REVIEW

Rational use of cetuximab in the treatment of advanced non-small cell lung cancer

Charu Aggarwal
Hossein Borghaei

Department of Medical Oncology,
Fox Chase Cancer Center,
Philadelphia, PA, USA

Abstract: Lung cancer is the leading cause of mortality in the United States. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. Most NSCLC patients present with loco-regionally advanced or metastatic disease where response rates are low and median overall survival approximates 8 to 10 months. Chemotherapy is the mainstay of treatment for NSCLC patients with metastatic disease. Epidermal growth factor receptor (EGFR) and family of receptors play a critical role in lung cancer tumorigenesis. Cetuximab, a monoclonal antibody that binds the EGFR, has demonstrated preclinical and clinical activity against NSCLC. This review focuses on the use of cetuximab in NSCLC.

Keywords: cetuximab, lung cancer, monoclonal antibody

Introduction

Lung cancer is the leading cause of cancer related mortality in the United States.[1,2] Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases and encompasses different histologies including squamous cell carcinoma, large cell carcinoma and adenocarcinoma with or without bronchioalveolar features.

NSCLC is staged according to the TNM (tumor, node, and metastasis) system.[3,4] Early stage lung cancer represents a minority of cases and is often curable with surgery with or without adjuvant chemotherapy. Adjuvant chemotherapy consisting of a cisplatin-based doublet is associated with improved survival in patients with resected stage II–IIIA lung cancer.[5–9] Some patients with stage IB lung cancer may also derive a benefit from chemotherapy.[10] The optimal management of unresectable stage IIIA NSCLC is controversial and depends on the nodal status and tumor size and location.[11]

A sizeable majority of patients with NSCLC present with distant metastases where chemotherapy is the mainstay of treatment. In the 1980s, doxorubicin- and cyclophosphamide-containing regimens were used without substantially improving survival.[12–14] Subsequently single-agent chemotherapy with paclitaxel, gemcitabine, and vinorelbine was compared to best supportive care, suggesting a favorable survival trend for chemotherapy with these agents.[15–17] Based on these encouraging results, trials of combination chemotherapy with cisplatin and the previously used single agents were conducted and showed a further improvement in overall and disease-free survival.[18,19] These trials established platinum doublet as the cornerstone of chemotherapy for advanced NSCLC. Equivalence of different platinum doublet combinations was demonstrated in randomized phase III studies.[20–22] In a recent landmark trial, addition of bevacizumab, an antibody against the vascular endothelial

Correspondence: Hossein Borghaei
Department of Medical Oncology,
Fox Chase Cancer Center,
333 Cottman Avenue,
Philadelphia, PA 19111, USA
Tel +1 215-214-4297
Email hossein.borghaei@fccc.edu

growth factor, to carboplatin and paclitaxel was associated with improved overall and progression-free survival (PFS) in patients with non-squamous histologies.[23] This was the first trial to show an improvement in survival with the use of targeted agents in addition to standard chemotherapy in patients with NSCLC. In another trial, addition of bevacizumab to cisplatin and gemcitabine was associated with significant improvement in PFS and response rate.[24]

A more recent trial compared cisplatin and pemetrexed to cisplatin and gemcitabine, with similar overall survival and somewhat better tolerability for the pemetrexed-containing arm. However, in a prespecified subset analysis, the cisplatin and pemetrexed arm demonstrated statistically significant improvement in survival for the adenocarcinoma and large cell carcinoma histologies.[25] Conversely, the cisplatin and gemcitabine arm proved to be superior for the squamous cell cancers of the lung.

Currently, palliative chemotherapy is the standard of care for patients with metastatic NSCLC. First-line treatment involves administration of 4 to 6 cycles of platinum-containing doublet chemotherapy[26,27] with or without bevacizumab.[23,24] The addition of bevacizumab and pemetrexed in specific subsets of NSCLC have resulted in modest improvements in survival, however these have only been seen in select patient populations. Newer therapies are therefore desperately needed to improve outcomes in the greater majority of patients with NSCLC.

Epidermal growth factor receptor

The epidermal growth factor receptor (EGFR) is one of a family of receptors that has growth promoting effects in NSCLC. EGFR is overexpressed in about 40% to 80% of NSCLC.[28] Downstream signaling by the activated EGFR can be abrogated by small molecule inhibitors, such as erlotinib and gefitinib or by monoclonal antibodies directed towards the extracellular domain of EGFR, such as cetuximab.

The EGFR (ErbB1) is a transmembrane receptor of the tyrosine kinase (TK) family of receptors. It is a 170 kDa protein and has 3 closely related members, HER2/Neu (ErbB2), HER3 (ErbB3), and HER4 (ErbB4). All members, except for HER2/Neu, have an extracellular ligand binding domain. Additionally all members, except HER3, are equipped with an intracellular domain with TK activity. Ligand binding results in receptor homodimerization or heterodimerization and consequent phosphorylation of the TK domain. EGF and transforming growth factor (TGF) alpha appear to be key ligands, but others, like epiregulin, betacellulin, epigen, and amphiregulin, have been shown to be relevant predictors of response and resistance.[29,30] A series of downstream signals lead to tumor proliferation, angiogenesis, and inhibition of apoptosis by the Ras-Raf-Mitogen activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI3)-Akt pathways.[31,32] Interaction between EGFR expression and STAT 3 (signal transducers and activators of transcription 3) has also been shown to be important in gene transcription.[33–35]

Small-molecule EGFR TK inhibitors (TKIs) are competetive inhibitors and bind reversibly to the intracellular catalytic domain of EGFR tyrosine kinase and, thus, inhibit EGFR autophosphorylation and downstream signaling. Anti-EGFR monoclonal antibodies, on the other hand, recognize EGFR exclusively and are therefore highly selective for this receptor. In addition, various small-molecule EGFR TKIs can block different growth factor receptor TKs, including other members of the EGFR family, while antibodies are fairly specific. Erlotinib is approved for second- or third-line treatment in chemotherapy-resistant advanced NSCLC based on superior overall survival results from a phase III randomized study.[36] Females, non-smokers, Asian patients, and patients with adenocarcinoma and EGFR mutations derive the maximum benefit when treated with small molecule TKIs.[37] In combination with chemotherapy, erlotinib did not confer any additional benefit over chemotherapy alone in two separate phase III trials.[38,39] Therefore, at this point erlotinib is used in patients with evidence of recurrent disease. A study to evaluate the role of this agent in the maintenance setting is ongoing. Also, the potential use of this agent in the front-line setting in patients with activating EGFR mutations is under investigation. This review will focus on pharmacology, safety, efficacy, and future directions of the use of cetuximab in NSCLC.

Pharmacology of cetuximab

Murine antibody to EGFR, mAb225, was initially developed from a panel of anti-EGFR antibodies based upon receptor affinity and efficacy.[40] All patients treated with this antibody in a phase I study developed human antimurine antibodies. Therefore a chimeric human–mouse version of mAb225 (C225, cetuximab) was produced. Cloned heavy and light chains of mAb225 were adapted for expression with a constant region of the human kappa light chain and human gamma 1 heavy chain. This antibody, cetuximab, binds to EGFR with higher affinity than its murine counterpart.[41–44]

Initial phase I trials established 400 to 500 mg/m^2 intravenously (iv) as loading dose to be followed by 250 mg/m^2 iv weekly based on adverse effect profile and pharmacokinetic parameters.[42,45,46]

Epithelial cancers are often associated with activation of growth factor receptors of the EGFR family. Anti-EGFR antibodies recognize EGFR exclusively and are therefore highly selective for this receptor. The EGFR has an extracellular and intracellular domain. The extracellular domain has 4 subunits, which exist in a compact, tethered auto-inhibited condition in the absence of a ligand.[47] Cetuximab prevents ligand binding to EGFR, inhibits receptor dimerization, and therefore blocks downstream signaling. Cetuximab binds to domain III of the receptor and sterically blocks access to the key ligand binding region of the receptor. There is also evidence that, in the presence of cetuximab, the EGFR extracellular component cannot adopt the extended dimerization configuration preventing its activation.[47] It binds with higher affinity than its endogenous ligands and promotes receptor internalization and degradation.[48] By promoting receptor removal from the cell surface, cetuximab also reduces the active pool of protein available to signal.[49]

EGFR pathway is important in proliferation, metastasis, cancer cell invasion, and angiogenesis.[50] Blockade of EGFR pathway by cetuximab leads to inhibition of cancer cell proliferation (blockade of cell cycle progression and G1 arrest through an increase in p27kip1 inhibitor of cyclin-dependent kinases),[51–53] inhibition of tumor-induced angiogenesis by blockade of production of angiogenic factors (transforming growth factor alpha, VEGF, IL8, basic FGF), inhibition of invasion and metastasis, and potentiation of antitumor activity of cytotoxic drugs and radiation therapy.[44,54] There is also evidence of IgG1-mediated antibody directed cell mediated cytotxicity (ADCC).[55]

In preclinical animal models, cetuximab and other epidermal growth factor receptor antagonists have been shown to be synergistic with cisplatin[56,57] and paclitaxel.[58,59] In a preclinical study, the efficacy of combination of cetuximab and paclitaxel was evaluated for treating human transitional cell carcinoma (TCC) of the urinary bladder of nude mice.[59] Paclitaxel demonstrated significant antitumor activity and the extent of paclitaxel-induced apoptosis was enhanced in the presence of reduced Raf-1 activity.[60] Cetuximab downregulates Raf-1 activity, and presumably by this mechanism cetuximab enhances the antiproliferative and apoptotic effects of paclitaxel in a dose-dependent manner in vitro. A second hypothesis for this synergy is that treatment with paclitaxel may upregulate EGFR receptors in tumor cells, making cells more susceptible to anti-EGFR therapies.

Resistance eventually emerges in most tumors initially susceptible to anti-EGFR approaches. Various mechanisms of resistance have been documented in preclinical and clinical models. Active EGFR signaling may lead to resistance by upregulation of ATP-binding cassette (ABC) proteins. ABC proteins confer resistance by actively pumping drugs out of the cancer cell. In breast adenocarcinoma cell lines, activation of the EGFR pathway is linked to activation of the multidrug resistance transporter family.[61] EGFR resistance may also be due to mutations in the receptor protein itself. The T790M mutation substitutes methionine for a threonine residue, leading to resistance by reducing affinity to small-molecule TKIs and increasing competitive ATP binding.[62] This mutation is seen in about 50% of patients demonstrating acquired resistance to TKIs. Heterodimerization with other HER partners may represent an alternative mechanism of resistance. Cancer cells expressing EGFR and ErbB2 are nonresponsive to inhibitors targeting one of these two proteins.[63] Similarly, overexpression of ErbB3 also confers resistance to EGFR inhibitors.[64] Expression of hepatocyte growth factor and c-Met dependent signaling is also an alternative pathway for signaling conferring resistance (seen in approximately 20% of patients with acquired resistance to TKIs).[65] Finally, interactions between EGFR and the insulin growth factor receptor (IGF-1R) can provide resistance to agents targeting EGFR.[66]

Although the above mechanisms are mainly responsible for resistance to TKIs, downstream activating mutations of the core effector pathway play a central role in mediating resistance to agents targeted both intracellularly and extracellularly. The most validated downstream resistance mechanism is the *KRAS* pathway. Mutant *KRAS* exists in the activated state and constitutively activates downstream signals of cell proliferation, motility and metastasis, and survival. Mutant *KRAS* (found in approximately 15% to 30% of patients with NSCLC) is associated with worse survival in response to EGFR antibodies in colorectal cancers.[67–69] In NSCLC, a retrospective analysis of tumor samples from erlotinib or gefitinib sensitive patients revealed that *KRAS* mutation was associated with resistance to either therapy.[70] Clinical data from the FLEX study[71] do not support the hypothesis that *KRAS* mutation status is predictive for cetuximab efficacy when combined with first-line chemotherapy in advanced NSCLC, whereas early acne-like rash of any grade appears to be associated with better outcome in patients treated with cetuximab.[72]

EGFR expression by immunohistochemistry and amplification by fluorescence in situ hybridization (FISH) have been evaluated as potential markers for response to EGFR targeted agents.[73,74] These have not been associated with differential outcomes in response to EGFR TKIs.

However, in a recent study, increase in EGFR gene copy number by FISH (4 or more gene copies per cell in ≥40% of the cells or gene amplification) was shown to predict for survival in advanced-stage NSCLC receiving sequential or concurrent chemotherapy (paclitaxel plus carboplatin) with cetuximab. Larger, prospective confirmatory studies are required for confirmation of this observation.[75]

Clinical efficacy in first-line setting

NSCLCs often overexpress EGFR, making cetuximab an attractive targeted agent for use in these patients.[76] It has been used in several trials in the first-line setting in stage IIIb/IV NSCLC (Table 1).

In a multicenter phase I/II study, Thienelt et al used cetuximab in the first-line setting in combination with carboplatin at an area under the curve (AUC) of 6 and paclitaxel (225 mg/m^2) in patients with advanced stage NSCLC.[77] Cetuximab was administered iv at 400 mg/m^2, 1 week before paclitaxel and carboplatin, then weekly at 250 mg/m^2 (standard dosing). Patients had to have EGFR positive disease by immunohistochemistry (IHC), performance status (PS) of 0 to 2, and measurable disease. The regimen was continued until disease progression or intolerable toxicity. Patients who did not tolerate chemotherapy because of toxicity could continue on weekly cetuximab monotherapy until disease progression or unacceptable toxicity. Thirty-one patients were treated and an objective response was observed in 8 patients (26%). At a median follow-up of 19 months, the median time to progression (TTP) was 5 months, median survival was 11 months, and the 1- and 2-year survival rates

Table 1 Trials evaluating use of cetuximab in combination with chemotherapy in first-line setting in Stage IIIb/IV NSCLC

Author	Phase	n	Chemotherapy[a]	Results for cetuximab group
Thienelt et al[77]	I/IIa	31	Cb AUC 6 T 225 mg/m^2 (every 3 wk)	Median OS 11 mos Median TTP 5 mos
Robert et al[78]	I/IIa	35	Cb AUC 5 Gem 1000 mg/m^2(d1,8) (every 3 wk)	Median OS 320 days Median TTP 165 days
Butts et al[79]	II	131	Cb AUC 5 or CDDP 75 mg/m^2 Gem 1000 mg/m^2 (d1,8) (every 3 wk)	Median OS 11.99 mos Median PFS 5.09 mos
Spigel et al[80]	II	27	Gem 1000 mg/m^2 IV Doc 30 mg/m^2 IV days 1, 8 (every 3 wk)	Median OS NR Median PFS NR
Belani et al[81]	II	80	Cb AUC 6 Docetaxel 75 mg/m^2 (every 3 wk)	Median OS 10.3 mos Median PFS 4.6 mos
Borghaei et al[82]	II	53	Cb AUC 6 T 100 mg/m^2 (d1,8,15) (every 4 wk)	Median OS 13.8 mos Median TTP 5.5 mos
Bradford et al[85]	II	57	Cb AUC 6	Pending
Lilenbaum et al[86] (PS 2 patients)	II	55	Doc (30 mg/m^2 wkly for 3 wk) *or* Bortezomib (1.6 mg/m^2 wkly for 3 wk) (every 4 wk)	Median OS 3.8 vs 3.3 mos Median PFS 3.1 vs 1.8 mos
Rosell et al[87]	II	86	CDDP 80 mg/m^2 Vinorlebine 25 mg/m^2 (d1,8) (every 3 wk)	Median OS 8.3 mos Median PFS 5 mos
Pirker et al[71,88]	III	1125	CDDP 80 mg/m^2 Vinorlebine 25 mg/m^2 (d1,8) (every 3 wk)	Median OS 11.3 mos Median PFS NR
Lynch et al[89]	III	676	Cb AUC 6 with T (225 mg/m^2) *or* Dose (75 mg mg/m^2) (every 3 wk)	Median OS NR Median PFS 4.4 mos

[a]All evaluated chemotherapy in addition to cetuximab (400 mg/m^2 iv during the first week followed by 250 mg/m^2 iv weekly) unless otherwise specified.
Abbreviations: Cb, carboplatin; T, paclitaxel; CDDP, cisplatin; Gem, gemcitabine; AUC, area under the curve; Doc, docetaxel; OS, overall survival; PFS, progression-free survival; mos, months; wk, weeks; NR, not reported; TTP, time to progression.

were 40% and 16%, respectively. Pharmacokinetic sampling did not reveal an interaction between carboplatin, paclitaxel, and cetuximab.

In another similar phase I/II study, Robert et al evaluated the use of cetuximab in combination with carboplatin and gemcitabine in previously untreated, advanced NSCLC patients.[78] All tumors were positive for EGFR receptor by IHC ($>$1+). Thirty-five patients received treatment with cetuximab with standard dosing. Carboplatin (AUC 5, day 1) and gemcitabine 1000 mg/m^2 on days 1 and 8 were administered every 3 weeks. Responses included 10 partial responses (PR) (28.6%). Twenty-one patients had stable disease (SD). The median TTP was 165 days, and the median overall survival (OS) was 310 days. Butts et al randomized 65 patients with advanced metastatic NSCLC in a phase II study to receive gemcitabine (1250 or 1000 mg/m^2 iv, days 1 and 8) plus cisplatin (75 mg/m^2 every 3 weeks) or carboplatin (AUC 5 every 3 weeks), with or without cetuximab in standard dosing.[79] Median PFS and OS were marginally better in patients that received cetuximab (PFS: 5.09 vs 4.21 months, OS: 11.99 vs 9.26 months). Spigel et al evaluated the combination of gemcitabine 1000 mg/m^2 iv and docetaxel 30 mg/m^2 iv days 1, 8 in combination with standard dosing of cetuximab in newly diagnosed unresectable stage III/IV NSCLC.[80] Twenty-seven patients were included in this analysis (n = 66 planned). Accrual was temporarily suspended due to a higher than anticipated rate of cetuximab-based hypersensitivity reactions. Overall response rate (ORR) was 13%, 9 patients (39%) had SD and 7 patients had progressive disease.

Several phase II studies examined the role of maintenance cetuximab in addition to its use with upfront chemotherapy. Belani et al enrolled 80 previously untreated patients in a phase II study to receive standard doses of cetuximab plus docetaxel (at a dose of 75 mg/m^2 on day 1) and carboplatin (AUC 6 on day 1) every 21 days for up to 6 cycles.[81] Thereafter, patients without evidence of disease progression

were continued on single-agent cetuximab for a maximum of 1 year or until disease progression. The objective response rate was 15.2%, with a median PFS of 4.6 months and a median OS of 10.3 months. Another similar phase II trial by Borghaei et al evaluated the use of standard doses of cetuximab in combination with monthly carboplatin (AUC 6 day 1) and weekly paclitaxel (100 mg/m^2 days 1, 8, and 15) every 4 weeks.[82] In patients without disease progression or limiting toxicity, cetuximab was continued as a single agent after 6 full cycles of therapy (28% of the patients). Fifty-three patients were accrued. ORR was 57% and 23% had SD. Median TTP was 5.5 months, median survival was 13.8 months; 1-year OS 53%, 2-year OS 18%. Saleh et al evaluated two different schedules of chemotherapy administration in addition to standard doses of cetuximab.[83] Beginning on day 8, a schedule of iv carboplatin (AUC 6) and paclitaxel 225 mg/m^2 given on a 3-week cycle was compared with a schedule of iv carboplatin (AUC 6) every 4 weeks and paclitaxel 100 mg/m^2 weekly for 3 weeks of each 4-week cycle. Patients who achieved CR, PR, or SD after 4 cycles continued on weekly cetuximab monotherapy until disease progression or unacceptable toxicity. Cetuximab combined with chemotherapy in both dose schedules demonstrated activity and an acceptable toxicity profile. The Southwestern Oncology Group (SWOG) randomized untreated patients with advanced stage NSCLC to receive paclitaxel 225 mg/m^2 and carboplatin (AUC 6) every 3 weeks plus standard doses of cetuximab concurrently followed by maintenance cetuximab or sequential chemotherapy for 4 cycles followed by cetuximab.[84] Treatment was continued until disease progression. Toxicities were significantly increased with concurrent therapy. A phase II trial of paclitaxel, carboplatin, cetuximab, and bevacizumab in this patient population is ongoing (SWOG 0536) in anticipation of a phase III trial. Carboplatin (AUC 6) every 3 weeks for 4 cycles (12 weeks) was used in combination with cetuximab in a phase II trial.[85] Final PFS and OS data are pending (Table 1).

Table 2 Trials evaluating the use of cetuximab with chemotherapy in relapsed/refractory in Stage IIIb/IV NSCLC

Author	Phase	n	Treatment	Results
Hanna et al[90]	II	66	Weekly cetuximab	ORR 4.5% Median OS 8.9 mos Median TTP 2.3 mos
Jalal et al[91]	I/IIa	23	Weekly cetuximab + Pem (750 mg/m^2 iv every 3 weeks)	ORR 9.5% Median TTP 5.5 mos
Kim et al[92]	II	47	Weekly cetuximab + Doc (75 mg/m^2 iv every 3 weeks)	Median TTP 89 days

Abbreviations: OS, overall survival; TTP, time to progression; Pem, pemetrexed; ORR, overall response rate.

Lilenbaum et al randomized untreated patients with advanced NSCLC and PS 2 to docetaxel (30 mg/m^2 weekly for 3 weeks in a 28-day cycle) in combination with either cetuximab or bortezomib (1.6 mg/m^2 weekly for 3 weeks in a 28-day cycle) for 4 cycles.[86] Patients whose disease was controlled (CR/PR/SD) were allowed to continue cetuximab or bortezomib until progressive disease. Sixty-four patients were enrolled; median PFS was 3.1 months for cetuximab and 1.8 months for bortezomib. Median survival was 3.8 months for cetuximab and 3.3 months for bortezomib.

In a randomized phase II study, Rosell et al randomized 86 chemo-naive patients with advanced EGFR($>$1 + IHC) expressing NSCLC to every 3 weeks cisplatin (80 mg/m^2, day 1) with vinorelbine (25 mg/m^2 on days 1 and 8) with or without weekly cetuximab.[87] Median PFS was higher for the cetuximab group (5.0 vs 4.6 months, hazard ratio 0.71). There was also a trend toward improved OS (8.3 vs 7.3 months, hazard ratio 0.71). The cetuximab combination was well tolerated. This combination was further validated in a prospective randomized phase III trial.[71,88] Tumor samples from 1688 patients were analyzed. A total of 1125 patients with EGFR expressing tumors ($>$1 + IHC) were randomized to the above combination. Primary endpoint was OS, and RR, PFS, disease control, and quality of life were secondary endpoints. Cetuximab was continued as maintenance therapy in the cetuximab arm until disease progression or unacceptable toxicity. The percentage of patients who received single-agent cetuximab and the duration of treatment with this agent were not reported. Addition of cetuximab was associated with a superior OS over chemotherapy alone in all patients with EGFR-detectable advanced NSCLC (median OS 11.3 vs 10.1 months, $P = 0.0441$). Even though the 121 Asian patients enrolled in the study had prolonged OS compared to Caucasians (median OS 19.5 mos vs 9.6 mos), they did not achieve a survival benefit by addition of cetuximab to chemotherapy compared to chemotherapy alone (17.6 vs 20.4 months, $P = 0.49$). There was also no significant difference in PFS in the two treatment arms.

In another large phase III trial, Lynch et al randomized previously untreated stage IIIb/IV NSCLC patients to receive either paclitaxel (225 mg/m^2 iv) or docetaxel (75 mg mg/m^2 iv) and carboplatin (AUC 6 iv) every 3 weeks with or without cetuximab.[89] The choice of taxane was at the discretion of the investigator. A total of 676 six patients were randomized at 97 centers in the United States. There were no statistically significant differences in PFS (4.4 vs 4.2 months, $P = 0.23$). ORR, however, was statistically significantly superior for the cetuximab arm (25.7% vs 17.2%, $P = 0.0066$).

Clinical efficacy in recurrent disease

Hanna et al evaluated single-agent cetuximab used at its standard dosing schedule in 66 recurrent NSCLC patients (60 EGFR positive by IHC), ORR was 4.5% and 30.3% of patients achieved SD. Median TTP and OS were 2.3 months and 8.9 months, respectively.[90] ORR in the EGFR positive population was 5%. All three patients with CR had EGFR positive tumors. An exploratory analysis of EGFR mutational status was performed on 38 tumor specimens. Three patients had activating mutations (2 patients with SD, 1 PD).

Jalal et al evaluated the feasibility of combining pemetrexed and cetuximab in a phase I/IIa study, in patients with recurrent, previously treated NSCLC with ≥1 prior platinum containing regimen.[91] Prior use of EGFR TKIs was permitted. Cetuximab was given at a standard dosing schedule. Pemetrexed, however, was administered at 750 mg/m^2 iv every 3 weeks. After completing at least 4 cycles, patients with non-progressive disease were allowed to continue cetuximab alone until progression. PR was seen in 2 patient (8.7 %), 8 patients (34.8%) had SD. Median TTP was 5.5 mos. This combination resulted in longer time to progression when compared with historical controls of pemetrexed alone administered at a dose of 500 mg/m^2 every 21 days.

In a phase II trial by Kim et al 47 patients with refractory NSCLC or who had disease recurrence within 3 months after chemotherapy and tumor overexpression of EGFR of at least 1+ by IHC received cetuximab with docetaxel (75 mg/m^2 iv every 3 weeks).[92] Thirteen patients (28%) achieved PR and 8 (17%) had SD. Median TTP was 89 days.

Clinical efficacy in combination with radiation therapy

Cetuximab when added to radiation therapy (RT) statistically significantly improved median survival and loco regional control in treatment of locally advanced squamous cell carcinomas of the head and neck.[93] Based on these encouraging results, a phase I study was designed to assess the safety of concomitant cetuximab and radical RT in patients with inoperable Stage III NSCLC.[94] Patients received weekly iv cetuximab (in an initial dose of 400 mg/m^2; maintenance dose 250 mg/m^2) after platinum-based induction therapy and concomitant RT (64 Gy/32fractions/45 days). The results suggested that the early and late toxicities of concomitant cetuximab and radical RT were acceptable.

An ongoing radiation therapy oncology group (RTOG) trial, RTOG 0324, is evaluating the combination of cetuximab with RT in unresectable stage III NSCLC patients.[95] Cetuximab in an initial dose of 400 mg/m^2 iv is

followed by weekly doses of 250 mg/m^2 until completion of therapy. RT was started the week after loading dose (63 Gy/35 fractions) with weekly carboplatin (AUC 2) and paclitaxel (45 mg/m^2 × 6 doses) to be followed by 2 cycles of carboplatin (AUC 6) and paclitaxel (200 mg/m^2). An interim analysis showed improvement in OS compared to historical controls (response rate 62% (n = 54), median survival 22.7 monthss and 2-year OS of 49.3%).

The Cancer and Leukemia Group B (CALGB) is evaluating the combination of carboplatin (AUC 5) iv and pemetrexed (500 mg/m^2) iv every 3 weeks with concurrent RT (70 Gy over 7 weeks) with or without the use of cetuximab followed by 4 cycles of consolidation with pemetrexed.[96] Early evaluation of this CALGB 30407 trial suggests that the combination of thoracic radiation with pemetrexed, carboplatin with or without cetuximab is feasible and is well tolerated.

Safety and tolerability

In phase I and II trials, cetuximab was safe and well tolerated. It has non-overlapping toxicities with most chemotherapy agents, making it an attractive agent to be incorporated into chemotherapy and radiation therapy regimens. In the phase I study dose finding trial, 5 episodes of grade 3 or higher toxicity were seen. Toxicity was not related to dose level or number of cycles administered and most common drug related adverse effects were fevers, chills, asthenia, transaminitis, and skin toxicity.[45]

Acneiform rash is one of the most common toxicities seen with cetuximab use and occurs in approximately 90% of treated patients at different grades.[97] There seems to be a higher response rate in patients in whom cetuximab induces a rash than in cetuximab-treated patients who do not experience a rash. Rash therefore could be a surrogate marker for response.[98] Cetuximab-induced rash is manageable with the use of topical steroids, topical antibiotics, topical emollients, oral antibiotics, and dose modifications.[99–104]

Other toxicities with cetuximab include infusion-related hypersensitivity reactions, which have been associated with the presence of an IgE antibody against glycosylation sites on cetuximab.[105,106] These reactions were more common in patients with prior allergy history and are less commonly seen with panitumumab, which is a fully human IgG2 antibody. Hypomagnesemia is a class effect of EGFR inhibitors and is commonly seen with use of cetuximab.[107,108]

Conclusions

The EGFR receptor is often overexpressed in NSCLCs, making cetuximab an attractive drug. Cetuximab is fairly well tolerated overall and has an acceptable safety and manageable tolerability profile.

In the first-line setting, most phase II studies suggest that adding cetuximab to platinum-based therapies is of clinical benefit. A recently reported phase III trial demonstrated a modest OS benefit when cetuximab was added to cisplatin and vinorelbine in the first-line treatment of NSCLC.[71] In a second phase III trial, addition of cetuximab to carboplatin and a taxane gave only a marginal additional PFS benefit.[89] Despite this improvement, there are still some unanswered questions, mainly in terms of patient selection. Optimal selection of patients who would benefit from cetuximab is challenging and is key in its further development as a therapeutic agent in lung cancer. The role of predictive markers like EGFR amplification by FISH, *KRAS* mutation are being explored and larger prospective studies are needed before they can be routinely used in clinical practice.

Combination studies with other targeted agents, especially vascular endothelial growth factor antagonist, are being explored. Ongoing studies are also evaluating the role of cetuximab in combination with radiation with or without chemotherapy[109] in locally advanced unresectable NSCLC. While final results are pending, interim analyses reveal that cetuximab is feasible and safe to use with radiation in this patient population.

Cetuximab adds to our arsenal of drugs and represents an improvement in survival outcomes in patients with NSCLC. In upcoming years we anticipate more clinical trials combining cetuximab with new targeted treatments which will hopefully improve outcomes while minimizing toxicity.

Disclosures

Dr Borghaei is on the speakers' bureau for Eli Lilly, Amgen, and Genentech.

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