient characteristics and objective response or survival, the power of those studies to detect small differences was low, with data sometimes conflicting. We undertook this analysis in an effort to overcome these limitations by combining data from several trials. Individual subject data from five phase II studies revealed that performance status, age, and development of rash, diarrhea, or oral stomatitis correlated with clinical benefit.

Performance status appears to be a universal predictive factor in oncology and is almost always associated with outcome. Studies administering cytotoxic chemotherapy in SCCHN have also demonstrated such an association¹³. Thus it was not surprising that better performance status predicted clinical benefit and survival.

Older age has also been associated with outcome in several cancer types, however, this is usually a negative association and, after correcting for other variables including co-morbidity and performance status, this association often disappears. In the present study older subjects appeared to derive a greater benefit from EGFR TKI, and when treating age as a continuous variable in the OS multivariate analysis, the data still showed a significant protective effect of older age. Whether there are biologic underpinnings to this observation is unclear; however, some molecular changes in SCCHN are correlated with age of onset¹⁴. Conversely, older age may be a surrogate for another variable. For example, since EGFR TKI tend to be well tolerated with manageable toxicities, older patients may have been preferentially offered these therapies earlier in the course of their disease.

Rash is the most common toxicity associated with administration of EGFR TKI. Development of the rash is likely mechanistically related to inhibition of the EGFR and has been associated

in several individual studies with better outcomes³. Thus it was not surprising to find the same phenomenon was evident in our data set. There has been debate about whether this observation is simply a pharmacokinetic effect, as higher exposure is associated with greater rash incidence and severity¹⁵. However, pharmacogenetic and immunologic factors have also been implicated¹⁶. Diarrhea is the second most commonly observed toxicity during EGFR TKI therapy and was also associated with outcome in this study. EGFR TKI associated diarrhea is unlikely to be immunologically mediated. Since pharmacogenetic determinants of rash and diarrhea appear to be different¹⁵, we postulate that the observations in this study are related to drug exposure. The corollary to this hypothesis is that a dose response relationship should exist for EGFR TKI in R/M SCCHN and, indeed, this appears to be the case^{6, 7}.

It is likely that efficacy of EGFR TKI is predicated on achieving a minimum systemic drug level though this is clearly not the only determinant. Theoretically, the dose of EGFR TKI could be titrated in each patient with the goal of achieving a specific drug level or until unacceptable toxicity arises. This would parallel prescribing habits in almost all other medical fields. Clinical trials exploring such administration schedules are currently ongoing. For example, if development of cutaneous toxicity is related to systemic EGFR TKI exposure, one could employ this parameter to escalate dose until grade 2 rash is observed.

Factors that were not associated with our primary endpoint included sex, race, disease status (locally recurrent, metastatic, or both), alcohol use, and smoking history. Some of these contrast with non-small cell lung cancer, which corresponds to the absence of EGFR tyrosine kinase mutations in SCCHN patients who respond to EGFR TKI⁵. Although some of these factors, such as race and disease status, have been linked with survival in this and other studies, it is likely these are prognostic and do not reflect an intrinsic resistance to EGFR TKI. A history of weight loss and co-morbidities have also been associated with outcome in SCCHN studies^{13, 17, 18}, however, these were not examined in our analyses due to lack of available data.

The choice of clinical benefit, which we defined as CR, PR, or SD > 4 months, was designed to select factors that were predictive of outcome with EGFR TKI therapy. We reasoned that subjects who either had RECIST-defined responses or SD for at least 4 treatment cycles were displaying an effect from the agents that would not be expected with best supportive care. Thus, the factors associated with this finding would more likely be predictive than prognostic. However, the optimal way to differentiate between a predictive and prognostic marker is in the randomized trial setting. The studies examined for this analysis did not include control arms and thus it is not possible to fully determine whether the associations are predictive or prognostic. In addition, one must be mindful that the trials analyzed employed different agents with varying activity. This heterogeneity introduces possible confounding effects. Nonetheless, we attempted to address this issue by including an indicator for trial in the regression analysis. Thus all the factors noted to be associated with benefit were independent of the study in which the subjects were enrolled.

The desire to discover predictive metrics of EGFR inhibitor therapy in SCCHN has been heightened by the recent approval of cetuximab in this disease. It appears from this analysis that specific clinical characteristics are associated with likelihood of benefit from EGFR TKI and whether the same parameters prove helpful in selecting patients for therapy with anti-EGFR antibodies remains to be determined. Further research is required in this area with efforts now being directed at finding molecular biomarkers for benefit. EGFR gene copy number has been associated with benefit in NSCLC patients treated with EGFR inhibitors¹⁹ and amplification has been noted in SCCHN²⁰. Whether EGFR gene copy number is predictive of benefit in SCCHN is currently being evaluated along with other potential markers. Clinical trials are continuing to be performed with EGFR TKI in SCCHN. This analysis suggests that eligibility criteria or stratification parameters should take into account the factors that appear to portend

a better outcome in these patients and that the development of mild to moderate drug related toxicity may positively influence outcome.

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Figure 1. Kaplan-Meier Curves for overall (A) survival for the entire cohort and as a function of performance status (B), age (C), and rash observed (D). PS = performance status.

Table 1

Protocols analyzed

Protocol	Accrual Dates	Treatment	No. patients included (%)	No. patients excluded
OSI	11/99-9/00	Erlotinib 150 mg	115 (36)	0
UC 10869	3/01–10/01	Gefitinib 500 mg	51 (16)	1
UC 11588	6/02-3/04	Gefitinib 250 mg	71 (22)	0
UC 11956	4/03-1/05	Erlotinib 150 mg Bevacizumab 15 mg/kg	56 (18)	0
UC 13394	12/04-10/05	Lapatinib 1500 mg	26 (8)	16
Overall			319 (100)	17

Table 2
Subject Demographics, Clinical Characteristics, Clinical Response, and Toxicity

Characteristic		N (%)
Gender	Male	253 (79)
	Female	66 (21)
Age	<50	55 (17)
	50–59	107 (34)
	60–69	94 (29)
	70+	63 (20)
Race	White	269 (84)
	Hispanic	6 (2)
	Black	33 (10)
	Asian	8 (3)
	Other	3 (1)
Disease Status	Local/Local Advanced	137 (43)
	Metastatic	92 (29)
	Both	86 (27)
Performance Status	0	79 (25)
	1	198 (62)
	2	41 (13)
Nicotine History	No	40 (14)
	Yes	236 (86)
Alcohol Use	No	114 (42)
	Yes	160 (58)
Prior chemo for recurrence/metastatic disease	No	144 (49)
	Yes	151 (51)
Response	Complete Response	3 (1)
	Partial Response	19 (6)
	Stable Disease >4mo	75 (24)
	Stable Disease <4mo	57 (18)
	Progressive Disease	142 (45)
	Not Evaluable	23 (7)
Toxicity	Worst Grade	N (%)
Rash	0	74 (24)

Characteristic		N (%)
	1	113 (37)
	2	102 (33)
	3+	20 (6)
Diarrhea	0	172 (55)
	1	93 (30)
	2	31 (10)
	2	14 (5)
Nausea	0	226 (73)
	1	52 (17)
	2	23 (7)
	3+	10 (3)
Respiratory *	0	231 (75)
	1	43 (14)
	2	20 (6)
	3+	14 (5)
Oral/Stomatitis	0	237 (76)
	1	42 (14)
	2	26 (8)
	3+	5 (2)

* Dyspnea or cough

Table 3

Likelihood of Clinical Benefit (CR + PR + SD>4mo) by Clinical Characteristic*

Factor	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (≥70 vs. less)	1.93 (1.04 – 3.59)	0.04	2.33 (1.18 – 4.59)	0.02
Adjusted for PS	2.14 (1.12 – 4.08)	0.02		
Performance Status		0.06		0.04
2	1.00		1.00	
1	3.07 (1.19 – 7.93)		3.60 (1.31 – 9.89)	
0	3.15 (1.14 – 8.72)		3.67 (1.22 – 10.97)	
Rash				
Any grade	3.60 (1.68 – 7.71)	<0.01	3.52 (1.58 – 7.84)	<0.01
0	1.00	<0.01		
1	2.70 (1.20 – 6.06)			
2+	5.42 (2.32 – 12.68)			
Diarrhea (any grade)	1.77 (1.05 – 2.97)	0.03	1.87 (1.07 – 3.26)	0.03
Prior chemotherapy for recurrence	0.62 (0.37 – 1.07)	0.08		
Female Gender	1.21 (0.66 – 2.23)	0.54		
Race		0.58		
White	1.00			
Black	0.90 (0.39 – 2.09)			
Other	0.44 (0.09 – 2.10)			
Alcohol use	0.68 (0.37 – 1.23)	0.20		
Nicotine History	1.60 (0.69 – 3.68)	0.27		
Disease Status		0.22		
Local	1.00			
Metastatic	0.66 (0.36 – 1.22)			
metastatic + local	0.60 (0.31 – 1.15)			
Respiratory Side Effects (any grade)	1.39 (0.75 – 2.56)	0.29		
Nausea (any grade)	1.60 (0.92 – 2.81)	0.10		

Factor	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Oral Side Effects (any grade)	2.10 (1.12 – 3.92)	0.02	2.34 (1.18 – 4.64)	0.02

* All analyses are adjusted for study trial cohort.

OR = Odds Ratio, CI = Confidence Interval

Table 4

Overall Survival and Progression-Free Survival by Clinical Characteristic*

Factor	Overall Survival		Progression-Free Survival	
	Univariate HR (95% CI) p-value	Multivariate HR (95% CI) p-value	Univariate HR (95% CI) p-value	Multivariate HR (95% CI) p-value
Age (≥70 vs. less)	0.78 (0.58 – 1.06) p=0.11	0.62 (0.45 – 0.85) p<0.01	0.69 (0.51 – 0.91) p=0.01	0.67 (0.50 – 0.92) p=0.01
Adjusted for PS	0.64 (0.47 – 0.86) p<0.01		0.63 (0.46 – 0.85) p<0.01	
Performance Status				
0	1.00	1.00	1.00	1.00
1	1.88 (1.39 – 2.53)	1.93 (1.41 – 2.64)	0.99 (0.76 – 1.30)	1.04 (0.78 – 1.39)
2	3.32 (2.18 – 5.05) p<0.01	3.73 (2.38 – 5.85) p<0.01	1.49 (1.01 – 2.20) p=0.06	1.69 (1.11 – 2.58) p=0.02
Rash				
Any grade	0.53 (0.40 – 0.71) p<0.01	.66 (0.49 – 0.89) p<0.01	0.50 (0.38 – 0.67) p<0.01	0.52 (0.39 – 0.69) p<0.01
0	1.00		1.00	
1	0.54 (0.39 – 0.74)		0.53 (0.39 – 0.72)	
2+	0.52 (0.38 – 0.72) p<0.01		0.48 (0.35 – 0.66) p<0.01	
Diarrhea (any grade)	0.65 (0.51 – 0.83) p<0.01	0.63 (0.49 – 0.80) p<0.01	0.80 (0.63 – 1.00) p=0.05	
Prior chemotherapy for recurrence	1.09 (0.85 – 1.40) p=0.48		1.17 (0.92 – 1.48) p=0.20	
Female Gender	0.85 (0.63 – 1.14) p=0.27		0.92 (0.69 – 1.22) p=0.55	
Race				
White	1.00	1.00	1.00	
Black	0.68 (0.45 – 1.04)	0.52 (0.33 – 0.82)	0.76 (0.51 – 1.12)	
Other	0.59 (0.34 – 1.02) p=0.04	0.44 (0.25 – 0.79) p<0.01	1.17 (0.71 – 1.92) p=0.30	
Alcohol use	1.15 (0.87 – 1.52) p=0.33		1.24 (0.95 – 1.62) p=0.12	
Nicotine History	0.90 (0.63 – 1.28) p=0.56		0.83 (0.59 – 1.17) p=0.28	
Disease Status				
Local	1.00	1.00	1.00	
Metastatic	0.86 (0.64 – 1.16)	0.99 (0.73 – 1.34)	1.18 (0.89 – 1.55)	

Factor	Overall Survival		Progression-Free Survival	
	Univariate HR (95% CI) p-value	Multivariate HR (95% CI) p-value	Univariate HR (95% CI) p-value	Multivariate HR (95% CI) p-value
metastatic + local	1.29 (0.96 – 1.73) p=0.04	1.42 (1.04 – 1.92) p=0.05	1.35 (1.02 – 1.79) p=0.10	
Respiratory Side Effects (any grade)	1.33 (1.00 – 1.75) p=0.05		1.17 (0.89 – 1.53) p=0.25	
Nausea (any grade)	1.31 (1.01 – 1.70) p=0.05		0.79 (0.61 – 1.02) p=0.07	
Oral Side Effects (any grade)	0.83 (0.62 – 1.12) p=0.22		0.75 (0.56 – 1.00) p=0.05	0.70 (0.52 – 0.94) p=0.02

* All analyses are adjusted for study trial cohort.

HR = Hazard Ratio, CI = Confidence Interval