Is There a Role for Cetuximab in Non–Small Cell Lung Cancer?

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Abstract

The epidermal growth factor receptor (EGFR) is commonly overexpressed in non–small cell lung cancer (NSCLC). In addition, activating mutations in the EGFR tyrosine kinase domain have been described almost exclusively in NSCLC. Cetuximab, a monoclonal antibody against EGFR, has only modest single-agent activity in advanced NSCLC. A few phase II studies conducted in advanced NSCLC show no significant benefit from adding cetuximab to chemotherapy. However, in vitro observations of synergy between EGFR inhibitors and radiation therapy have been confirmed in the clinical setting of head and neck cancer. The addition of cetuximab to radiotherapy improves survival in patients with locally advanced unresectable squamous cell cancer of the head and neck compared with radiotherapy alone and this combination is being actively studied in locally advanced NSCLC. Research is also ongoing to define the role of cetuximab in combination with other targeted agents. This review will summarize the results of recently published studies on cetuximab and outline current research with this agent in NSCLC.

Inhibitors of the epidermal growth factor receptor (EGFR) pathway now have an established role in the treatment of head and neck, lung, and colon cancer. Erlotinib, a specific inhibitor of EGFR tyrosine kinase, improves survival in patients with advanced non–small cell lung cancer (NSCLC) that has progressed following platinum-based chemotherapy. Inhibition of the EGFR pathway by antibodies is routinely used in the treatment of advanced colon cancer and head and neck malignancies. Despite several years of research, the role of EGFR antibody-directed therapy in the treatment of NSCLC remains unclear. This review will summarize the available data from prospective studies exploring the role of the anti-EGFR antibody cetuximab in NSCLC and discuss strategies for future research with this agent.

Cetuximab is a chimeric human-murine monoclonal IgG1 antibody against the extracellular domain of EGFR. Cetuximab binds to the receptor with higher affinity than its endogenous ligands and promotes its internalization with subsequent degradation (1). In addition to the direct inhibitory effects on tumor growth through EGFR blockage, cetuximab may also induce the activation of immune effector cells through antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity (2).

Single-Agent Activity

To the best of our knowledge, no studies have been conducted using cetuximab as a single agent in previously untreated patients with advanced NSCLC. In a phase II study, single-agent cetuximab was administered to 66 patients with recurrent NSCLC (3). Although patients with EGFR-negative tumors were also allowed to participate, this group was represented by only six patients. The most common toxicity was skin rash. Partial responses were seen in 3 patients (4.5%) and stable disease in 20 patients (30%). The median time to progression, overall survival, and 1-year survival were 2.3 months, 8.9 months, and 43.9%, respectively. EGFR status was not associated with significant differences in response rates or survival. More than two thirds of the patients enrolled in the study received subsequent systemic therapy, including EGFR tyrosine kinase inhibitors, and systemic chemotherapy. Analysis of EGFR mutation status was done in 38 tumor samples, including those of 2 patients with partial responses, neither of whom had a mutation. Among the three patients found to have mutation, two achieved stable disease, and one had progressive disease. The single-agent activity of cetuximab was quite disappointing, and in the limited samples studied, there seemed to be no correlation between the previously described EGFR tyrosine kinase–activating mutations and response to therapy.

Combination with Cytotoxic Chemotherapy

Based on encouraging clinical trial results suggesting that the addition of cetuximab to chemotherapy could overcome chemotherapy resistance in some patients with colon cancer (4, 5) or with head and neck cancer (6), several studies have been launched to explore this strategy in advanced NSCLC.

First-Line Therapy

Four studies examined the role of cetuximab in augmenting responses to chemotherapy in previously untreated patients with advanced NSCLC (Table 1). In a prospective study enrolling 31 patients with previously untreated advanced NSCLC and good performance status, cetuximab was administered at an initial loading dose of 400 mg/m² followed by weekly doses of 250 mg/m² in conjunction with standard paclitaxel/
carboplatin chemotherapy (7). The most common grade 3 adverse events related to cetuximab were fatigue, acne-like rash, myalgias, and neuropathy. The overall disease control rate was 65%, with 26% objective responses and 39% stable disease. With a median follow-up time of 19 months, the median time to disease progression and median overall survival times were 5 and 11 months, respectively. In a similarly designed phase II study of 35 patients, cetuximab was combined with gemcitabine and carboplatin (8). In the absence of progressive disease or excessive toxicities, chemotherapy was discontinued after six cycles but cetuximab was continued until disease progression. Skin rash was predictably the most common adverse effect of therapy. Partial responses and stable disease were seen in 28% and 60% of patients, respectively. With a median follow-up of 618 days, the progression-free survival was 5.3 months, overall survival was 10.3 months, and 1-year survival was 45%.

Eighty-six patients with advanced NSCLC were enrolled in a randomized phase II study of cisplatin/vinorelbine chemotherapy with or without cetuximab (9). In this study, improved response rates (35% versus 28%), disease control (84% versus 67%), median progression-free survival (4.8 versus 4.2 months), median overall survival (8.3 versus 7 months), and 1-year survival (32% versus 26%) were seen with the addition of cetuximab to cisplatin and vinorelbine. Responses were seen in 2 of 8 patients without rash (25%) and in 13 of 35 patients with any degree of rash (37%). All five patients with grade 3 rash achieved a partial response. Based on the improved response rates seen in the cetuximab arm, a phase III study with the same design was initiated in 2004 (10). This large multicenter trial, known as the FLEX study, has recently completed accrual with 1,124 patients enrolled.

Because four prospective studies reported no benefit to adding EGFR tyrosine kinase inhibitors to chemotherapy in patients with advanced NSCLC, there was some legitimate concern that concurrent EGFR inhibition may even be antagonistic to chemotherapy. The Southwest Oncology Group (SWOG) conducted a randomized trial (SWOG 0342) to compare the efficacy of cetuximab administered either during chemotherapy with carboplatin and paclitaxel or following the same chemotherapy (11). There were 225 patients enrolled, 106 in the concurrent arm and 119 in the sequential arm. Regardless of the initial treatment, all patients without disease progression received maintenance weekly cetuximab for 1 year. Toxicity and efficacy were similar in both groups, and because the concurrent arm achieved a median survival above 10 months, this regimen was selected for further studies in combination with bevacizumab. The SWOG 0536, a phase II trial evaluating the combination of paclitaxel, carboplatin, bevacizumab, and cetuximab followed by bevacizumab and cetuximab, has been recently activated.

Despite marginally improved response rates, the time to disease progression of 4 to 5 months reported thus far in the studies discussed has been achieved in several multi-institution studies of platinum doublets without the addition of cetuximab. To the best of our knowledge, a significant and meaningful prolongation of progression-free survival has not been reported with the addition of cetuximab to chemotherapy in the first-line setting. Two large randomized studies comparing platinum-based doublets (one study with paclitaxel and carboplatin and another with cisplatin and vinorelbine) with or without cetuximab have been completed and results are expected soon. Unless these studies show compelling evidence of improvement in survival, we do not advocate the use of cetuximab in combination with chemotherapy in patients with previously untreated advanced NSCLC.

### Recurrent or Refractory Disease

The combination of docetaxel and cetuximab was tested in 54 patients with EGFR-positive NSCLC who had progressive disease during first-line therapy with platinum-based chemotherapy or who relapsed within 3 months of completing the therapy (12). Among the 47 evaluable patients, 13 (28%) achieved objective responses and 8 (17%) had stable disease. The median time to progression and median overall survival were 3 and 7.5 months, respectively. Similar results have been previously reported with docetaxel alone.

### Locally Advanced Disease

Preclinical studies have shown that overexpression of EGFR is associated with cellular resistance to radiation and the use of cetuximab significantly increases the cytotoxic effects of radiotherapy (13–15). In a randomized phase III study, radiotherapy with cetuximab was superior to radiotherapy alone in patients with locally advanced head and neck cancer, leading to increased duration of locoregional disease control and survival (16). A preclinical study showing improved tumor growth inhibition by the combination of cetuximab and radiation compared with either treatment alone in EGFR-expressing NSCLC cell lines provided additional support for further research evaluating this combination in patients with locally advanced NSCLC (17).

### Table 1. First-line cetuximab and chemotherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>No. patients</th>
<th>PR (%)</th>
<th>TTP/PFS (mo)</th>
<th>MST (mo)</th>
<th>1-y survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thienelt et al. (7)</td>
<td>PCbC</td>
<td>31</td>
<td>26</td>
<td>5</td>
<td>11</td>
<td>40</td>
</tr>
<tr>
<td>Robert et al. (8)</td>
<td>GCbC</td>
<td>35</td>
<td>28</td>
<td>5.3</td>
<td>10.3</td>
<td>45</td>
</tr>
<tr>
<td>Rosell et al. (9)</td>
<td>VCPc</td>
<td>43</td>
<td>35</td>
<td>4.8</td>
<td>8.3</td>
<td>32</td>
</tr>
<tr>
<td>Kelly et al. (11)</td>
<td>PCbC (concurrent)</td>
<td>106</td>
<td>37</td>
<td>4.2</td>
<td>10.5</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>PCbC (sequential)</td>
<td>119</td>
<td>26</td>
<td>4.4</td>
<td>8.7</td>
<td>43</td>
</tr>
</tbody>
</table>

Abbreviations: C, cetuximab; Cb, carboplatin; Cp, cisplatin; P, paclitaxel; V, vinorelbine; MST, median survival time; PFS, progression-free survival; PR, partial response; TTP, time to progression.
The Radiation Therapy Oncology Group is currently evaluating the role of cetuximab in combination with chemoradiation in patients with unresectable stage III NSCLC (18). In this study (Radiation Therapy Oncology Group 0324), cetuximab is administered in conventional doses with six cycles of standard weekly paclitaxel (45 mg/m²) and carboplatin (area under the curve of 2) as well as concurrent radiation therapy for a total of 63 Gy in 35 fractions. The chemoradiotherapy is followed by two cycles of paclitaxel and carboplatin administered in systemic doses. The ongoing Cancer and Leukemia Group B 30407 trial, a phase II study, is currently evaluating the combination of carboplatin and pemetrexed during concurrent radiation therapy (70 Gy over 7 weeks), with or without the addition of cetuximab, followed by four cycles of consolidation therapy with pemetrexed. The results of these studies will hopefully clarify the role of cetuximab in the treatment of patients with locally advanced NSCLC.

Comments

Despite encouraging preliminary results, the role of cetuximab in patients with NSCLC remains unclear. The single-agent activity of cetuximab in heavily pretreated patients with advanced NSCLC is rather unimpressive. Similarly, there has been no meaningful improvement in the time to disease progression with the addition of cetuximab to standard platinum doublets in the first-line setting. We do not advocate the use of cetuximab alone or in combination with chemotherapy in patients with advanced NSCLC at the present time.

EGFR and vascular endothelial growth factor share common downstream pathways, and the combination of the vascular endothelial growth factor inhibitor bevacizumab with the EGFR tyrosine kinase inhibitor erlotinib showed promising results as second-line therapy for patients with advanced NSCLC (19). The ongoing SWOG 0536 study will explore whether the combination of bevacizumab and cetuximab can lead to similar or improved benefits in patients with advanced NSCLC.

There are no reliable predictors of response to cetuximab monotherapy in NSCLC. EGFR expression by immunohistochemistry does not seem to be a reliable predictor of efficacy with cetuximab (3). Furthermore, unlike the case for small-molecule tyrosine kinase inhibitors (20, 21), EGFR tyrosine kinase–activating mutations do not predict response to cetuximab monotherapy (3). This lack of significant responses for cetuximab in patients with EGFR tyrosine kinase activation mutations has also been described in a preclinical study where NSCLC cells carrying wild-type or mutant EGFR were treated with cetuximab or gefitinib (22). Although both agents induced similar absent to moderate apoptosis in cells with wild-type EGFR, gefitinib was significantly more effective than cetuximab in inhibiting the growth of cells with mutant EGFR. To support these differences, four patients with advanced NSCLC and EGFR mutations were identified. Although none responded to cetuximab, all achieved partial response to gefitinib.

Two potential predictors for response to cetuximab have been evaluated in patients with colorectal cancer. Increased EGFR copy number was present in 8 of 9 patients achieving objective response and in only 1 of 21 nonresponders (23). Polymorphisms in both EGFR and cyclin D1 have been associated with better outcomes in patients treated with cetuximab, where any G allele for cyclin D1 A870G and any A allele for EGF A61G were associated with increased median survival (24).

Because the antibody-dependent cell-mediated cytotoxicity mechanism seems to be important for the efficacy of monoclonal antibodies, unlike tyrosine kinase inhibitors, Fc γ receptor (FcγR) polymorphisms may potentially be a predictive marker. In antibody-dependent cell-mediated cytotoxicity, the antibody binds to tumor cells and is engaged by the effector cells through their receptors for immunoglobulin (FcγRs). There are three classes of FcγRs involved in the regulation of antibody-dependent cell-mediated cytotoxicity, two stimulatory, FcγRIIa (CD16) and FcγRIIa (CD16), and one inhibitory, FcγRIib. The FCG3A gene encodes for FcγRIIa with either phenylalanine (F) or valine (V) at the position 158. It has been shown that IgG1 has stronger binding to homozgyous 158V/V than 158 F/F or 158 V/F. In follicular lymphoma patients treated with first-line rituximab, the FcγRIIa 158 V/V polymorphism was associated with better tumor response and progression-free survival than 158F carriers (25). Because cetuximab is also an IgG1 chimeric antibody, FcγRs may similarly be associated with differences in outcomes. In colorectal cancer patients, a recent study evaluated the significance of two polymorphisms in the FcγRIIa receptors, 158 V/F and 131 H/R (26). Patients with 131 H/H or H/R had better outcomes compared with the R/R genotype. In addition, there was a trend toward increased response rates in patients with 158 V/F genotype.

Future Directions

Despite the disappointing results from early clinical studies of cetuximab in NSCLC, there is a sound rationale for exploring cetuximab in combination with thoracic radiation in patients with locally advanced NSCLC. Up-regulation of EGFR may contribute to the accelerated repopulation of cells following radiation and EGFR inhibition has the potential to reverse this phenomenon. This concept has already been tested in patients with locally advanced unresectable cancer of the head and neck, where the addition of cetuximab to radiation improved outcomes when compared with radiation alone. The combination of cetuximab and vascular endothelial growth factor inhibitors is worth studying in advanced NSCLC. In the era of molecularly targeted therapy, it is not enough simply to understand the molecular pathways inhibited by the drug, but it is critical to identify the patients who are good candidates for the drug of interest.

Open Discussion

Dr. Thomas Lynch: Here, you have a drug that is strong in colorectal cancer and in head and neck cancer. It works with chemotherapy, so why shouldn’t it work in lung cancer?

Dr. Roman Perez-Soler: It has been speculated that colorectal cancer is a ligand-driven disease. Too much ligand is being produced and the antibody antagonizes the ligand, like bevacizumab for VEGF, whereas tumors like lung are more...
Dr. Lynch: The rationale for doing both the cisplatin/vinorelbine trial and the carboplatin/paclitaxel trial was the observation that in a number of settings the drug enhances cytotoxic therapy, they use the EGFR pathway as a survival pathway overproducing EGFR. So these are the two speculative hypotheses.

Dr. Lynch: The little data that we have seem to be leaning toward perhaps improved response rate with the EGFR antibodies combined with chemotherapy, unlike the EGFR TKIs. However, the data with cetuximab and chemotherapy suggest that the magnitude of benefit, if there is one, may not be large enough to lead to a positive trial.

Dr. Bruce Johnson: I predict that it will be negative and that we will again say that we need to look at markers to select out the patient population better.

Dr. Mark Socinski: I think it will be negative too. One issue is that all these patients are going to get second line and then something else afterwards. We saw how good the single-agent cetuximab trial did: 8.9 months, 43% 1-year survival with a response rate of 5% but less than 50% stable disease. That was an impact of subsequent therapy. In first-line therapy trials with an overall survival end point, where the preliminary data are weak, it is going to be a long, long day before something like this will turn out positive.

Dr. Lynch: In colorectal cancer, they are moving toward therapies with double monoclonal antibodies, anti-VEGF and anti-EGFR. Does anyone here think that we would have merit in lung cancer?

Dr. Roy Herbst: SWOG is doing a study [SWOG 0536] adding bevacizumab to carboplatin/paclitaxel/cetuximab, but this has a scientific basis only if the prior study [SWOG 0342] is positive. That speaks to the difficulty we are having in designing big trials in the groups. If those data from S0342 hold up, and they will be looked at one more time at ASCO, then the next trial will be to add bevacizumab. If we can show cetuximab has some role in lung cancer, then I think that trial makes sense.

Dr. Lynch: The U.S. trial is powered for time to progression not for overall survival. The European trial is powered for overall survival. Would it be the feeling of the group that if both of those studies are negative and don’t meet their end points, monoclonal antibodies for EGFR are dead in lung cancer?

Dr. Socinski: In drug development in lung cancer, we often do the studies in stage IV disease. If an agent does not look good there, that quells enthusiasm, but here is a drug that may actually be optimized in the context of radiotherapy. We have an understudied population that does not get aggressive therapy. That is why I think the RTOG 0324 and CALGB 30407 trials are important for EGFR antibodies.

References
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