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PHASE II STUDIES

A phase II trial of gefitinib for recurrent or metastatic cancer of the esophagus or gastroesophageal junction

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Summary *Background* Conventional chemotherapeutic agents are of limited benefit in patients with recurrent or metastatic cancer of the esophagus or gastroesophageal junction (GEJ). We report results from a phase II trial in this population using gefitinib, an oral epidermal growth factor receptor inhibitor. *Patients and methods* Eligibility required a diagnosis of esophageal or GEJ adenocarcinoma or squamous cell carcinoma, which was either metastatic or recurrent and incurable after initial therapy. No more than one prior chemotherapy regimen was permitted. Treatment consisted of gefitinib 250 mg daily for a minimum of 8 weeks. *Results* Between April 2003 and January 2010, 58 patients, including 18 who were chemotherapy-naïve, were entered into this trial. Toxicity was modest, although most experienced grade 1–2 diarrhea and/or skin rash. There were 4 partial responders (7%) and 10 patients with stable disease (17%). The clinical benefit (partial response and stable disease) lasted for a median 6.1 months. Median survival for all patients was 5.5 months with survival projections at 1-year of 24.6% and at 2-years of 12.5%. *Conclusion* Gefitinib was well tolerated but of limited efficacy in patients with recurrent or metastatic esophageal or GEJ cancer. Further study of this or similar agents will require better patient selection.

Keywords Esophageal cancer · EGFR inhibitors · Gastroesophageal cancer · Gefitinib

Introduction

American Cancer Society 2010 estimates predicted 16,640 new cases of esophageal cancer and 14,500 deaths in the United States [1], reflecting the development of advanced, incurable disease in most patients. Despite the modest gains that have been made in the management of patients with locoregionally confined disease, the care of patients with metastatic esophageal or gastroesophageal junction cancer remains palliative with little improvement in outcome from current treatments [2]. Several modestly effective chemotherapeutic agents have been identified, including the platins, the fluoropyrimidines, the taxanes and epirubicin. Even the most aggressive of combinations, however, will produce response rates of 50% or less and the associated toxicity can be significant [2–7]. Although meta-analysis of the results in gastric and gastroesophageal junction cancer suggests the possibility of a modest survival advantage from the addition of chemotherapy to best supportive care, the overall treatment results remain disappointing [8]. A clear need exists to identify better therapeutic options for advanced disease, and newer approaches, especially those

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incorporating molecularly targeted therapies are of obvious interest.

The epidermal growth factor receptor (EGFR) pathway appears to be important in this disease as in many other solid tumors. EGFR over expression has been reported in up to 90% of patients with esophageal and gastroesophageal junction (GEJ) carcinoma and correlates with increased invasion and poor prognosis [9–12]. Inhibition of the epidermal growth factor receptor would seem to be a promising approach in the management of this disease. Similar observations have been made in a number of other solid tumors, and there is a growing experience and role for EGFR inhibitors, including the monoclonal antibodies cetuximab and panitumumab, and the oral tyrosine kinase inhibitors gefitinib, erlotinib, and others in cancer management. In non-small cell lung cancer, specific EGFR mutations have been identified which have proven highly predictive for response to EGFR inhibitors [13, 14]. Similar mutations have not commonly been identified in other solid tumors, however, including esophageal cancer [15]. Nonetheless we chose to study the oral EGFR inhibitor gefitinib in an unselected population of patients with recurrent or metastatic esophageal or gastroesophageal junction cancer in an effort to identify any potential activity of this agent.

The study of new agents for the treatment of patients with metastatic cancer is often colored by prior exposure to systemic chemotherapy. As such we looked both at patients who had not received prior systemic chemotherapy and at those patients with prior chemotherapy exposure, whether given definitively or for metastatic disease. It was considered acceptable to administer this experimental agent to previously untreated patients given the limited available evidence suggesting that systemic chemotherapy produced a meaningful survival benefit and given the availability of conventional chemotherapy options for those patients progressing during gefitinib therapy. Accrual goals were defined separately for these two cohorts and the data analyses were conducted both separately and together.

Patients and methods

Study design

This was an open label phase II study of single agent gefitinib in patients with recurrent or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or gastroesophageal junction. Support for this trial and the experimental agent gefitinib was provided by Astra-Zeneca pharmaceuticals (reference no.: IRUSIRES0115). Although financial support was provided by this sponsor, the study was developed, supervised, analyzed and reported by the principal investigator (DJA) who vouches for the accuracy and completeness of the data.

The objectives of this study were to assess the activity of single agent gefitinib and its toxicity in a patient population with recurrent or metastatic cancer of the esophagus or gastroesophageal junction. This clinical trial was approved and reviewed yearly by the Cleveland Clinic Institutional Review Board and all patients signed written informed consent before entry on study.

Patient eligibility

Eligibility for this trial required a histologically confirmed diagnosis of squamous cell carcinoma or adenocarcinoma of the esophagus or gastroesophageal junction, and disease which was either metastatic, or recurrent and incurable after initial definitive therapy. Patients could not have received more than one prior chemotherapy regimen whether given for metastatic disease or as part of their initial definitive treatment. An Eastern Cooperative Oncology Group performance status of 0 to 1 was required, as was adequate hematologic, renal, and hepatic function to tolerate the proposed treatment. Response to therapy was the primary endpoint, and measurable disease was required for patient entry. Patients were excluded if they had received any investigational drug within the previous 30 days, if they had a small cell or mixed small cell/non-small cell histology or if there were any evidence of another uncontrolled malignancy. Concomitant use of phenytoin, carbamazepine, barbiturates, rifampin, or St. John's Wort excluded patients from study entry due to potential interference with gefitinib metabolism. Pregnant or breast-feeding women, patients with hypercalcemia, and those with pre-existing clinically evident interstitial lung disease were also excluded.

Evaluation and treatment

All patients underwent an initial history and physical examination, as well as staging radiographs of the chest and CT scans of the brain, chest, abdomen and pelvis. Radionuclide imaging for possible bone metastases was also performed as well as a complete blood count and full battery of serum chemistries. Quality of life data was collected at patient entry and during therapy using the Fact E quality of life questionnaire. The results of this quality of life analysis are not being reported at this time.

All patients received oral gefitinib 250 mg once daily, the recommended dose identified by the IDEAL1 and IDEAL2 trials of gefitinib in advanced lung cancer [16, 17]. The treatment plan called for this therapy to continue for a minimum of 8 weeks, at which time measurable disease would be reassessed, and response assigned using RECIST 1.0 criteria [18]. Gefitinib would be discontinued if there was objective evidence of disease progression, subjective

evidence of clinical deterioration, or drug intolerance. Patients with stable or responding disease would remain on treatment. Gefitinib pill counts were conducted at every clinic visit to monitor medication compliance.

Any intolerable toxicity, as defined by the patient or the investigator, mandated discontinuation of the experimental gefitinib and removal from study. The development of any CTCAE (v.3.0) grade 3 or 4 toxicity (or grade 2 diarrhea), not felt to reflect disease progression required temporary interruption of gefitinib therapy until resolution or improvement of the toxicity. If this did not occur within 2 weeks, the drug was discontinued and the patient was taken off study. Resolution or improvement of the toxicity would allow for reinstitution of full dose gefitinib therapy. Consistent with the very infrequent need for gefitinib dose reduction below 250 mg daily, seen in both the IDEAL1 and IDEAL2 trials [16, 17], dose reduction was not permitted in this study. All appropriate supportive care, particularly for skin rash and diarrhea, was provided to patients during the course of their therapy.

Statistical considerations

The primary objective of this study was to explore the activity of gefitinib in patients with recurrent or metastatic cancer of the esophagus or gastroesophageal junction. The secondary objective was to assess toxicity of the agent in this patient population. Chemotherapy-naive patients and patients previously treated with chemotherapy were included although these two groups had separate hypotheses and separate accrual goals.

In previously untreated patients, a complete or partial response rate of 45% or more was felt to justify future study with this drug, whereas a response rate of 25% or less suggested that the agent would not warrant further study. Seventeen previously untreated patients were to be entered during the first stage of a planned two stage design. If response occurred in three or fewer patients, than this portion of the study would be closed. If four or more patients responded then an additional 19 patients would be accrued. If at least 14 of the 36 patients entered responded then the agent would be considered active in the previously untreated patient population, with a significance level and power of 5% and 80% respectively.

In the previously treated patient cohort our expectations were lower. A response rate of 25% or more was felt to justify future study whereas a response rate of 10% or less would suggest that the activity of the agent did not warrant further study. Twenty-one previously treated patients were to be entered during the first stage of this study. If at most one patient responded then this cohort would be closed. If two or more patients responded then an additional 19 patients were to be accrued. The agent would be considered active if at least eight or more of the 40 patients responded, with a significance level and power of 5% and 81% respectively.

Categorical variables were summarized as frequency counts and percentages; continuous variables were summarized as median with range (minimum and maximum). Response rate and clinical benefit, or disease-control rate (defined as response or stable disease) were estimated using exact 95% confidence intervals (95% CI). Fisher's exact test was used to compare the clinical benefit rate in patients experiencing, and not experiencing toxicity. Overall survival was estimated using the Kaplan-Meier method and compared between sub-groups using the log-rank test. Gefitinib compliance was characterized by the percentage of prescribed pills taken per patient.

Results

Between April 2003 and January 2010, 58 eligible patients were entered onto this clinical trial. All patients have now been taken off study because of either disease progression or death. Table 1 details the patient and tumor characteristics. As noted, the population was predominately com-

Table 1 Patient and tumor characteristics (N=58)

Age (median)	60 (range 33–82) years
Race:	
White	57 (98%)
Black	1 (2%)
Gender:	
Male	48 (83%)
Female	10 (17%)
Performance status:	
0	32 (55%)
1	26 (45%)
Tumor location:	
Proximal/Mid Esophagus	6 (10%)
Distal Esophagus	20 (35%)
Gastroesophageal Junction	32 (55%)
Histology:	
Adenocarcinoma	54 (93%)
Squamous cell carcinoma	4 (7%)
Prior Surgery:	24 (41%)
Prior Radiation:	
Definitive	31 (53%)
Palliative	12 (21%)
None	15 (26%)
Prior Chemotherapy:	
Definitive	30 (52%)
Palliative	10 (17%)
None	18 (31%)

posed of white, male patients with adenocarcinoma. Only four patients had a squamous cell carcinoma involving the proximal esophagus. Twenty-four patients (41%) had previously undergone surgical resection, with or without pre-operative chemotherapy and radiation. Measurable disease was identified most frequently in liver (59%), node (41%), and lung (31%). Other sites of involvement included bone, peritoneum, adrenal, skin and other soft tissue.

Because of an insufficient response rate in the chemotherapy-naive patients, this cohort was closed after the first 18 patients were entered. The first-stage response rate in the previously-treated cohort, however, was sufficient to allow the full, 40 patient accrual.

Toxicity and compliance

In general, gefitinib was well tolerated. The most commonly reported toxicities are detailed in Table 2, although it was not always possible to assign causality to the gefitinib. Diarrhea and skin rash were common but mild. Additional toxicities noted included grade 1 mucositis or stomatitis in two patients, cracking and splitting of fingers and or toes in two patients, and fatigue in two patients. Only one patient experienced toxicity sufficient to mandate treatment discontinuation. This patient developed a transient mental status change while on gefitinib. Neurologic function returned to normal after discontinuation of the medication and he was taken off study.

Compliance with the medication was monitored by gefitinib pill counts, an imperfect measure which was easily compromised. Although it could only be assessed in 47 of the 58 patients, these patients took a median 100% (range 90%–100%) of their prescribed pills. In 11 patients early disease progression and clinical deterioration precluded obtaining these pill counts. The possibility exists that the compliance may have been significantly less in the patients in whom it could not be assessed.

Table 2 Most common toxicities (CTCAE v3.0)

Diarrhea	
None	32 (55%)
Grade 1	25 (43%)
Grade 2	1 (2%)
Skin rash	
None	19 (33%)
Grade 1	38 (66%)
Grade 2	1 (2%)
Nausea	
None	51 (88%)
Grade 1	6 (10%)
Grade 2	1 (2%)
Anorexia	
None	53 (91%)
Grade 1	5 (9%)

Response to therapy

In the 18 chemotherapy-naive patients there was one partial response and one patient with stable disease for a clinical benefit rate of 11% (95% CI 1.4%–35%). In the 40 patients with previous exposure to chemotherapy there were three partial responders and nine patients with stable disease, for a clinical benefit rate of 30% (95% CI 17%–46%). The clinical benefit rate for the entire patient population was therefore 24% (95% CI 14%–37%) with four partial responders (7%) and ten patients with stable disease (17%). This clinical benefit lasted for a median duration of 6.1 (range 3.4–18.8) months; 10.3 (range 4.6–18.8) months in the partial responders and 5.2 (range 3.4–13.8) months in those with stable disease. Clinical benefit was observed in patients with both adenocarcinoma and squamous cell carcinoma, although given the small numbers of patients with squamous cell carcinoma, meaningful comparison between the histologic sub-types was not possible.

Gefinitib toxicity during the first 8 weeks of therapy was correlated with clinical benefit. Of the 39 patients who developed a skin rash, 13 experienced a clinical benefit, as opposed to only one patient who benefited from the drug among the 19 patients who did not develop a rash (33% vs. 5%; $P=0.023$). A similar trend was seen for diarrhea. Of the 24 patients who developed first-cycle diarrhea there were eight who experienced clinical benefit, while of the 34 without diarrhea only six benefited (33% vs. 18%; $P=0.17$).

Survival

The median survival for all 58 patients was 5.5 months (Fig. 1). The Kaplan-Meier estimate of 1-year survival is 24.6% and 2-year survival 12.5%. No survival difference was observed between those patients previously exposed to

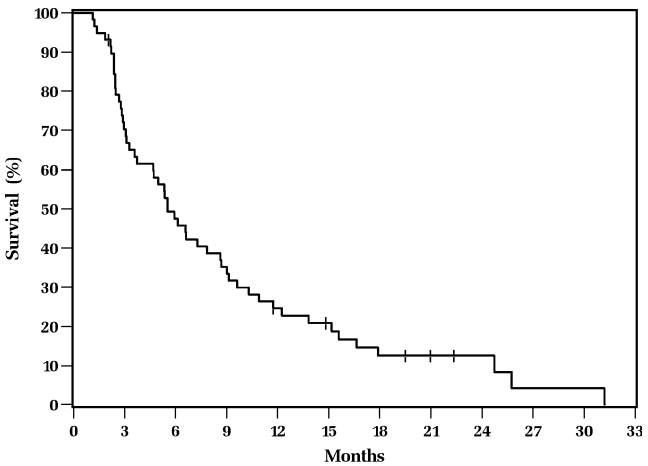

Fig. 1 Overall survival

chemotherapy and those patients with no prior chemotherapy (P=0.52). Although there was also no survival difference identified between patients with adenocarcinoma and squamous cell carcinoma (P=0.67), this observation is limited by the very small number of patients with squamous cell carcinoma. After progressing on gefitinib, 13 patients received additional chemotherapy and 14 received palliative radiation.

Discussion

At the onset of this study we considered a response rate of 25% or greater in the previously-treated patients, and 45% or greater in previously untreated patients to be indicative of an interesting agent worthy of further study. Neither milestone was achieved and this must be considered a negative study. Although the overall clinical benefit rate of 24% is of interest, it is less than the 40%–60% clinical benefit or disease-control rate generally achieved with this class of agents in treating other epithelial malignancies [19, 20]. It should be pointed out that most esophageal cancers are EGFR positive, but that the patients entered on this trial were not selected for EGFR overexpression. Although EGFR gene mutations have been identified in patients with esophageal cancer, unlike in non-small cell lung cancer no specific EGFR mutations have proven predictive for disease responsiveness to EGFR inhibition [13–15].

Clinical benefit, i.e. response and stable disease rate, is an interesting endpoint. Although it may to some extent only reflect an indolent disease natural history, it has been accepted as a meaningful endpoint particularly after the use of molecularly targeted therapies [19, 21]. Evidence exists that it correlates with overall survival but it remains unclear how much the agent itself is contributing to this clinical benefit. Clearly disease stabilization after a period of disease growth would allow better assessment of treatment efficacy. However, the presence of advanced measurable disease, not progressive disease was the entry criterion for this study.

The results we report are not dissimilar to those reported by other investigators using either gefitinib or erlotinib in advanced esophageal cancer [22–26]. Response rates below 10% and clinical benefit rates below 30% have consistently been reported, and the impact of these agents in patients with advanced disease remains unclear. The occasional patient with prolonged disease stability is of interest and at least suggests the possibility that there may be some benefit from these agents or from the monoclonal anti-EGFR antibodies if used in conjunction with conventional chemotherapy, radiation and or surgery as part of palliative or even definitive management [27–30].

Indeed, our experience at the Cleveland Clinic suggests this possibility in patients with locoregionally-confined esophageal and GEJ cancer [29]. When retrospectively compared to a historical control population, the addition of gefitinib to a standard multimodality treatment schedule produced a marginal survival benefit. We could not identify such a benefit in patients with squamous cell head and neck cancer [31], however, and others have not found benefit from the addition of this agent to definitive treatment in non-small cell lung cancer [32].

Perhaps the epidermal growth factor receptor (EGFR1) targeted by these agents is not the best target. The epidermal growth factors actually consist of a family of related receptors, all of which may serve as potential targets. EGFR2 or HER2 may be a more attractive candidate [26]. Recent reports have identified HER2 overexpression in up to 34% of patients with gastric and GEJ adenocarcinoma [33]. Furthermore, a large phase III randomized trial has now demonstrated a survival benefit for patients with metastatic HER2 positive gastric and GEJ adenocarcinoma given chemotherapy and trastuzumab, an antibody to HER2, when compared to treatment with chemotherapy alone [34]. Retrospective review of our Cleveland Clinic patients with esophageal adenocarcinoma has demonstrated HER2 overexpression in 15% [35], suggesting that targeting HER2 in the HER2 positive patients may be more fruitful than blindly targeting HER1 (EGFR).

In conclusion we have found little evidence that there is major benefit from the single agent use of gefitinib in patients with recurrent or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or GE junction. While the possibility exists that there is a sub-population of patients for whom this agent may prove valuable, no clinical, pathological or molecular markers have yet been found to identify these patients. Further study of gefitinib and similar agents will require better patient selection or more innovative treatment approaches.

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