New Drug

Cetuximab: An Epidermal Growth Factor Receptor Monoclonal Antibody for the Treatment of Colorectal Cancer

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ABSTRACT

Background: Cetuximab is a recombinant human/mouse chimeric epidermal growth factor receptor (EGFR) monoclonal antibody. It was approved by the US Food and Drug Administration in February 2004 to be used in combination with irinotecan for the treatment of EGFR-expressing, metastatic colorectal cancer in patients who had failed to improve with irinotecan-based chemotherapy. Cetuximab was also approved for administration as a single agent in the treatment of patients with EGFR-expressing, metastatic colorectal cancer who are intolerant to irinotecan-based chemotherapy.

Objective: This article reviews the role of cetuximab, an EGFR monoclonal antibody, in the treatment of colorectal cancer.

Methods: A MEDLINE search was conducted of articles published from 1976 to the present using the terms *cetuximab, C225, IMC-C225, colon cancer, colorectal cancer, monoclonal therapy,* and *target therapy*. Abstracts presented at the American Society of Clinical Oncology annual meetings from 2000 to 2004 and the 2004 Gastrointestinal Cancers Symposium were reviewed and included as applicable.

Results: In a Phase III trial, cetuximab was administered to 329 patients with colorectal cancer who were irinotecan refractory and/or had failed to respond to oxaliplatin treatment. Partial response was achieved in 10.8% of patients who received cetuximab monotherapy and 22.9% of patients who received cetuximab plus irinotecan therapy (P = 0.007). The overall response rate in 2 Phase II trials using the conventional dosing regimen of cetuximab to treat EGFR-expressing, metastatic colorectal cancer that was refractory to irinotecan therapy ranged from 9% to 12%. The drug was well tolerated with proper administration precautions. The most common adverse events reported included acnelike rash and hypersensitivity reaction. The positive correlation of the incidence of skin reactions to response rates and median survival is one aspect that warrants further investigation in terms of its use as a response predictor. Unfortunately, the role of immunohistochemistry for EGFR expression continues to be a poor predictor of patients who may benefit from cetuximab. Clinical studies are ongoing of cetuximab in combination with radiation therapy and/or platinum in patients with squamous cell head and neck cancer, as well as cetuximab in combination with various antineoplastic agents in the treatment of non–small cell lung cancer and pancreatic cancer.

Conclusions: Cetuximab has shown considerable activity—both as monotherapy and in combination with chemotherapy—in the treatment of metastatic colorectal cancer that is resistant to chemotherapy. The future of cetuximab lies in its use in combination with antineoplastic agents and/or radiation therapy in the treatment of colorectal cancer, head and neck cancer, non–small cell lung cancer, and pancreatic cancer. The lack of a predictive marker that would allow clinicians to select patients who are most likely to benefit from cetuximab therapy, especially taking into consideration the high costs of this medication, remains a challenge. (*Clin Ther.* 2005;27:684–694) Copyright © 2005 Excerpta Medica, Inc.

Key words: cetuximab, epidermal growth factor receptor monoclonal antibody, colorectal cancer, chemotherapy.

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INTRODUCTION

An estimated 150,000 Americans were diagnosed with colorectal cancer in 2004.[1] Despite a decreased incidence of colorectal cancer since the mid-1980s, this disease continues to rank as the third most common cancer in incidence and cancer-related death in the United States, accounting for an estimated 57,100 deaths each year.[1] Mortality from colorectal cancer has been reduced over the past decade due to excellent screening techniques, more patient awareness, and better treatment modalities.[2]

Despite surgical resection, about 20% to 30% of patients with stage II disease and 50% to 80% of patients with stage III disease will relapse.[3] The long-term survival is 62% for all stages combined; <4% of patients with stage IV colorectal cancer reach 5-year survival time despite aggressive chemotherapy treatments.[1] With the introduction of a variety of active agents such as irinotecan and oxaliplatin, improvement in progression-free and overall survival has been reported in several Phase III trials.[4–6] Based on these encouraging results, the currently recommended first-line therapy for metastatic colorectal cancer includes 5-fluorouracil and leucovorin with irinotecan or oxaliplatin.[2] Despite these advances, no established treatment regimens are available when patients fail to improve with these agents. Therefore, further studies to find new strategies that will improve disease outcomes are warranted. The discovery of epidermal growth factor receptor (EGFR) and vascular endothelial growth factor in the process of cell proliferation has produced an exciting era in the treatment of cancer. The use of these target agents alone or in combination with chemotherapy has been extensively studied over the last few years, leading to many developments in cancer management.

OVERVIEW OF TARGET THERAPY

Over the past 3 decades, it has been recognized that the development and spread of cancer involve more than the growth and proliferation of tumor cells themselves; instead, they involve a complex interaction of cancer cells, immune cells, endothelial cells, fibroblasts, and the extracellular matrix.[7] Therefore, treatment of cancer also includes biological therapy that targets growth signals, including cell surface receptors, ligands, and downstream signal transduction molecules, apoptotic pathways, and angiogenesis.[7]

Two major enzyme classes act as switches to regulate signal transduction by activating or deactivating pathways according to the signals received by the cell. The first class is the kinase enzymes, which regulate the function of other proteins and/or enzymes as well as various target molecules.[8] Tyrosine kinases accomplish signal transduction by transferring an activating γ-phosphate group from adenosine triphosphate to a tyrosine residue on the substrate molecule, usually another protein. The second class of enzymes is the phosphatases, which remove phosphate on the substrate molecules and thus oppose kinase activity and inhibit the signal transfer.[8]

One aspect of the molecular-targeted strategies for the treatment of cancer focuses on the family of receptor and nonreceptor tyrosine kinases, and more specifically, on the growth factors and EGFR inhibitors.[8] The ErbB family is a receptor tyrosine kinase that comprises 4 transmembrane receptors: Erb1 (EGFR or HER1), Erb2 (HER2 or neu), Erb3 (HER3), and Erb4 (HER4). These receptors function to transmit signals from the cell surface into the cytoplasm and nucleus, thus regulating cell growth. The activation of these receptors occurs after a ligand binds to the extracellular domain, triggering formation of a dimer, which can be a homodimer or heterodimer. The dimerization then causes activation of the intracellular domain and transmission of downstream signaling molecules.[8]

In normal cells, EGFR expression ranges from 40,000 to 100,000 receptors per cell.[9] It has been shown that many human malignancies—including head and neck, colorectal, non–small cell lung, gastric, pancreatic, ovarian, breast, and prostate cancers and glioma—have overexpression of EGFR.[10–12] This overexpression in these cancers is also linked to more advanced disease and poor prognosis.[13] Several therapeutic approaches to target the EGFR are being explored. Of these, monoclonal antibodies that block ligand binding to the receptors and small-molecule tyrosine kinase inhibitors are the furthest along in clinical development.

The therapeutic strategy developed for antibodies is based on the concept of harnessing the immune system to fight cancer. This is done by inciting the patient's immune system to recognize the cancer cells as foreign and consequently to mount a meaningful reaction against them.

The development of monoclonal antibodies was made possible by the hybridoma technique developed by Kohler and others in 1975, research that eventually led to a Nobel Prize in 1993.[14,15] The problem of al-

lergic reaction and development of human antimouse antibodies secondary to the administration of the original murine antibodies was eventually overcome by the availability of chimeric and humanized versions of the molecule.[16–18] Although the development of human antichimeric antibody (HACA) and human antihuman antibody remains possible, the chimeric and humanized antibodies have been shown to be less toxic and have a longer $t_{1/2}$ than the murine model.

Another barrier faced by the initial antibodies was the inability of these molecules to produce desirable clinical outcomes using antibody-dependent, cell-mediated cytotoxicity or complement-dependent cytotoxicity. A new generation of antibodies was subsequently developed to target specific signaling proteins located at the cell surface or their circulating proteins. An example of these proteins is EGFR, where inhibiting the binding of cognate ligands to EGFR in EGFR-positive tumors can result in inhibition of tumor growth.[19–21]

The purpose of this article was to review the role of cetuximab, an EGFR monoclonal antibody, in the treatment of colorectal cancer. The development as well as the pharmacology and clinical data of cetuximab are summarized.

MATERIALS AND METHODS

A MEDLINE search was conducted from 1976 to the present to identify pertinent published data. Search terms included *cetuximab, C225, IMC-C225, colon cancer, colorectal cancer, monoclonal therapy*, and *target therapy*. In addition, abstracts presented at the American Society of Clinical Oncology annual meetings from 2000 to 2004 and the 2004 Gastrointestinal Cancers Symposium (January 22–24, 2004, San Francisco, California) were reviewed and included as applicable.

DEVELOPMENT OF CETUXIMAB

Cetuximab* (C225, IMC-C225) was chimerized from the murine fraction variable regions of the myeloma cell line 225, a mouse monoclonal antibody that blocks the ligand-binding site of the EGFR, and a human immunoglobulin G constant region gene segment (**Figure**) (Investigator's Brochure #10, ImClone Systems Incorporated, Branchburg, New Jersey,

*Trademark: Erbitux® (ImClone Systems Incorporated, Branchburg, New Jersey, and Bristol-Myers Squibb Company, Lawrenceville, New Jersey).

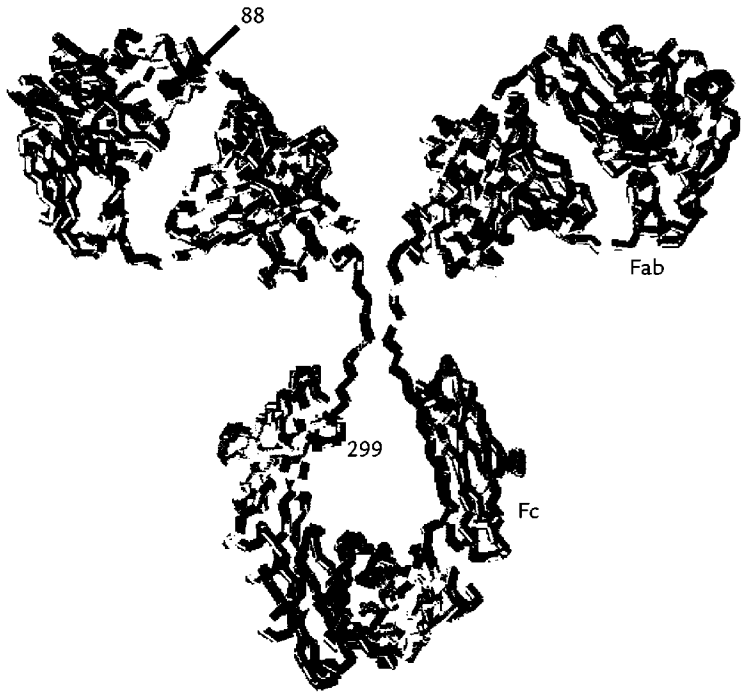

Figure. Structure of cetuximab.

2004). In vitro studies demonstrated broad antitumor activities of cetuximab in numerous cancer cell lines and human tumor xenografts.[22–24] Cetuximab was not active in EGFR-negative tumor models (Investigator's Brochure #10).

Cetuximab's mechanism of action in tumor cells is thought to involve the binding of cetuximab to the EGFR, preventing normal ligand binding and subsequent activation of the receptor's tyrosine kinase activity. The outcome of this blockade is reflected in the disruption of any number of processes regulated by EGFR pathways in a given tumor cell. Several mechanisms have been identified in preclinical models whereby cetuximab inhibits the growth and survival of EGFR-positive tumors. These include: (1) inhibition of cell cycle progression; (2) inhibition of survival pathways; (3) inhibition of tumor cell motility and invasion; (4) inhibition of angiogenesis; and (5) interruption of EGFR-activated survival and proliferation signaling by cytotoxic drugs or radiation.[25]

The in vitro activity of several anticancer agents (eg, doxorubicin, cisplatin, paclitaxel, docetaxel, gemcitabine) and radiation therapy has been enhanced in a variety of human cancer cell lines when combined with cetuximab.[26,27] Cetuximab potentiates the cytotoxic effects of chemotherapeutics and radiation therapy by the interruption of EGFR-activated survival and proliferation signaling.[26,27] These mechanisms appear to contribute to the enhanced cytotoxic response observed when cetuximab is combined with chemotherapy or radiation.

PHARMACOKINETICS OF CETUXIMAB

Pharmacokinetic analysis of cetuximab has been conducted using single-dose and multiple-dose regimens, in combination with other antineoplastic agents and radiation therapy. Cetuximab administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy exhibits nonlinear pharmacokinetics.[28,29] After a 2-hour infusion of 250 and 400 mg/m^2 of cetuximab, C_{max} was reached at 3 hours after initiation of infusion at 158.1 and 205 µg/mL and the elimination $t_{1/2}$ was 71 and 75.1 hours, respectively; these findings support the weekly dosing of cetuximab.[30] The volume of distribution for cetuximab appeared to be dose independent and approximated the vascular space of 2 to 3 L/m^2.[31] At the antibody doses in the range of 200 to 400 mg/m^2, complete saturation of systemic clearance has been observed.[29] The addition of chemotherapy and radiation therapy did not appear to alter the pharmacokinetic parameters of cetuximab.[28,29,32]

A population pharmacokinetic analysis of 960 patients from 19 clinical trials did not show any effect of patient covariate factors (eg, age, body weight, height, body surface area, race) on the pharmacokinetics of cetuximab or suggest the need for dosage adjustments.[33] In this study, female patients had a 25% lower intrinsic cetuximab clearance than male patients. Similar efficacy and safety data were observed for female and male patients in the clinical trials; therefore, dose modification based on sex is not necessary. Cetuximab has not been studied in pediatric populations. According to the package insert,[31] a population pharmacokinetic analysis was performed to explore the potential effects of hepatic and renal function on cetuximab pharmacokinetics, but none of the information was outlined in the package insert. However, there are no dosage modifications recommended in the presence of hepatic and/or renal dysfunction. A drug interaction study between cetuximab and irinotecan was performed by the manufacturer, and no evidence of any pharmacokinetic interactions was observed.[31]

CLINICAL ACTIVITIES OF CETUXIMAB

Registration Trials

Cetuximab's antitumor activity has been observed in patients with colorectal, head and neck, lung, and pancreatic carcinomas. It was approved by the US Food and Drug Administration (FDA) in February 2004 to be used in combination with irinotecan for the treatment of EGFR-expressing, metastatic colorectal cancer in patients who had failed to improve with irinotecan-based chemotherapy. Cetuximab was also approved for administration as a single agent in the treatment of EGFR-expressing, metastatic colorectal cancer in patients who are intolerant to irinotecan-based chemotherapy. This approval was based on 3 registration trials, 2 of which have been published.[34,35] The third study is on file at ImClone Systems Incorporated (Investigator's Brochure #10).

The first study, conducted by Saltz et al,[34] used cetuximab monotherapy in a multicenter, open-label, single-arm trial in patients with EGFR-expressing, metastatic colorectal cancer whose disease had progressed after undergoing an irinotecan-containing regimen. Cetuximab was administered at a loading dose of

400 mg/m^2 as an IV infusion over 2 hours followed by weekly treatments of 250 mg/m^2 infused intravenously over 1 hour. Fifty-seven patients with a median age of 56 years (range, 28–80 years) were enrolled; 28 patients had documented progression despite irinotecan use. The median performance score on the Eastern Cooperative Oncology Group Scale was 0 (range, 0–2), which means that most patients were fully ambulatory. The 2 most common sites of metastasis were liver (70.2%; n = 40) and lung (40.4%; n = 23). The median duration of treatment on study was 6.4 weeks (range, 1–67 weeks). Thirty-six (63.2%) patients received all planned doses of cetuximab during study participation. Eighteen (31.6%) patients missed either 1 or 2 planned doses of cetuximab, and 1 (1.8%) missed >2 planned doses. Two patients (3.5%) received only the test dose of cetuximab. An independent radiographic review committee determined that 5 patients (8.8%) achieved a partial response, and 21 (36.8%) patients had stable disease or minor responses that lasted for at least 12 weeks from the start of cetuximab treatment. None of the responses correlated with the observed degree of EGFR expression or the number of previous chemotherapy regimens the patients had received. The median time to progression was 1.4 months in the 5 partial responders, and their median duration of response was 4.2 months. The median survival for all 57 patients treated was 6.4 months.

The second study was a Phase III, randomized, open-label, controlled clinical trial by Cunningham et al[35] that was conducted in 56 centers across 11 European countries. This study enrolled 329 patients who were randomized to receive cetuximab plus irinotecan (218 patients) or cetuximab monotherapy (111 patients). In both arms of the study, cetuximab was administered as a 400-mg/m^2 loading dose intravenously, followed by 250-mg/m^2 weekly IV infusions until disease progression or unacceptable toxicity, which would require discontinuation of therapy as deemed by the investigators or as requested by the study subject. Disease progression was defined as an increase in the size of at least 1 dimensionally measurable lesion by at least 25% and the appearance of new lesions. All patients received a 20-mg test dose on day 1. In the cetuximab plus irinotecan arm, irinotecan was added to cetuximab using the same dose and schedule for irinotecan that the patient had previously failed to respond to. Acceptable irinotecan schedules were 350 mg/m^2 every 3 weeks, 180 mg/m^2 every 2 weeks, or 125 mg/m^2 weekly for 4 doses every 6-week cycle. An independent radiographic review committee, blinded to the treatment arms, assessed both the progression with prior irinotecan therapy and the response to protocol treatment for all patients. Of the 329 randomized patients, 206 (62.6%) were male. The median age was 59 years (range, 26–84 years), and 323 (98.2%) patients were white. A total of 289 (87.8%) patients had a baseline Karnofsky performance status of 80% or higher. Two hundred sixty-one (79.3%) patients who underwent randomization had received ≥2 previous regimens of treatment for colorectal cancer. All the patients had received irinotecan, and 206 (62.6%) had received oxaliplatin. The efficacy of cetuximab plus irinotecan or cetuximab monotherapy was evaluated in all 329 randomized patients.

Analyses were also conducted in 2 prespecified subpopulations: irinotecan refractory and oxaliplatin failures.[35] The irinotecan-refractory population was defined as randomized patients whose disease progressed during or within 1 month after the end of the prestudy irinotecan treatment. The oxaliplatin failure population was defined as patients who had received previous oxaliplatin treatment. All patients received at least 1 infusion of cetuximab. The median number of cetuximab infusions was 18 in the combination-therapy group and 7 in the monotherapy group. The response rates in these populations are summarized in Table I.[35] The median duration of response in the overall population was 5.7 months in the combination arm and 4.2 months in the monotherapy arm. Compared with patients randomized to cetuximab alone, patients randomized to cetuximab and irinotecan experienced a longer median time to disease progression of 4.1 months versus 1.5 months in the monotherapy group (*P* values not reported). Cetuximab-based therapy was similarly effective in patients who had previously received oxaliplatin in addition to irinotecan before entering the study. Although the status of EGFR positivity of the tumor cells and the staining intensity did not appear to correlate with the clinical response, the response rates in patients with skin reactions after cetuximab treatment were higher than those in patients without skin reactions (25.8% vs 13.0%; $P = 0.005$). A more detailed analysis of the correlation of response rate to grading of skin reactions is outlined in Table I.

The third trial was a multicenter, open-label, Phase II study in 138 patients with EGFR-expressing, meta-

Table I. Summary of response rates and their correlations to epidermal growth factor receptor (EGFR) expression and skin reactions in 329 patients with colorectal cancer.[35]

	Cetuximab Plus Irinotecan	Cetuximab	P*
No. of patients (intent to treat)	218	111	
Response, no. (%)			
Complete response	0 (0.0)	0 (0.0)	
Partial response	50 (22.9)	12 (10.8)	0.007
Stable disease	71 (32.6)	24 (21.6)	
Progressive disease	68 (31.2)	59 (53.2)	
Not evaluated	29 (13.1)	16 (14.4)	
Subgroup with progression during or within 4 weeks after prestudy irinotecan			
No. of patients	135	71	
Response, no. (%)	34 (25.2)	10 (14.1)	0.07
Subgroup with prior oxaliplatin therapy			
No. of patients	135	71	
Response, no. (%)	30 (22.2)	6 (8.5)	0.01
EGFR-expressing cells, n/N (%)			0.87†
≤10	25/109 (22.5)	4/56 (7.1)	
>10 to ≤20	4/20 (20.0)	5/16 (31.3)	
>20 to ≤35	6/27 (22.2)	0/7 (0.0)	
>35	15/62 (24.2)	3/32 (9.4)	
EGFR staining intensity, n/N (%)			0.64†
Faint	11/53 (20.8)	1/21 (4.8)	
Weak or moderate	22/89 (24.7)	7/55 (12.7)	
Strong	17/75 (22.7)	4/34 (11.8)	
Acnelike rash, n/N (%)‡			0.001†§
None	8/48 (16.7)	2/28 (7.1)	
Grade 1 or 2	29/148 (19.6)	9/79 (11.4)	
Grade 3 or 4	13/22 (59.1)	1/4 (25)	
Skin reaction, n/N (%)‡			<0.001†§
None	2/32 (6.3)	0/19 (0.0)	
Grade 1 or 2	32/157 (20.4)	10/86 (11.6)	
Grade 3 or 4	16/29 (55.2)	2/6 (33.3)	

*Differences in response rates were evaluated by means of the 2-sided Fisher exact test. $P < 0.05$ was used to indicate statistical significance.

†*P* value for trend using stratified permutation test to explore the association between tumor response and rash, and between tumor response and EGFR expression.

‡Grading of toxicity according to the National Cancer Institute (Bethesda, Maryland) common toxicity criteria.

§None versus grade 1 or 2 versus grade 3 or 4.

static colorectal cancer who were refractory to irinotecan treatment (Investigator's Brochure #10). Patients received cetuximab 400 mg/m^2 as an IV infusion followed by weekly administration of 250 mg/m^2 until disease progression or unacceptable toxicity. Each patient also received the same dose and schedule of irinotecan that he or she had previously failed to respond to. Acceptable irinotecan schedules were 350 mg/m^2 every 3 weeks or 125 mg/m^2 weekly for 4 doses every 6-week cycle. A total of 138 patients

were enrolled; 74 patients had documented disease progression with irinotecan, as determined by an independent review committee. The overall response rate was 15% for the study population and 12% for the irinotecan-refractory population. The median durations of response were 6.5 and 6.7 months, respectively.

The results of these 3 studies suggest that the use of cetuximab as monotherapy or in combination with chemotherapy for patients failing to respond to irinotecan and oxaliplatin may achieve modest response rates, with acceptable toxicity. The median survival has yet to reach statistical significance, but further investigations are needed to determine the impact of the therapy on patients' overall quality of life.

Other Clinical Studies

Preliminary results were recently reported from 2 Phase II studies of cetuximab with oxaliplatin-based (ie, the FOLFLOX4 regimen) or irinotecan-based (ie, the FOLFIRI regimen) combination therapy with 5-fluorouracil and leucovorin calcium as first-line treatment for metastatic colorectal cancer.[36,37] Both studies reported that the combination regimens were well tolerated and active. A Phase III trial is ongoing using cetuximab plus FOLFLOX4 versus FOLFLOX4 alone as second-line treatment for metastatic colorectal cancer.[38] Preliminary safety analysis of this study did not show increased toxicities in the cetuximab and FOLFLOX4 combination arm; efficacy data are not yet available. Lenz et al[39] also reported a 12% partial response in 235 patients with colorectal cancer who had failed to respond to both irinotecan and oxaliplatin treatment and were receiving cetuximab monotherapy. Interestingly, 2 of the 9 patients enrolled who were EGFR negative achieved a partial response.

This observation by Lenz et al[39] supported recent concerns about the reliability of EGFR staining to predict the response to cetuximab therapy. In most of the clinical trials, any level of EGFR immunohistochemical expression in tumor cells has been considered adequate for predicting sensitivity to therapy, irrespective of both the percentage of neoplastic cells stained and the intensity of the staining.[34,35] However, a considerable proportion of these patients with high EGFR expression did not respond to cetuximab treatment, and yet patients with low expression of EGFR did respond. A recent retrospective evaluation conducted by Scartozzi et al[40] studied the EGFR immunohistochemistry of the primary tumors and related metastatic sites of 99 patients with metastatic colorectal cancer. In 53 patients whose primary site was found to stain positive for EGFR, 36% of the corresponding metastatic sites were negative. Fifteen percent of the EGFR-negative tumors had positive staining of the corresponding metastatic site. The differences in these results were statistically significant ($P = 0.036$), suggesting that the detection of EGFR in primary colorectal cancer could be inadequate to predict the response of the metastatic disease to EGFR-targeted monoclonal antibody therapy.

Markers are needed to predict responders to EGFR-targeted monoclonal antibody therapy, because the current FDA-approved indication limits the use of cetuximab to patients with detectable EGFR expression. Some patients are being denied this treatment option because of the absence of EGFR expression. In addition, the average wholesale price of cetuximab is $576 per 100-mg vial; this results in an estimated average cost of $4032 for the loading dose and $2880 for each weekly maintenance dose (based on an average body surface area of 1.7 m^2). The cost of cetuximab can impose a substantial financial strain on the patient, even if he or she is responsible for the copayment only. A recent editorial by Schrag[41] discussed the costs of various treatment options for colorectal cancer generated by recent trial results and the inconclusive therapeutic benefits obtained in terms of disease survival and progression-free survival. This editorial highlighted the need to conduct comprehensive pharmacoeconomic studies that would allow clinicians to streamline the chemotherapeutic treatment options available for colorectal cancer.

Currently, efficacy data from Phase II and III studies of cetuximab in combination with radiation therapy and/or platinum in patients with squamous cell head and neck cancer are available.[28,42,43] Phase II clinical trial data have also been reported on the use of cetuximab in combination with various antineoplastic chemotherapies in the treatment of non–small cell lung cancer and pancreatic cancer.[44–47]

DOSAGE AND ADMINISTRATION OF CETUXIMAB

According to the manufacturer's package insert,[31] cetuximab injection is a sterile, clear colorless liquid for IV administration, which may contain a small amount of easily visible, white amorphous cetuximab particu-

lates. Each single-use, ready-to-use 50-mL glass vial contains 100 mg of cetuximab as a 2-mg/mL preservative-free solution in phosphate-buffered saline. The product should be stored in the refrigerator at 2°C to 8°C; the product should not be frozen or shaken. The recommended dose of cetuximab, in combination with irinotecan or as monotherapy, is a loading dose of 400 mg/m^2 intravenously as a first infusion over 2 hours with a maximum infusion rate of 5 mL/min. The weekly maintenance dose of 250 mg/m^2 should be infused over 60 minutes and should begin at week 2. The recommended dose should be drawn up and transferred into a sterile-evacuated glass container or bag for IV infusion and must not be diluted. The prepared solution is physically and chemically stable in the refrigerator for 12 hours and at room temperature for 8 hours. The solution should be administered through a low protein–binding, 0.22-μm in-line filter.

Patients receiving cetuximab should be prophylactically premedicated with diphenhydramine 50 mg IV to prevent allergic anaphylactoid reactions.[31] Emergency medications should also be readily available in case of more severe reactions. All patients should be monitored for 1 hour after the completion of drug administration. Since this reaction can occur at any time in the course of the patient's treatment, allergic reaction precautions must be taken for the duration of therapy.

ADVERSE EVENTS

Phase I dose-escalation studies examined cetuximab doses of between 5 and 500 mg/m^2.[28,29] In the study by Baselga et al,[29] 1.6% (5 episodes in 317 administrations) of grade 3 or higher cetuximab-related toxicity was observed up to and including the 400-mg/m^2 weekly dose in combination with cisplatin. However, in the study by Robert et al,[28] 1 patient experienced grade 3 skin toxicity (a follicular/maculopapular rash) outside of the radiation therapy field on receiving the 500-mg/m^2 loading dose plus radiation therapy to the head and neck area, and only grade 1 skin toxicity was observed at the lower loading-dose levels. Therefore, only doses <500 mg/m^2 were evaluated in further clinical development and are recommended.

The most common adverse events associated with cetuximab therapy reported in the Phase I studies were asthenia (13.5%, grades 1 and 2), fever (13.5%, grades 1 and 2), nausea (11.5%, grades 1 and 2), and skin toxicities (20.9%, grades 1 and 2).[28,29] These toxicities are believed to be unrelated to dose or number of cycles administered. The possible exception is acnelike rashes, which have been reported in 86% of the patients in the registration trials.[34,35] Grade 3 or 4 skin reactions were observed in 5.2% to 18% of patients in the registration trials.[34,35] The rash usually manifested within the first 1 to 3 weeks of therapy. Standard topical administration of drying agents, topical antibiotics, or topical steroids did not appear to substantially affect the course of the rash, except in cases where bacterial superinfection had occurred. Topical or oral antibiotics appeared to accelerate resolution of the lesions. According to the observations made by the investigators in the Phase I trials,[28,29] some degree of spontaneous partial improvement can occur within the first 1 to 2 months while continuing the same dose of cetuximab. Dose-modification recommendations for dermatologic reactions are outlined in the manufacturer's package insert.[31]

Another characteristic manifestation of cutaneous toxicity with cetuximab is paronychial cracking, which occurred on the fingers and/or toes of 12% of patients.[34] This reaction tended to persist throughout the patient's treatment and appeared to require several months to heal after cessation of therapy.

Grade 3 or 4 allergic reactions were reported in 1.2% to 3.5% of patients in the registration trials, which led to the cessation of therapy.[34,35] Strict administration guidelines should be followed to ensure use of an appropriate infusion rate, prophylactic premedication, and a postinfusion monitoring schedule. All these precautions should be conducted for the duration of therapy, since allergic reactions can occur at any time throughout treatment. Although some of these reactions occurred during the test dose, it is believed that the test dose may not be helpful in predicting those patients at risk of developing allergic reactions.

Recent safety updates by the manufacturer revealed reports of hypomagnesemia during cetuximab therapy. Low serum magnesium levels were noted during routine electrolyte monitoring, although no clinical symptoms were observed. The manufacturer has recommended that all patients currently being treated with cetuximab have routine monitoring of serum magnesium levels and repletion as necessary (Investigator's Brochure #11, 2005).

When cetuximab was used in combination with irinotecan, the incidence of grade 3 or 4 diarrhea and

neutropenia was also significantly increased ($P < 0.001$). A summary of grade 3 or 4 cetuximab-related adverse reactions appears in **Table II.**[34,35]

Evaluable pre- and posttreatment immunogenicity samples were available for 606 cetuximab-treated patients.[31] Similar to that seen in the monkey study, the incidence of an anticetuximab response in humans (HACA) across all trials was low (5%) (Investigator's Brochure #10). It is unclear if the presence of HACA has any clinical impact on the response to therapy.

CONCLUSIONS

Although colorectal cancer continues to be a major cause of cancer death worldwide, the availability of new chemotherapeutic agents such as irinotecan and oxaliplatin have improved the treatment options over the last decade, especially in patients with stage IV disease. Cetuximab, a new antibody to EGFR, has shown considerable activity in the treatment of metastatic colorectal cancer that is resistant to chemotherapy, both as monotherapy and in combination with chemotherapy. Data evaluating the use of cetuximab with oxaliplatin- or irinotecan-based combination therapy with 5-fluorouracil and leucovorin calcium as first-line treatment for metastatic colorectal cancer is maturing. A Phase III trial of cetuximab plus FOLFLOX4 as second-line treatment for metastatic colorectal cancer is ongoing. The future of cetuximab lies in its use in combination with other active antineoplastic agents in the treatment of colorectal cancer. Data on the activity of cetuximab in combination with chemotherapy and/or radiation therapy in the treatment of head and neck cancer are forthcoming. Ongoing investigations of the clinical activities of cetuximab in non–small cell lung cancer and pancreatic cancer will add valuable information on potential treatment options for these cancers. The lack of a predictive marker that would allow clinicians to identify patients who are most likely to benefit from cetuximab therapy, especially taking into consideration the high costs of this medication, remains a challenge.

Table II. Grade 3 and 4 adverse events (no. [%]) reported in the Phase II and Phase III registration trials.

	Cunningham et al[35]			Saltz et al[34]
Adverse Events	Cetuximab Plus Irinotecan (n = 212)*	Cetuximab Monotherapy (n = 115)*	*P*	Cetuximab Monotherapy (N = 57)
Diarrhea	45 (21.2)	2 (1.7)	<0.001	1 (1.8)
Asthenia	29 (13.7)	6 (5.2)	0.49	2 (3.5)
Acnelike rash	20 (9.4)	6 (5.2)	0.20	9 (15.8)
Neutropenia	20 (9.4)	0 (0.0)	<0.001	-
Nausea/vomiting	15 (7.1)	5 (4.4)	0.47	1 (1.8)
Anemia	10 (4.7)	3 (2.6)	0.55	-
Abdominal pain	7 (3.3)	6 (5.2)	0.39	-
Stomatitis	5 (2.4)	1 (0.9)	0.67	-
Fever	5 (2.4)	0 (0.0)	0.17	-
Dyspnea	3 (1.4)	15 (13)	<0.001	-
Thrombocytopenia	1 (0.5)	1 (0.9)	1.00	-
Hypersensitivity reaction	0 (0.0)	4 (3.5)	0.01	3 (5.3)
Death	0 (0.0)	0 (0.0)	1.00	-
All	138 (65.1)	50 (43.5)	<0.001	-

*Four patients who were randomly assigned to the combination-therapy group did not receive irinotecan and were evaluated for safety in the monotherapy group. Two patients who were randomly assigned to the combination-therapy group did not receive any study medication.

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