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ORIGINAL ARTICLE

Phase I study of cetuximab, erlotinib, and bevacizumab in patients with advanced solid tumors

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Abstract
Background Complex interrelationships exist between the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) receptor pathways. EGFR activation elicits cell proliferation and increased VEGF expression. To maximally inhibit EGFR and then downstream VEGF activity, this phase I study was initiated to determine the maximum tolerated dose (MTD) of erlotinib with fixed-dose cetuximab, and then combine with bevacizumab in patients with advanced malignancies.
Patients and methods Patients with advanced malignancies likely to express EGFR were treated with a full dose of cetuximab intravenous weekly, combined with various doses of oral erlotinib daily (Part 1). Once the MTD was determined in Part 1, escalating doses of bevacizumab were administered intravenously biweekly (Part 2).
Results Forty patients were enrolled and received 155 courses over four dose levels. In Part 1, dose-limiting grade 3 rash occurred in two patients administered with erlotinib at 100 mg daily, and the MTD of erlotinib for this combination was 50 mg daily with standard-dose cetuximab (11 patients treated). Other adverse events included rash, diarrhea, fatigue, and hypomagnesemia. In Part 2, bevacizumab at 10 mg/kg intravenous every 2 weeks was safely added, with additional nondose-limiting headache, proteinuria, and hypertension. There was one partial response in a patient with renal cell carcinoma. Durable stable disease was observed in five patients for 6–11 months.

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Conclusions The MTD for Part 1 was 50 mg daily of erlotinib combined with standard cetuximab. Bevacizumab at 10 mg/kg biweekly can be safely administered with the MTD for erlotinib and cetuximab combination.

Keywords Epidermal growth factor receptor · Vascular endothelial growth factor · Renal cell carcinoma

Introduction

Currently approved mechanisms to inhibit the epidermal growth factor include both monoclonal antibodies (MoAb) (e.g. cetuximab, panitumumab) and tyrosine kinase inhibitors (TKIs) (e.g. erlotinib) [1]. Although both MoAbs and TKIs inhibit epidermal growth factor receptor (EGFR)-mediated signaling and induce objective responses in selected solid tumors, the mechanisms of action, toxicities, and proven efficacy of EGFR-targeting MoAbs and TKIs are not overlapping [2]. The MoAbs, but not the TKIs, have the capacity to form receptor–antibody complexes that result in receptor internalization and degradation, as well as potentially eliciting antibody-dependent cellular cytotoxicity [3]. In contrast, TKIs appear to have maximal benefit on tumors that possess activating mutations in the EGFR kinase domain [3]. Furthermore, each agent alone may not maximally inhibit the EGFR. In preclinical studies, combinations of an EGFR-targeting MoAb with gefitinib demonstrate additive antitumor activity when combined at maximally effective single agent doses [4–6].

Moreover, the EGFR and vascular endothelial growth factor (VEGF) receptor pathways are interrelated with activation of EGFR resulting in the induction of a number of angiogenic factors in tumor cells, including hypoxia-inducible factor-1 stabilization through PI3 kinase/AKT pathway activity as well as an increase in the transcription of the VEGF gene by signaling through MAPK pathway [7–10]. This interrelationship is further supported by preclinical studies demonstrating dual blockade of EGFR and VEGF producing additive or synergistic antitumor activity [11–13]. Taken together, it is hypothesized that maximal inhibition of EGFR, combined with inhibition of VEGF-mediated angiogenesis, will result in improved antitumor activity in malignancies that depend upon EGFR and VEGF receptor (VEGFR) signaling for growth and proliferation.

To permit the testing of this hypothesis, a two-part phase I trial was initiated. In Part 1 of the present study, the feasibility of administering both erlotinib and cetuximab was determined. Once the maximum tolerated dose (MTD) was determined for this combination, the feasibility of adding bevacizumab to the erlotinib and cetuximab combination was explored.

Patients and methods

The Institutional Review Boards of Cancer Therapy and Research Center (San Antonio, TX, USA) and Brooke Army Medical Center (Fort Sam Houston, TX, USA) approved this trial.

Patient eligibility

Patients who had histologically proven, unresectable or metastatic carcinoma with a high likelihood of EGFR expression [head and neck squamous cell carcinoma (HNSCC), nonsmall cell lung cancer (NSCLC), pancreatic cancer, colorectal cancer, or clear-cell renal cell carcinoma (RCC)] were eligible. Additional inclusion criteria included Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, absolute neutrophil count $\geq 1{,}500/\mu L$, platelet $\geq 100{,}000/\mu L$, total bilirubin ≤ 1.5 mg/dL, aspartate transaminase/alanine transaminase $\leq 2.5 \times$ upper limit of normal (ULN) or $\leq 5 \times$ ULN if liver metastasis is present, and creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 60 mL/min per 1.73 m^2.

Specific exclusion criteria for Part 2 of this study included major surgery within 28 days before the initiation of study treatment, preexisting bleeding diatheses, INR between 2 and 3 on a stable dose of warfarin, clinically significant cardiovascular disease, and known brain metastasis. Prior exposure to any of the study agent was also an exclusion criterion. All patients gave written informed consent according to federal and institutional guidelines.

Study designs and treatments

In Part 1, cetuximab was administered at the fixed dose of 400 mg/m^2 intravenously over 120 min on day 1, followed by 250 mg/m^2 intravenously over 60 min weekly. Doses of erlotinib administered orally once daily were explored. In Part 2, bevacizumab at two dose levels (5 and 10 mg/kg) was administered intravenously every 2 weeks with the MTD of the erlotinib and cetuximab combination (Table 1).

The MTD was defined as the highest dose level at which less than two of six patients experienced dose-limiting toxicities (DLTs). A DLT was defined as any ≥grade 3 nonhematologic toxicity or ≥grade 4 hematologic toxicity occurring during cycle 1, or recurrent symptomatic ≥grade 2 and intolerable nonhematologic toxicity. Exception to this included grade 3 hypertension that warranted initiation of antihypertensive agents, and asymptomatic grade 3 or 4 hypomagnesemia that was documented toxicity of cetuximab, had limited clinical consequence, and could be managed with either intravenous or oral supplements [14, 15]. Toxicity was graded before every cycle according to the

Table 1 Dose escalation scheme

	Cetuximab (dose level: mg/m^2 IV weekly)	Erlotinib (dose level: mg PO daily)	Bevacizumab (dose level: mg/kg IV biweekly)
Part 1			
−1	400/250	50	–
1	400/250	100	–
2	400/250	150	–
Part 2			
1	400/250	MTD (Part 1)	5
2	400/250	MTD (Part 1)	10

MTD maximum tolerated dose

National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3.0.

If ≥2+ proteinuria was present on urinalysis, bevacizumab was held and a 24-h urine collection was obtained for quantitative proteinuria assessment. Bevacizumab administration continued if the 24-h urine protein remained less than 2 g. If proteinuria was ≥2 g/24 h, bevacizumab was held until the proteinuria decreased to <2 g/24 h.

Study assessments

A complete medical history and physical examination as well as routine laboratory studies were performed prior to treatment and weekly. Routine laboratory studies included complete blood cell counts (CBC), liver and renal function tests, and serum electrolyte levels including magnesium. Pretreatment studies also included relevant radiologic studies for evaluation of all measurable or evaluable lesions of malignancy, as well as an assessment of relevant tumor markers. Radiologic studies for disease status assessments were repeated after every other course or as needed to confirm response by using Response Evaluation Criteria in Solid Tumors (RECIST) [16]. Patients were able to continue treatment if they did not develop progressive disease unless they had intolerable toxicity despite two dose reductions or wished to voluntarily withdraw from the study.

EGFR protein analysis

EGFR protein expression was evaluated from the tumor specimens by immunohistochemistry and scored based on intensity and fraction of positive cells by a single pathologist blinded to clinical results using the mouse antihuman EGFR, clone 31G7 monoclonal antibody (Zymed Laboratories, San Francisco, CA). The intensity score, defined as 1–4, was multiplied by the fraction of positive cells (0–100%) for a total score range of 0–400. For statistical analysis, scores of 0–200 were considered negative/low for EGFR expression, whereas scores of 201–400 were considered positive/high for EGFR expression [17]. Response rates were compared between groups (those with positive/high EGFR expression and those with negative/low EGFR expression, those with no/mild skin rash and those with moderate/severe skin rash) using the chi-square or Fisher exact test.

Results

General

Forty patients, whose pertinent demographics are listed in Table 2, received 155 courses of cetuximab and erlotinib (Part 1) or with bevacizumab (Part 2). The numbers of patients and courses at each dose level, as well as the rates of DLT as a function of dose level, are detailed in Table 3. The median number of courses administered per patient was 2 (range 1–19). Dose reductions, due to toxicity that resulted in patients being treated with multiple intermediate dose levels, are outlined in Table 3.

Table 2 Patient characteristics

Characteristics	Number of patients
Total number of patients (median age = 62 years; range = 30–80 years)	40
Gender	
Male	32
Female	8
ECOG performance status	
0	26
1	9
2	5
Prior therapy types (median = 1; range = 0–5)	
None	9
Chemotherapy only	7
Cytokine only	3
Radiotherapy only	2
Chemotherapy and targeted therapy	1
Chemotherapy and radiotherapy	12
Cytokine and radiotherapy	1
Chemotherapy, targeted therapy, and radiotherapy	2
Chemotherapy, targeted therapy, and cytokine	2
Tumor types	
Head and neck cancer	11
Non-small cell lung cancer	7
Pancreatic cancer	5
Colorectal cancer	1
Kidney cancer	16

ECOG Eastern Cooperative Oncology Group

Table 3 Dose escalations

Dose level			Number of patients			Number of courses	Patients with DLT	
Cetuximab (mg/m^2 per week)	Erlotinib (mg/day)	Bevacizumab (mg/kg biweekly)	New	Modified to this dose	Total		First course	All courses
400/250	100	–	8	0	8	35	2	3
400/250	50	–	11	2	13	53	1	2
400/250	50	5	8	0	8	18	0	0
400/250	50	10	13	0	12	49	0	0
Total			40			155		

DLT dose-limiting toxicity

Table 4 Non-hematological toxicity

Dose level			Number of patients	Number of DLT	First cycle (all cycles)			
Cetuximab (mg/m^2 per week)	Erlotinib (mg/day)	Bevacizumab (mg/kg biweekly)			Diarrhea grade 1 or 2	Diarrhea grade 3	Rash grade 1 or 2	Rash grade 3
400/250	100	–	8	2	3 (32)	0 (0)	3 (43)	2 (4)
400/250	50	–	11	1	0 (4)	0 (0)	9 (33)	1 (1)
400/250	50	5	8	0	2 (3)	0 (0)	7 (16)	0 (1)
400/250	50	10	13	0	2 (4)	0 (0)	11 (38)	0 (2)

Dose level			Number of patients	Number of DLT	First cycle (all cycles)			
Cetuximab (mg/m^2 per week)	Erlotinib (mg/day)	Bevacizumab (mg/kg biweekly)			Hypertension grade 3	Proteinuria grade 3	Hypomagnesemia grade 3 or 4	Fatigue grade 2
400/250	100	–	8	2	–	–	0 (26)	1 (26)
400/250	50	–	11	1	–	–	0 (0)	1 (12)
400/250	50	5	8	0	0 (0)	0 (0)	0 (2)	0 (10)
400/250	50	10	13	0	0 (0)	0 (0)	0 (2)	0 (17)

DLT dose-limiting toxicity

In Part 1, the initial four patients received cetuximab at 400 mg/m^2 loading and then 250 mg/m^2 per week with erlotinib at 100 mg/day. One of four patients was inevaluable and an additional patient experienced grade 3 rash in the first course. Four additional patients were treated at this dose level. One patient experienced grade 3 hypersensitivity reaction to cetuximab in the first week, received erlotinib alone from the second week on, and was considered not fully evaluable for safety of the combination. Again, one of these additional four patients experienced grade 3 rash in the first cycle. Dose level de-escalation proceeded to 400/250 mg/m^2 per week and 50 mg/day of cetuximab and erlotinib, respectively, which resulted in an acceptable toxicity profile in 11 patients. The other five patients were not evaluable, because they received treatment of less than one cycle. Therefore, the MTD for Part 1 was full dose cetuximab in combination with erlotinib 50 mg/day. In Part 2, eight patients received cetuximab, erlotinib at MTD from Part 1 with bevacizumab at 5 mg/kg biweekly. One patient received only one dose of treatment and another reduced the dose of erlotinib in the first cycle by himself. Hence, both were considered not evaluable. The next six patients tolerated the treatment without DLT. Dose level escalation proceeded to 10 mg/kg biweekly of bevacizumab, which was well tolerated without DLT, and a total of 12 patients were entered. Therefore, bevacizumab at 10 mg/kg biweekly can be safely combined with full dose of cetuximab and erlotinib at 50 mg/day.

Toxicity

Grade 3 or 4 toxicities (excluding hypomagnesemia) occurred in three patients, all in Part 1 (Tables 3, 4). These included two patients with grade 3 rash with desquamation at the erlotinib 100 mg daily dose level combined with cetuximab, and one patient with grade 3 rash with desquamation at the erlotinib 50 mg daily dose level. The rash/desquamation of any grade 3 did not increase in incidence in Part 2 with the addition of bevacizumab.

There was no grade 3 or 4 diarrhea observed in this study. Grade 1 or 2 diarrhea occurred in 32 (60%) cycles in the standard-dose cetuximab in combination with erlotinib

100 mg daily. However, grade 1 or 2 diarrhea occurred only in 17% of cycles when cetuximab combined with erlotinib 50 mg daily, with or without bevacizumab.

Hypomagnesemia is a documented toxicity of cetuximab and had no clinical consequence. Grade 3 or 4 asymptomatic hypomagnesemia occurred in 26 (49%) cycles when the standard-dose cetuximab combined with erlotinib 100 mg daily. However, when a lower dose of erlotinib 50 mg daily was combined with cetuximab, regardless of presence or absence of bevacizumab, the incidence of grade 3 or 4 hypomagnesemia was much lower (11% of all cycles).

In Part 2, non-DLT attributed to the addition of bevacizumab occurred and included headache, proteinuria, and hypertension. All were grade 1 or 2. No life-threatening toxicity specifically attributable to bevacizumab (e.g. bowel perforation) was observed in this study.

Antitumor activity

In Part 1, one partial response that lasted for 17 months was observed in a 66-year-old man with RCC refractory to interleukin-2 and with lung and bone metastases treated at the dose level of erlotinib 100 mg daily. Durable (>6 months) stable disease was observed in two patients, one with RCC at dose level of erlotinib 100 mg daily (11 months) and the other with HNSCC at the dose level of erlotinib 50 mg daily (7 months). In Part 2, durable stable diseases were observed in three patients, one with RCC (8 months) and two patients with NSCLC (6 and 7 months). All were at the dose level of bevacizumab 10 mg/kg biweekly.

An analysis was performed to explore the relationships between antitumor activity (partial response plus stable disease > 6 months) and either EGFR protein expression (20 patients) or the severity of rash/desquamation (all 39 patients). Among 28 patients with archival tumor tissue available, 20 (71%) tumors were considered positive/high EGFR expression based on the score of intensity multiplied by fraction of positive cells. However, there were no significant differences in the extent of EGFR protein expression, or the severity of rash/desquamation in the patients who had PR/SD or not (data not shown).

Discussion

Strategies for combining targeted agents proposed to date can be divided into three broad categories: combinations to maximally inhibit a specific target, combinations to maximally inhibit a specific pathway, and combinations to inhibit multiple pathways [18]. Based on our current understanding of EGFR and VEGF pathways and their interrelationship, the availability of agents, and evidence of additive or synergistic activity in preclinical studies, this study was initiated to maximally inhibit EGFR by the combination of cetuximab and erlotinib and then to simultaneously inhibit multiple (EGFR and VEGFR) pathways.

Our data suggest that maximal inhibition of a specific target may augment target inhibition and toxicity associated with such inhibition. It is in line with other studies, which combine anti-EGFR MoAb (cetuximab) and EGFR TKI (erlotinib or gefitinib) leading to increased toxicity of skin rash [19, 20], but in our current study, erlotinib at doses above 50 mg/day with full dose cetuximab were associated with an unacceptable severity of rash, which differs somewhat from those reported by other investigators [19, 20]. Baselga et al. [19] reported the results of a phase I trial using cetuximab combined with gefitinib in patients with HNSCC, NSCLC, and CRC. In this study, gefitinib at 250 mg/day could be combined with full-dose cetuximab, with rash which is not the dose-limiting toxicity. Naret et al. [20] also reported the results of a phase I trial using cetuximab combined with gefitinib in patients with NSCLC. Again, gefitinib at 250 mg/day could be combined with full-dose cetuximab, with rash which is not the dose-limiting toxicity. However, the dose of gefitinib used in both studies was 250 mg orally daily, which is 1/3rd of the MTD and phase II dose of 750 mg/day [19, 20]. A phase I trial of cetuximab and erlotinib was recently reported. The full dose of erlotinib, 150 mg orally daily, can be combined with cetuximab and the skin toxicity was not dose-limiting. However, the loading dose of cetuximab, 400 mg/m^2, dropped to 250 mg/m^2. None of the 22 patients had an objective response [21]. The overlapping toxicity profile might necessitate dose reduction of individual agents to ensure tolerability as in the current study. It remains to be determined if a combination of agents in which one agent cannot be administered at full dose will result in enhanced activity or not as compared with single agents at full doses.

Part of this study was to explore a combination that inhibits more than one pathway, EGFR and VEGF. In terms of toxicity of multiple pathways' inhibition, our data, like others, suggest that agents are more likely to be combined at doses and schedules established for the single agents if toxicity of the individual agents (due to inhibition of purported targets) is nonoverlapping [22–30]. In terms of biologic activity of multiple pathways' inhibition, it would be interesting if AKT, hypoxia-inducible factor-1, MAPK, or VEGF is evaluated in a larger cohort of patients using the doses recommended from this study to validate the primary hypothesis.

In this study, we explored the relationships between antitumor activity and EGFR protein expression. There was no significant difference in the extent of EGFR protein expression in patients who had PR/SD or not. There are inherent

drawbacks of this analysis. First, tumors are heterogeneous at the molecular level with varying levels of EGFR protein expression (primary site vs. metastasis, original diagnosis vs. recurrence). However, it was very difficult to strictly limit the source of specimens, because most patients in this phase I trial were referred from different institutions and sometimes from other states. Second, EGFR protein expression as a predictive marker of response or survival is conflicting. In this study, we used the scoring system based on intensity and fraction of positive cells and developed by the Colorado group. They have demonstrated a relationship between EGFR expression and tumor response to gefitinib in NSCLC [17]. However, when this scoring system was later applied to the randomized phase III trial of erlotinib in NSCLC, the survival difference between the positive group and the negative group was not observed [31]. Third, other EGFR response predictors such as EGFR gene copy number and mutations were reported later after we had started this phase I trial in 2003 [32–34]. It would be interesting to analyze EGFR mutations and EGFR gene copy number in patients of this study.

The central hypothesis that enhanced antitumor activity may be achieved with combinations of molecular targeted agents cannot be answered in this phase I study of a heterogeneous population and requires well-controlled randomized studies. However, randomized trials so far have not yet yielded positive results. For example, while results from uncontrolled clinical trials suggested promising response data for the combination of bevacizumab with erlotinib in NSCLC [23] and RCC [24], the randomized phase II trial in RCC failed to demonstrate improvement in objective response rate or progression-free survival compared with bevacizumab alone [29]. Furthermore, although the initial result suggested promising response data for the combination of bevacizumab with cetuximab in CRC [30], a recent preliminary report suggests that panitumumab combined with bevacizumab and FOLFOX did not lead to improved outcome [35].

Multiple signaling pathways can be targeted in various ways. Besides the EGFR inhibitors combined with the anti-VEGF monoclonal antibody used this study, multitargeted TKIs targeting both EGFR and VEGF receptor (e.g. AEE788, ZD6474, XL647) are currently in the clinical testing and could be more cost-effective compared with chronic administration of three molecular targeted agents used in this study [36].

In conclusion, the MTD for erlotinib combined with standard dose and schedule of cetuximab is 50 mg daily. Bevacizumab at 10 mg/kg biweekly can be safely combined with this combination. The future development of the maximal inhibition of EGFR by erlotinib and cetuximab as well as the simultaneous inhibitions of EGFR and VEGF pathways is warranted but needs more sophisticated identification of optimal target populations and indications.

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