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Dual Inhibition of the Epidermal Growth Factor Receptor Pathway with Cetuximab and Erlotinib: A Phase I Study in Patients with Advanced Solid Malignancies

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Abstract

Purpose—To determine the optimal dose of the antiepidermal growth factor receptor (EGFR) monoclonal antibody cetuximab that can be safely administered in combination with a standard daily dose of erlotinib in patients with advanced solid malignancies.

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Patients and Methods—Patients with advanced solid malignancies who had failed standard chemotherapies received escalating doses of cetuximab without a loading dose (100, 200, 250 mg/m² i.v. weekly) in combination with a fixed dose of erlotinib (150 mg daily orally) until disease progression or unacceptable toxicity.

Results—Twenty-two patients were treated, including 14 patients (64%) with non-small cell lung cancer. Twenty patients received combination treatment at the highest dose level for a median of 5.5 weeks (range, 1–31 weeks). One dose-limiting toxicity was observed: grade 3 skin rash. Overall, the most common adverse events (any grade, grade 3/4) were consistent with the safety profiles of the individual drugs: acneform rash (100%, 9%), diarrhea (77%, 5%), and hypomagnesemia (59%, 12%). Seven of 18 evaluable patients (38.9%) had stable disease lasting for a median of 16.6 weeks (range, 6.1–25.1 weeks).

Conclusion—Dual EGFR inhibition with cetuximab and erlotinib is feasible; the observed toxicities were manageable and consistent with the safety profiles of the individual drugs. The recommended doses for phase II studies are 250 mg/m² i.v. weekly for cetuximab and 150 mg daily orally for erlotinib.

Keywords

Cetuximab; Erlotinib; Phase I; Solid malignancies

Introduction

The epidermal growth factor receptor (EGFR) is overexpressed in a variety of solid tumors; increased EGFR expression has been associated with poorer clinical outcomes in some of these malignancies [1–3]. The anti-EGFR chimeric monoclonal IgG₁ cetuximab (Erbix®; ImClone Systems Incorporated, New York, and Bristol-Myers Squibb Company, Princeton, NJ) is approved by the U.S. Food and Drug Administration for use in combination with irinotecan for the treatment of metastatic colorectal cancer and for use with radiotherapy for treatment of locoregionally advanced squamous cell carcinoma of the head and neck (SCCHN) [4, 5]. Single-agent cetuximab is also approved for metastatic colorectal cancer in patients intolerant to irinotecan and in SCCHN patients after failure of prior platinum-based therapy [6–9]. Clinical trials show that cetuximab may also have promising activity when used with chemotherapy in first-line treatment of non-small cell lung cancer (NSCLC) [10–15]. Erlotinib (Tarceva®; Genentech, Inc, South San Francisco, CA and OSI Pharmaceuticals Inc., Melville, NY) is a tyrosine kinase inhibitor (TKI) that improves the survival time of patients with advanced NSCLC who progress after one or two prior chemotherapy regimens [16]. Erlotinib is approved for use in advanced NSCLC after failure of previous chemotherapy, and in combination with gemcitabine in first-line treatment of advanced pancreatic cancer [16, 17].

The combination of an anti-EGFR monoclonal antibody and a TKI may enhance the inhibition of downstream signaling and lead to better treatment responses and outcomes [18–20]. This phase I study was designed to assess the feasibility and safety of administering an optimal dose of cetuximab in combination with a standard 150-mg/day dose of erlotinib in

patients with advanced malignancies who had previously failed standard chemotherapy regimens.

Patients and Methods

Eligibility Criteria

Patients were treated at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (Baltimore, MD) and the Helen F. Graham Cancer Center (Newark, DE). Patients aged 18 years with advanced solid malignancies who had failed standard chemotherapies and had Eastern Cooperative Oncology Group performance status score of 0–1, at least one bidimensionally measurable lesion, and a life expectancy \geq 3 months were eligible. Prior chemotherapy, major surgery, or radiation therapy were acceptable (\leq 4 weeks, \leq 3 months if radiation therapy to chest area). Patients with inadequate hematologic, hepatic, or renal function, symptomatic or uncontrolled central nervous system metastases, uncontrolled heart disease, or pulmonary fibrosis, and those who had received prior anti-EGFR therapy were excluded.

All patients provided written informed consent before any study procedures were performed. The study was approved by the investigational review board at both participating sites, and was conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with good clinical practice and national regulatory guidelines.

Trial Design

This was an open-label, dose-escalation, phase I trial with an accelerated titration design. Cetuximab was administered once weekly, without an initial 400-mg/m² dose, in sequential cohorts at dose levels of 100, 200, and 250 mg/m², via 60-minute i.v. infusion after diphenhydramine pre-medication. After the first cetuximab dose, patients started erlotinib at a fixed dose of 150 mg/day orally. Each treatment cycle was 4 weeks regardless of omitted doses; doses could be omitted, but no delayed cycles were allowed. Treatment was continued until disease progression or unacceptable toxicity. Dose modifications of cetuximab or erlotinib were allowed in the event of severe toxicity.

One patient per cohort was to be treated until a dose-limiting toxicity (DLT) was observed during the first treatment cycle; that cohort was to be expanded to a total of six patients before further dose escalation was considered. If two instances of grade 2 toxicity were observed in the first cycle, the cohort was to be expanded to three patients before further escalation. The maximum-tolerated dose (MTD) was defined as the highest dose at which less than one third of the patients experienced a DLT during the first cycle. The recommended phase II dose (RPIID) was to be defined by the MTD or the highest dose level (250 mg/m²) if an MTD was not reached. Up to 15 additional patients were to be enrolled at this RPIID to confirm its safety. Intrasubject dose escalation to a new level shown to be safe was allowed provided the patient did not experience a DLT after at least 4 weeks on the lower dose level.

DLT was defined by any of the following events occurring during the first cycle only: any grade 4 toxicity other than infusion reaction; any grade 3 skin toxicity that required

treatment interruption for >14 days; grade 3 or 4 diarrhea, vomiting, or nausea that could not be controlled with medical intervention or prophylaxis; any other grade 3 nonhematologic toxicity except for asthenia or infusion reaction; delayed recovery from toxicity (other than skin toxicity) resulting in withholding of retreatment >4 weeks; grade 4 neutropenia for at least five consecutive days or grade 3 or 4 neutropenia with sepsis or fever; or thrombocytopenia $\geq 25,000$ cells/mm³ or bleeding requiring a platelet transfusion.

Assessments

High-resolution computed tomographic (CT) scans of the chest and of other tumor-bearing regions were performed within 4 weeks of the first dose of study treatment. All other baseline evaluations were performed within 14 days of the first dose.

The primary endpoint was identification of the RPIID for cetuximab in combination with erlotinib. Secondary endpoints included safety—defined by the MTD and incidence of adverse events (AEs) and abnormal laboratory parameters—and objective tumor response. AEs were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 and coded to the Medical Dictionary for Regulatory Activities version 10.

Patients were evaluated for response according to modified World Health Organization criteria. CT analyses of tumor-bearing regions and other tumor response assessments were performed every 8 weeks, or more frequently if indicated. Responses to treatment required confirmation at least 4 weeks later. Criteria for stable disease (SD) had to be met 35 days after the first dose. The duration of SD was defined by the time between the first dosing date and the documented progression date in patients with SD as the best tumor response. Tumor measurements made by the investigator were reviewed by the study sponsor to determine the best tumor response and date of progression.

Evaluations for demographic and baseline characteristics, as well as safety, efficacy, and dosing, were carried out on the total group of treated patients, using descriptive statistics.

Results

Patient Disposition and Demographics

From August 2005 to December 2006, 25 patients in total were screened and 22 patients were treated. One patient each was treated at the first two dose levels, and 20 patients were treated at the third dose level with cetuximab weekly at 250 mg/m² i.v. plus 150 mg erlotinib orally. All patients had been treated previously with chemotherapy in the adjuvant or metastatic setting, most of them (77.3%) with two or more prior regimens. Most patients (64%) had NSCLC (supplemental online data, supplemental Table S1).

Treatment Exposure

One patient was enrolled in each of the first two cohorts. Those patients received cetuximab for 8 weeks and erlotinib for 7.9 and 7.3 weeks, respectively, without dose modification or omission. In the third dose-level cohort, 20 patients were enrolled in total; cetuximab and erlotinib were each administered for a median duration of 5.5 weeks (range, 1.0–31.0 weeks

and 1.0–30.1 weeks, respectively). In total, 135 infusions of cetuximab (250 mg/m²) were administered, and 28 planned infusions were omitted for toxicity or other reasons. Four cetuximab infusions were administered at a reduced dose: two because of skin toxicity, one as a result of delayed recovery from asthenia, and one because of an unknown reason. In total, 980 doses of erlotinib were administered, and 142 planned doses were omitted. The erlotinib dose was reduced in one patient for 11 days.

The most common drug-toxicity reasons for study treatment discontinuation were: five patients with acneform rash (four with grade 1 or 2 and one with grade 3), one patient with grade 3 diarrhea, one patient with grade 2 hypomagnesemia and hypocalcemia, and one patient with mild eye and skin pain.

Safety

No DLT was reported at the first two dose levels. One DLT (grade 3 rash) was reported in the third dose-level cohort. The cohort was expanded to six patients without another DLT, and subsequently to a total of 20 patients to collect additional safety data at this dose level. The MTD was not reached at the third dose level, and consequently, 250 mg/m² of cetuximab and 150 mg of erlotinib were determined to be the RPIIDs.

Overall, the safety profile of the combination was consistent with the individual safety profiles of each drug (Tables 1 and 2). The most common AEs were acneform rash and diarrhea. No grade 4 acneform rash was reported. Two patients (9.1%) had grade 3 acneform rash, whereas the rash was mild to moderate (grade 1 or 2) in the other 20 patients. Severe infusion reactions were not reported; three patients (13.6%) had grade 1 infusion reactions. Grade 3 or 4 hypomagnesemia was reported in two patients (12%).

Hematologic abnormalities were mostly mild to moderate, with grade 3 leukopenia reported in one patient (4.8%), grade 2 neutropenia in one patient (4.8%), and 16 patients (76.2%) experiencing anemia (none of them severe). No grade 3 or 4 values in liver or renal function tests were reported.

Efficacy

Eighteen patients were evaluable for response. No objective responses were observed. Seven patients (38.9%)—four with NSCLC and one each with colorectal cancer, cervical cancer, and an epithelial neoplasm with neuroendocrine features—had SD lasting for a median of 16.6 weeks (range, 6.1–25.1 weeks). All SD was seen in the highest dose-level cohort.

Discussion

This study demonstrates that the combination of cetuximab and erlotinib is feasible and tolerable in patients with advanced malignancies who had previously failed standard chemotherapies. The safety profile of the combination was consistent with each of the individual drugs, with no unexpected toxicities seen during the study. The doses recommended for phase II evaluation were 250 mg/m² weekly for cetuximab and 150 mg daily erlotinib.

An accelerated-titration dose escalation design was used for cetuximab. Given that the safety profile of each individual drug is well characterized, this design enabled us to escalate doses rapidly, starting from a 100-mg/m² dose of cetuximab that would allow detecting and monitoring potentially prohibitive or unexpected safety signals, minimizing the number of patients treated with a dose below the approved cetuximab standard (250 mg/m²). The intermediate level (200 mg/m²) was included to merely avoid a dose gap larger than twofold, because, with one single patient enrolled, potential interpatient variability could override any relevant exposure difference between this and the highest dose allowed (250 mg/m²).

Although the initial dose of cetuximab has been used in other phase I studies of cetuximab plus TKI combinations [21, 22], the 400-mg/m² initial cetuximab dose was not included in this trial, an omission designed to curtail potential overlapping toxicities. This approach was considered acceptable based on previous pharmacokinetic studies showing that weekly administration of cetuximab at 250 mg/m² [2] without the initial higher dose still resulted in serum levels providing >50% target occupancy, and therefore would not compromise activity [23].

This study did not include a pharmacokinetic analysis for the potential interaction between the two drugs. This approach was based on the expected lack of drug interactions between an antibody and an oral small molecule and the fact that the individual pharmacokinetic profiles of cetuximab and erlotinib were well characterized, as both agents were already commercially available when the study was conducted.

Rash affected every patient and was the most frequent reason for toxicity-related treatment discontinuation; it may therefore emerge as a relevant safety concern with this combination. Even with the caveats implicit in any comparison across trials, a 100% incidence with concurrent use appears greater than the 76%–80% rates reported in studies of single-agent erlotinib or cetuximab; interestingly, however, there was no apparent increase in the rate of severe events [4, 6]. Whether a potential exacerbation of this toxicity may have a meaningful impact on the clinical use of this regimen will not be clear until larger trials are conducted.

Other studies have recommended more conservative dosing schemas, lowering the erlotinib dose to 50 mg in combination with the full dose of cetuximab [22]. In this trial, the tolerability of the highest dose in the 20 patients from the expansion cohort would validate cetuximab at a dose of 250 mg/m² weekly plus erlotinib at 150 mg daily as the recommended doses for future investigation. Although objective responses were not seen, seven of 18 evaluable patients had SD lasting for a median of nearly 4 months. In conclusion, this regimen warrants further evaluation in malignancies where either cetuximab or erlotinib is known to be active, including colorectal cancer, NSCLC, and SCCHN, with some studies already initiated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1Adverse events of special interest ($n = 22$)

Adverse event	<i>n</i> (% of patients)	
	Any grade	Grade 3 or 4
Acneform rash ^a	22 (100)	2 (9.1)
Diarrhea	17 (77.3)	1 (4.5)
Hypomagnesemia ^b	10 (58.8)	2 (11.8)
Infusion reaction ^c	3 (13.6)	0

^aAcneform rash was a composite of the Medical Dictionary for Regulatory Activities version 10 preferred terms: rash, rash pustular, rash erythematous, dermatitis acneform, dermatitis exfoliative, rash papular, rash pruritic, rash generalized, rash macular, rash maculopapular, acne, acne pustular, skin desquamation, and dry skin.

^bIncidence of hypomagnesemia in 17 patients who had serum magnesium measured.

^cInfusion reaction was a composite of the following preferred terms: infusion reaction, infusion-related reaction, hypersensitivity, anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction. In addition, the terms dyspnea, pyrexia, and chills were grouped under infusion reaction when their onset occurred on the first day of study treatment.

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Table 2Drug-related adverse events ($n = 22$)

Adverse event	<i>n</i> (% of patients)	
	Any grade	Grade 3 or 4
Nausea	7 (31.8)	1 (4.5)
Fatigue	7 (31.8)	1 (4.5)
Pyrexia	5 (22.7)	0
Decreased weight	3 (13.6)	0
Vomiting	2 (9.1)	0
Asthenia	2 (9.1)	1 (4.5)
Anorexia	2 (9.1)	0
Headache	2 (9.1)	0
Hypoaesthesia	2 (9.1)	0
Glossodynia	2 (9.1)	0
Anorexia	2 (9.1)	0

All drug-related adverse events are those occurring in two or more patients.

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