Epidermal Growth Factor Receptors as a Target for Cancer Treatment: The Emerging Role of IMC-C225 in the Treatment of Lung and Head and Neck Cancers

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Epidermal growth factor receptor is one of four receptors critical to cellular proliferation, differentiation, and survival, and is widely expressed in malignant tissue, particularly in squamous cell carcinoma of the head and neck. Expression has been associated with malignant progression, inhibition of apoptosis, neoplastic angiogenesis, enhanced metastatic potential, and both chemoresistance and radioresistance. IMC-C225 is a chimeric monoclonal antibody that targets extracellular epidermal growth factor receptor; it has shown both in vitro and in vivo antitumor activity in tumor cells lines expressing epidermal growth factor receptor, including heightened radiation response in vitro in cultured human squamous cell carcinoma and enhancement of taxane- and platinum-induced cytotoxicity in non–small cell lung cancer xenografts. In A431 head and neck squamous cell xenografts, IMC-C225 administered both before and after radiation therapy yields a radiation enhancement factor of 3.62, attributable to both tumor necrosis and antiangiogenesis. In phase I pharmacokinetic studies, IMC-C225 has a long half-life, lending itself to convenient weekly administration. It has shown a favorable toxicity profile, limited primarily to allergic and dermatologic reactions, the latter characterized by a self-limited, sterile, acneiform rash. Anaphylaxis is rare. Standard treatment entails a loading dose of 400 mg/m^2 at week 1, followed by a maintenance dose of 250 mg/m^2 weekly. An ongoing phase III international multicenter, randomized study in locally advanced squamous cell carcinoma of the head and neck is evaluating therapeutic radiation therapy, either alone or in conjunction with IMC-C225. In a pilot trial, six of nine patients with platinum-exposed squamous cell carcinoma of the head and neck exhibited objective response. In an ongoing phase II trial in patients with stable or progressive disease on platinum-based therapy, the preliminary response rate is approximately 20%, far higher than one would expect with standard salvage regimens. The Eastern Cooperative Oncology Group has completed a placebo-controlled phase III registration trial assessing cisplatin 100 mg/m^2 every 4 weeks with or without IMC-C225. Three separate phase II trials in non–small cell lung cancer have been launched: one trial tests IMC-C225 in combination with standard paclitaxel/carboplatin; another integrates IMC-C225 into the gemcitabine/carboplatin combination in treatment-naive patients; and a third trial evaluates IMC-C225 in combination with docetaxel 75 mg/m^2 every 3 weeks in the second-line setting.

TRADITIONAL cytotoxic therapies, chemotherapy and radiation therapy (RT), used in the management of solid tumors are associated with significant therapeutic and safety limitations. The successful administration of cytotoxic therapy can be limited by nonspecific toxicities sustained by healthy tissues. These limitations can result in poor outcomes in terms of disease control and overall survival, thus emphasizing the need for treatment approaches that demonstrate efficacy in targeting tumor cells while limiting damage to healthy cells. There is increasing evidence that newer biologic agents targeting cellular protein receptors or other components of the tumor microenvironment may work synergistically with conventional cytotoxics. Many of these targeted agents have been considered cytostatic, but there are emerging data to suggest that they may be cytotoxic as well.

Treatment targeted to growth factor receptors has shown promise in the management of solid tumors. Growth factor receptors are important in regulating cellular processes such as proliferation, differentiation, and survival (Fig 1). There are four related growth factor receptors that share similarities in structure and function: HER1 (epidermal growth factor receptor [EGFR] or c-erbB-1), HER2 (c-erbB-2), HER3 (c-erbB-3), and HER4 (c-erbB-4).[1-3] The EGFR is a 170-kd transmembrane glycoprotein that is encoded by the c-erbB-1 proto-oncogene.[4,5] Epidermal growth factor receptor and c-erbB-2 proteins show 82% homology in the ty-

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Dr Langer has received research grant support from ImClone, Bristol-Myers Squibb, Aventis, Eli lilly, Intrabiotics, Genentech, Pharmacia, AstraZeneca, Vertex, OrthoBiotech, and Amgen.

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doi:10.1053/sonc.2002.31525

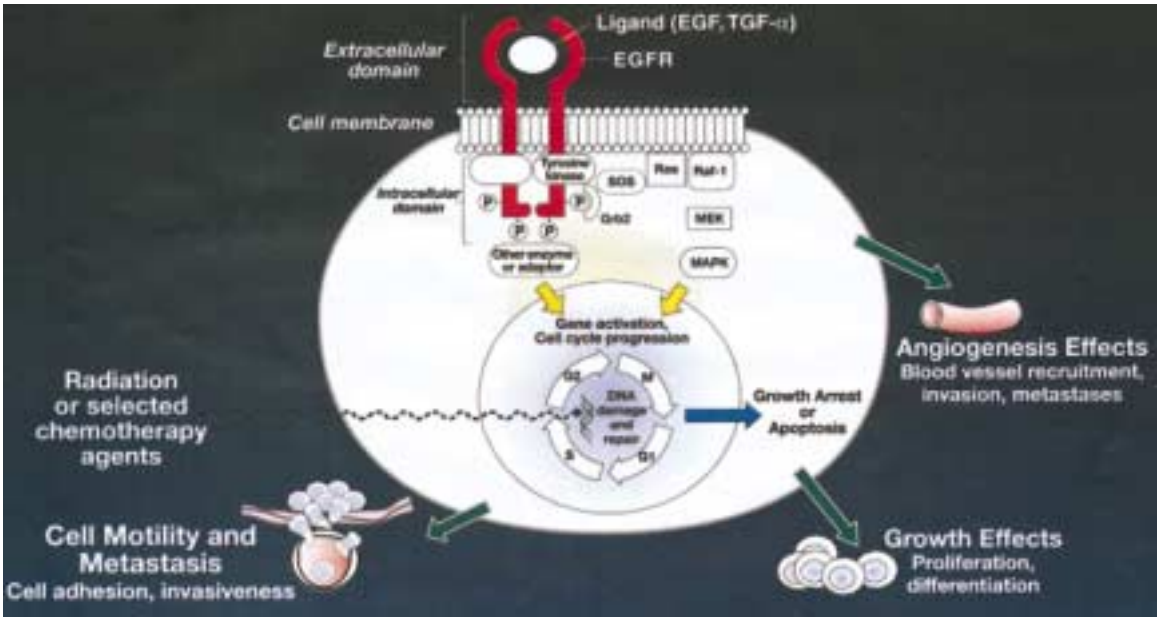

Fig 1. Epidermal growth factor receptor (EGFR) pathways. EGFR regulates cellular processes via multiple mechanisms. (Reprinted with permission from Harari PM, Huang S-M: Modulation of molecular targets to enhance radiation. Clin Cancer Res 6:323-325, 2000. Copyright © 2000 by the American Association for Cancer Research.)

rosine kinase domain, and cross-reactivity appears to exist between the EGFR and HER2 receptors.[6,7] Epidermal growth factor receptor inhibitors block the HER1 receptor.

Epidermal growth factor receptor is expressed on healthy cells that originate from all three germ cell layers, particularly those of epithelial origin (eg, skin, liver, and gastrointestinal tract) as well as on malignant tissues.[8-11] There are a number of endogenous ligands for the EGFR including epidermal growth factor (EGF), transforming growth factor alpha, amphiregulin, heparin-binding EGF, and betacellulin.[1] Epidermal growth factor and transforming growth factor alpha are the most important stimulatory ligands for the EGFR. After ligands bind to the EGFR, the receptor undergoes dimerization, followed by internalization of the receptor/ligand complex and autophosphorylation.[2] Finally, the tyrosine kinase signal transduction pathways that control cellular proliferation, differentiation, and survival are activated.[3]

Epidermal growth factor receptor is important in the maintenance of normal cellular function and survival, and EGFR expression contributes to the growth and survival of tumor cells (Fig 1). The EGFR signal transduction pathways have been correlated with various processes that contribute to the development of malignancy, such as effects on cell cycle progression, inhibition of apoptosis, angiogenesis, tumor cell motility, and metastasis. The EGFR pathway is important in controlling cell cycle events that affect survival. There is in vivo and in vitro evidence that numerous growth factors, including EGF and transforming growth factor alpha, possess angiogenic activity.[12] The EGFR pathway has been shown to regulate tumor cell motility and metastasis in a variety of studies.[13-16] Given the role of the EGFR pathways in cell cycle progression and tumor proliferation, it has been proposed that combining anti-EGFR therapy with chemotherapy or RT may result in synergistic antitumor activities by inhibiting various processes that contribute to tumor growth.[17-20]

EPIDERMAL GROWTH FACTOR RECEPTOR EXPRESSION AND MALIGNANCY

Epidermal growth factor receptor expression on normal cells ranges from 40,000 to 100,000 receptors per cell.[2] Expression of EGFR has been documented extensively on a wide variety of malignant cells including colon, head and neck,

pancreatic, non–small cell lung, breast, kidney, ovarian, glioma, and bladder cancers both in vitro and in vivo. In many cases, the number of EGFRs expressed on malignant cells is greater than on normal cells; up to 2 million EGFRs per cell have been seen in some breast cancers.[21-23] The percentage of tumors that express EGFR varies by tumor type; for example, for some cancers such as squamous cell carcinomas of the head and neck and lung, EGFR is expressed on the majority of tumors (Table 1). Several studies have shown that EGFR expression correlates with reduced disease-free and overall survival, poor prognosis, increased risk of recurrence, advanced tumor stage, and increased risk of metastasis, although others report conflicting results.[1,24,25]

Given the role of EGFR in contributing to the development of malignancy and the presence of EGFR on numerous cancer cell types (and, in some cases, at increased frequency), there is an opportunity to target and block the EGFR pathways to treat tumors that express EGFR. The specificity of EGFR blockade by monoclonal antibodies results in a favorable safety profile that differs from that of chemotherapy and RT.

ANTIEPIDERMAL GROWTH FACTOR RECEPTOR TARGETED APPROACHES

Numerous EGFR blockers have been investigated including anti-EGFR monoclonal antibodies, tyrosine kinase inhibitors, ligand conjugates, immunoconjugates, and antisense oligonucleotides. Small molecules that target the intracellular tyrosine kinase signaling pathways, such as the tyrosine kinase inhibitors, can inhibit the EGFR pathway.[26-29] Anti-EGFR monoclonal antibodies target the extracellular receptor and thus are able to effectively block the EGFR pathways in a highly specific manner. They have been shown to successfully target malignant cells.[30] However, anti-EGFR monoclonal antibodies do not exclusively target tumor cells; they will also affect normal tissues. The effects of anti-EGFR monoclonal antibodies on normal tissues are minimal, because many healthy cells expressing the EGFR do not turn over rapidly.

Table 1. Solid Tumor Epidermal Growth Factor Receptor Expression Shown by Primary Tumor Site

Primary Tumor Site	U.S. Annual Incidence*	% of Tumors Expressing EGFR
Head and neck	30,200	80% to 100%
Colorectal	130,200	25% to 77%
Pancreatic	28,300	30% to 50%
Lung	164,000	40% to 80%
Esophageal	12,300	43% to 89%
Renal cell	31,200	50% to 90%
Prostate	180,400	65%
Bladder	53,200	31% to 48%
Cervical/uterus	48,900	90%
Ovarian	23,100	35% to 70%
Breast	184,200	14% to 91%

Abbreviation: EGFR, epidermal growth factor receptor.
*American Cancer Society, 2000.

The intestinal epithelium is a notable exception because it is in a constant state of self-renewal. The newly formed epithelial cells that originate from the crypt epithelium express EGFR, which is important for maintaining normal structure and function. While tyrosine kinase inhibitors, which are given orally, are associated with intestinal epithelial toxicity, anti-EGFR antibodies, which are given intravenously, are not associated with these effects. It has been speculated that the oral delivery directly exposes the intestinal epithelium to the toxic effects of the agent while intravenous delivery makes direct access to the epithelium from the systemic circulation more difficult. In addition, the larger IgG molecule might not penetrate the crypts to have this effect.

A number of anti-EGFR monoclonal antibodies have been tested in vitro and in vivo using animal models, and a few have entered clinical trials. Examples of those that have undergone or are currently in clinical testing are IMC-C225, a chimeric monoclonal antibody; EMD 55900 (monoclonal antibody 425), a murine anti-EGFR monoclonal antibody[31-33]; ICR 62, a rat monoclonal antibody[32,34]; and ABX-EGF, a fully human anti-EGFR antibody.[35] IMC-C225, as an example, is an anti-EGFR monoclonal antibody currently in phase II and III trials. Studies include colorectal carcinoma,[36] pancreatic carcinoma,[37] breast carcinoma,[11] prostatic carcinoma,[38] renal cell carcinoma,[39] as well as squamous cell carcinoma of the head and neck (SCCHN).[40]

EMERGENCE OF IMC-C225

Much of the data regarding the efficacy and safety of anti-EGFR monoclonal antibody in solid

tumors come from clinical experience with IMC-C225. IMC-C225 is a human:murine chimeric anti-EGFR IgG monoclonal antibody that has demonstrated both in vitro and in vivo antitumor activity in tumor cell lines expressing the EGFR. Treatment of cultured human squamous cell carcinoma cells with C225 has been shown to heighten radioresponse in vitro. In vitro studies have also shown cell growth inhibition and, in some cases, cytotoxicity. IMC-C225 enhances the cytotoxic effect of chemotherapeutics, like taxanes and platinum, and radiation in human non–small cell lung cancer (NSCLC) xenograft models.[41,42]

In vitro and in vivo studies have confirmed the antitumor activity of IMC-C225. Treatment of a human colorectal carcinoma cell line, DiFi, with IMC-C225 resulted in G_1 cell cycle arrest and induction of apoptosis as evidenced by reduction in cell volume and DNA fragmentation.[43] IMC-C225 has been shown to inhibit cellular proliferation of a number of squamous cell carcinoma head and neck cell lines in vitro.[19] Renal cell carcinoma cell lines treated with IMC-C225 showed dose-dependent inhibition of DNA synthesis resulting in inhibition of cellular proliferation.[44] Human prostatic carcinoma cell lines DU145 treated with IMC-C225 showed effects on cell cycle progression.[45] There was an increased G_1/G_0 peak in comparison with control cells and a decreased number of cells in the S phase. IMC-C225 showed significant inhibitory effects in the athymic nude mice inoculated with the human prostatic cell lines DU145 and PC-3 in comparison with control mice.

IMC-C225 has also been shown to inhibit neoangiogenesis. A study by Perrotte et al[46] of IMC-C225 showed inhibition of messenger RNA and protein production of vascular endothelial growth factor in human bladder cancer xenografts in nude mice. Milas et al[47] showed significant inhibition of new vessels at the site of A531 inoculation and tumor xenografts (Fig 2); furthermore, angiogenesis inhibition was associated with significant tumor growth delay.

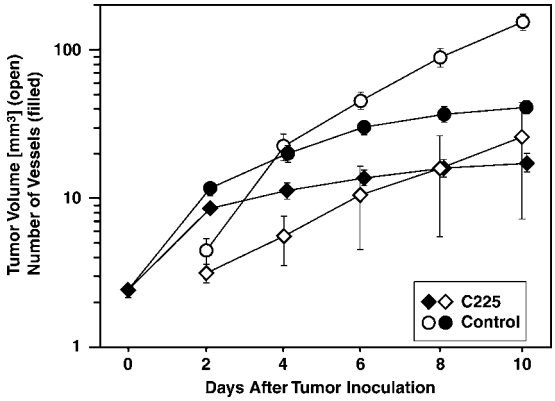

Fig 2. The effect of C225 antibody on tumor angiogenesis is shown. Mice were given intradermal inoculation of 10^6 A431 tumor cells, and the number of vessels at the injection site was determined in C225-treated (◆) and control (●) mice. Tumor volumes in C225-treated (◇) and control (○) mice were also plotted. Treatment with C225 (1 mg intraperitoneally) was given 1 day after tumor cell inoculation. (Reprinted with permission.[47])

EFFECT OF IMC-C225 AND RADIATION

IMC-C225 resulted in enhanced radiosensitivity and radiation-induced apoptosis as well as significantly diminished cell survival.[41,48] In human squamous cell carcinoma of the head and neck, IMC-C225 and radiation appear synergistic. A number of putative mechanisms of action have been postulated, including: (1) induction of G_1 cell cycle arrest, (2) inhibition of cellular proliferation, (3) promotion of radiation-induced apoptosis, (4) inhibition of radiation-induced damage repair, and (5) inhibition of tumor angiogenesis.[41,42,45,47]

Blockade of EGFR by IMC-C225 has shown in vitro inhibition of growth in multiple human squamous cell carcinoma cell lines, including A431, UMSCC-1, and UM-SCC-6. IMC-C225 produces apoptosis, which appears to be independent of cellular exposure time when given alone. However, exposure of tumor cells to radiation following IMC-C225 yields synergistic apoptosis, which increases with exposure time to IMC-C225. This is associated with a corresponding decrease in activated STAT-3 (signal transduction and transcription activation) proteins. In vivo studies of A431 xenografts implanted in nude mice corroborate in vitro work.[49]

In a separate study by Milas et al[47] of A431 xenografts treated with radiation and IMC-C225 3 hours prior, 3 days after, and 6 days after RT yielded a radiation enhancement factor of 3.62 compared with radiation alone (Table 2, Fig 3). The primary mechanism of action appeared to be tumor necrosis. There was abundant evidence of antiangiogenic effect, with microscopic sections

Table 2. Effect of C225 on Radioresponse of A431 Tumor Xenografts in Nude Mice

Treatment	Days Required for Tumors to Grow from 8 mm to 12 mm	Absolute Growth Delay	Normalized Growth Delay	Enhancement Factor
No treatment	6.5 ± 0.4			
C225 (single)	12.0 ± 2.8	5.5 ± 2.8		
C225 (multiple)	13.9 ± 3.5	7.4 ± 3.5		
18 Gy	25.8 ± 3.4	19.3 ± 3.4		
C225 single plus 18 Gy	42.7 ± 3.3	36.2 ± 3.3	30.7 ± 3.32	1.59
C225 multiple plus 18 Gy	83.8 ± 10.1	77.3 ± 10.1	69.9 ± 10.14	3.62

NOTE. A single dose of C225 resulted in an absolute growth delay of 5.5 ± 2.8 days, and multiple doses yielded an absolute growth delay of 7.4 ± 3.5 days in the A431 tumor xenograft model. Eighteen Gy yielded an absolute growth delay of 19.3 ± 3.4 days. In combination with 18 Gy, a single dose of C225 resulted in an absolute growth delay of 36.2 ± 3.3 days. Normalized growth delay of 30.7 days ± 3.32 was determined by subtracting the absolute growth delay with C225 alone from that observed with combination C225 plus 18 Gy; hence, the enhancement factor. This figure divided by absolute growth delay observed with 18 Gy alone was 1.59. Multiple doses of C225 yielded an enhancement factor of 3.62.

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showing hemorrhage, vascular thrombosis, and diminished microvessel density. Other mechanisms included retardation of tumor growth, with evidence of terminal cell differentiation and inhibitory effect on tumor cell repopulation. The investigators concluded that IMC-C225 enhances tumor radioresponse by multiple mechanisms involving both direct and indirect actions on tumor cell survival.

CLINICAL ASPECTS OF IMC-C225

IMC-C225 is characterized by a long half-life (approximately 8 days), which lends itself to relatively convenient weekly administration. It is highly selective and specific, has a good side-effect profile, and yields no apparent exacerbation of chemotherapy or radiation toxicity. However, several potential drawbacks exist. It targets only one of four Erb-B family members. The antibody appears bulky and may not necessarily penetrate large tumors or into the central nervous system. It appears to be inactive against truncated forms of the receptor, and may induce an immunologic response. In addition, there is no oral formulation.

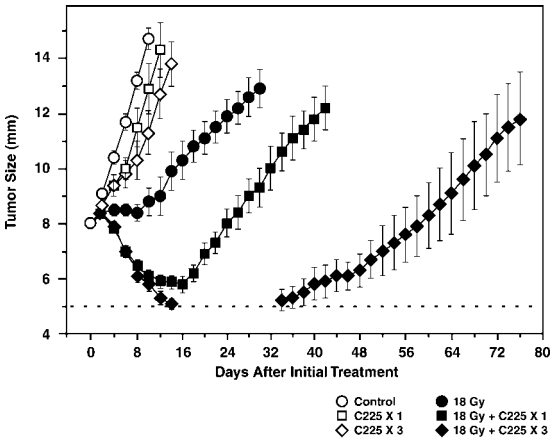

Fig 3. Effects of IMC-C225 and RT on A431 xenografts are shown. Tentative synergy is observed for the combination of IMC-C225 and radiation, and the therapeutic effect is accentuated by multiple administrations of IMC-C225. (Reprinted with permission.[47])

In phase I studies, IMC-C225 has proven well tolerated, with minimal overlapping toxicities to conventional therapy.[50] A safety review showed that adverse events were generally mild to moderate.[51] The percentage of adverse events of grade 3 severity or greater was 12%. Major toxicities associated with IMC-C225 are allergic and skin reactions. Of 189 patients treated, 2% experienced grade 3 and 2% experienced grade 4 allergic reactions. Patients with low-grade allergic reactions were successfully continued on therapy by administering prophylactic antihistamine therapy and by slowing the infusion rate. At current phase II dosing, nearly all patients developed some form of dose-related acne-like rash. These sterile, suppurative rashes, characterized as multiple pustular lesions that generally occur on the face, neck, and upper trunk, tend to manifest during the first 2 weeks of therapy. Despite their frequent occurrence, the acne-like rashes did not prove to be

dose-limiting and resolved completely without scarring after cessation of therapy in all cases. Given that EGFRs are expressed in epithelial tissues, skin reactions are a toxicity shared by the class of EGFR inhibitors.

Anaphylactic reactions are rare. They have been reported in less than 2% of patients and invariably occur during the test dose or first infusion; they respond to standard treatments, including antihistamines and corticosteroids. No fatalities have been associated with IMC-C225 administration.

ONGOING RESEARCH IN HEAD AND NECK CANCER

Most current studies in upper aerodigestive malignancy have focused on SCCHN.[52] In early-stage squamous cell carcinoma, a "window of opportunity" study is assessing the role of weekly IMC-C225 for three doses before surgery in resectable stage II, III, and IV disease. The primary objectives of this effort are pharmacokinetics, tumor localization, and receptor saturation. A separate single-center study is assessing the role of IMC-C225, in conjunction with cisplatin and concurrent RT, with concomitant boost administered at the end of RT, in locally advanced, unresectable, newly diagnosed SCCHN. The primary objectives in this study are response rate and safety.

The largest effort to date in locally advanced, newly diagnosed squamous cell carcinoma is a phase III international multicenter, randomized study evaluating RT, either alone or given concurrently with IMC-C225 (Fig 4). Three different forms of radiation are permitted: single daily fractionation; twice a day; and concomitant boost. As of October 2000, 178 of the 450 patients targeted for accrual have been enrolled. The majority (61%) have received concomitant boost RT. Eighteen percent have received twice-a-day RT, and 21% have received once-daily RT. No untoward toxicities or significant adverse events have been observed.

IMC-C225 IN RECURRENT AND/OR METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

IMC-C225 has been evaluated in recurrent and metastatic SCCHN. One of the earlier studies combined cisplatin 100 mg/m^2 every 3 weeks $\times$ 3 with IMC-C225 given weekly in an escalating dose. The primary objective of this effort was to determine the tumor–EGFR saturating dose of IMC-C225, to gauge the optimal biologic dose of IMC-C225, and to establish a safety profile over a range of dose levels in combination with cisplatin therapy. Eligibility was restricted to patients with locally advanced, recurrent, or metastatic EGFR-positive head and neck cancer; measurable or evaluable disease; tumor accessible to repeat biopsies for EGFR determination; up to one prior chemotherapy regimen; acceptable performance status; adequate renal, hepatic, and marrow function; at least 2 months elapsed since prior surgery or radiation; and no severe intercurrent medical ill-

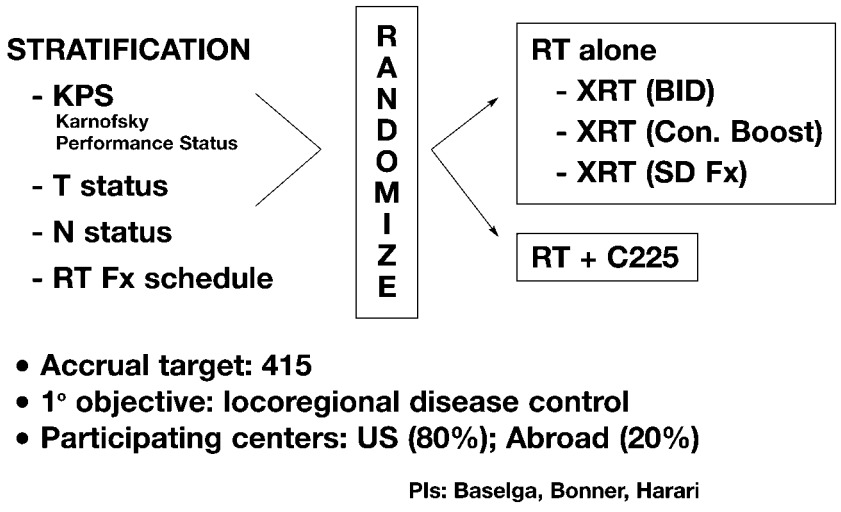

Fig 4. An ongoing phase III trial in locally advanced squamous cell carcinoma of the head and neck is testing radiation alone versus concurrent radiation and IMC-C225. Stratifications include Karnofsky performance status, tumor and nodal (T and N) status, and radiation fraction (RT) and schedule. BID, twice a day; Con Boost, concomitant boost; SD, standard daily; Fx, fractionation.

nesses. Twelve patients with a variety of head and neck primary sites were enrolled. Adverse events included skin toxicity, fever, chills, and asthenia, all relatively mild. There was one anaphylactic reaction, one relatively severe episode of cytotoxicity, and two fairly marked rashes. Of nine evaluable patients, two patients (both previously treated with cisplatin) exhibited a complete response; four other patients, all previously treated, experienced a partial response. The overall response rate in this small cohort was 67%. It should be noted that response rates in this setting using conventional therapy are generally much lower, with a median survival of 4 to 6 months and 1-year survival rate of 5% at best.[53]

This experience has given rise to an evaluation of IMC-C225 in patients who have failed to obtain partial or complete response with standard treatment. Patients with metastatic or recurrent SCCHN were given a choice of two different cytotoxic regimens, either cisplatin or paclitaxel in combination, or standard fluorouracil infusion with cisplatin. Those with stable disease or tumor progression after two courses of standard therapy then proceeded to weekly IMC-C225/cisplatin given every 3 weeks for a total of four courses. In the absence of tumor progression, IMC-C225 alone is continued until disease progression. As of January 2001, over 100 patients have been enrolled on this effort; 33 patients responded to the primary chemotherapy and did not proceed to IMC-C225. Of the remaining patients, 45 had stable disease and 27 had progressive disease. The unverified response rates in these two categories were 20% and 21%, respectively, considerably higher than one might expect with standard cytotoxic therapy alone.[53]

Finally, the Eastern Cooperative Oncology Group completed a phase III registration trial assessing cisplatin 100 mg/m^2 every 4 weeks in combination with either IMC-C225 or placebo. A loading dose of 400 mg/m^2 IMC-C225 was given at week 1, followed by a maintenance dose of 250 mg/m^2 weekly thereafter. This study targeted 114 patients for accrual and completed enrollment in the summer of 2001.

ROLE OF IMC-C225 IN LUNG CANCER

Epidermal growth factor receptor expression is relatively higher in squamous cell malignancy compared with nonsquamous NSCLC. Expression in small cell lung cancer has been low; in one series of 37 specimens, no expression was noted.[55] Preclinical work has shown an additive effect between IMC-C225 and radiation in both H226 and A549 NSCLC cell lines, with potential synergy at higher doses of IMC-C225. In the A549 line, IMC-C225 showed synergy with escalating doses of either cisplatin or vinorelbine, and an additive effect positive/negative synergy with paclitaxel.[54,56] In combination with RT, IMC-C225 also has shown synergy or additivity with vinorelbine and paclitaxel.[56]

Three separate studies in NSCLC are ongoing for IMC-C225 (Table 3). The Colorado study targets treatment-naive patients, and grafts full-dose IMC-C225 onto standard paclitaxel/carboplatin. Eligibility stipulates chemotherapy-naive, pathologically documented, measurable EGFR-positive advanced NSCLC; adequate performance status; age $\geq$ 18 years; and adequate physiologic indices, including an absolute neutrophil count of 1,500/mL, platelet count of $\geq$ 100,000/mm^3, bilirubin $\leq$ 1.5 upper limit of normal, with transami-

Table 3. IMC-C225: Non–Small Cell Lung Cancer Studies

Setting	Target	Regimen	Site(s)
First line	40	Paclitaxel 225 mg/m^2 every 3 wk Carboplatin AUC 6 every 3 wk IMC-C225 400 mg/m^2 load→ 250 mg/m^2 IV every wk	Colorado (Bunn)
First line	30	Gemcitabine 1000 mg/m^2 days 1, 8 Carboplatin AUC 5.5 every 3 wk IMC-C225 400 mg/m^2 load→ 250 mg/m^2 IV every wk	Alabama (Robert) M.D. Anderson (Blumenschein)
Second line	50	Docetaxel 75 mg/m^2 every 3 wk IMC-C225 400 mg/m^2 load→ 250 mg/m^2 IV every wk	M.D. Anderson (Herbst) University of Chicago (Vokes)

nases ≤ 2.5 upper limit of normal. In addition, no other active malignancy in the past 3 years and no evidence of grade ≥ 2 neuropathy is permitted. Patients must not have received radiation within 4 weeks of treatment and must have no clinically significant cardiac disease, arrhythmias, or conduction deficits. The primary objective of this study is a safety assessment, with secondary objectives including antitumor activity (response rate and duration of response) and an evaluation of the effect of IMC-C225 on paclitaxel and carboplatin pharmacokinetics.

The second study grafts full-dose IMC-C225 onto standard doses of gemcitabine and carboplatin. This study targets 30 patients for accrual. The assessment occurs every 6 weeks (two cycles). Eligibility is virtually identical to the Colorado trial. The primary objectives include safety and toxicity; secondary objectives include response rate and time to progression.

Finally, a third study grafts full-dose IMC-C225 onto standard salvage therapy with docetaxel 75 mg/m^2 every 3 weeks. Eligibility stipulates pathologically documented, docetaxel-naive, EGFR-positive NSCLC refractory to one prior chemotherapy regimen, with progressive disease occurring either during treatment or within 3 months after discontinuation of prior therapy. Patients are required to have Karnofsky performance score ≥ 60 and adequate physiologic indices (absolute neutrophil count ≥ 1,500/mm^3, platelets ≥ 100,000/m^3, hemoglobin ≥ 9 g/dL, bilirubin ≤ 1.5 X upper limit of normal, alkaline phosphatase, SGOT/SGPT ≤ 5 X upper limit of normal, and serum creatinine ≤ 1.5 mg/dL). Patients must be 18 years of age or older, with no other active invasive malignancy in the past 3 years, no chemotherapy or radiation within 30 days of enrollment, and no evidence of grade ≥ 2 neuropathy. The primary objective of this trial is response rate; secondary objectives include safety and toxicity, duration of response, survival, and the effect of IMC-C225 on docetaxel pharmacokinetics. This study targets 50 patients for accrual. If two or fewer of the first 21 patients respond, the trial will be closed. If, however, three or more of the first 21 patients respond, 29 additional patients will be accrued to demonstrate whether a 25% response rate is reached.

CONCLUSIONS AND UNANSWERED QUESTIONS

The EGFR pathway plays an important role in cellular proliferation, angiogenesis, and survival. Epidermal growth factor receptor is expressed in approximately one third of human tumors, and expression can affect overall prognosis and survival. Monoclonal antibodies directed at the EGFR have been extensively studied. IMC-C225, a human:murine chimeric anti-EGFR IgG_1 monoclonal antibody, has shown both in vitro and in vivo antitumor activity in tumor cell lines expressing the EGFR. Activity in combination with chemotherapy has been shown in colon cancer (with CPT-11), head and neck cancer (with cisplatin), and in pancreatic cancer (with gemcitabine).[54,57]

The role (if any) of IMC-C225 in thoracic malignancy has not yet been defined. In this regard, although studies for advanced disease are being conducted, the work in SCCHN and preclinical work with radiation provides hope for a potential role in locally advanced NSCLC that is only beginning to be investigated. In addition, it must be determined whether there is enhanced treatment efficacy in tumors with high- versus low-level EGFR expression and whether IMC-C225 is more effective against tumors with squamous cell histology compared with other NSCLC types. The current lung cancer studies described herein, if they show feasibility and early activity, will constitute the cornerstone of this process.

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