The clinical role of cetuximab in the management of non-small-cell lung cancer

Ezzeldin M Ibrahim^{*1}

Turki M Al-Fayea²

Ghieth A Kazkaz¹

Non-small-cell lung cancer (NSCLC) is the most frequent cause of cancer death worldwide. Despite recent progress, survival of patients with advanced disease has remained disappointing. In recent years, EGFR emerged as a potential target for developing newer agents. Currently, there are two classes of EGFR antagonists in clinical use: antibodies against the extracellular portion of EGFR and inhibitors of the tyrosine kinase intracellular domain of EGFR. Cetuximab is a chimeric monoclonal antibody that inhibits the extracellular domain of EGFR, preventing the ligand from interacting with the receptor and preventing the receptor from undergoing dimerization [1].

Clinical benefit of cetuximab in NSCLC

Using combinations of cetuximab and platinum-based chemotherapy in advanced NSCLC in the first-line setting showed conflicting results [2,3]. In the Phase III FLEX study, chemotherapy-naïve patients with advanced NSCLC expressing EGFR were randomly assigned to chemotherapy (cisplatin–vinorelbine) plus cetuximab

or just chemotherapy [2]. Patients given chemotherapy plus cetuximab survived longer than those in the chemotherapy-alone group (median 11.3 vs 10.1 months; hazard ratio [HR] for death: 0.871 [95% CI: 0.762–0.996]; $p = 0.044$). On the other hand, in another Phase III trial (BMS099), chemotherapy-naïve patients with advanced NSCLC, without restrictions by histology or EGFR expression, were randomly assigned to carboplatin–taxane with or without cetuximab [3]. Median progression-free survival (PFS) was 4.40 months with cetuximab plus chemotherapy versus 4.24 months with chemotherapy only (HR: 0.902; 95% CI: 0.761–1.069; $p = 0.236$). Median overall survival was 9.69 months with cetuximab plus chemotherapy versus 8.38 months with chemotherapy only (HR: 0.890; 95% CI: 0.754–1.051; $p = 0.169$).

Nevertheless, two recently published meta-analyses, including the aforementioned two studies and two additional randomized studies, showed modest survival benefit [4,5]. In the two meta-analyses, it was shown that the addition of

“Using combinations of cetuximab and platinum-based chemotherapy in advanced NSCLC in the first-line setting showed conflicting results.”

¹Oncology Center of Excellence, International Medical Center, PO Box 2172, Jeddah 21451, Saudi Arabia

²Princess Noorah Oncology Center, King Abdulaziz Medical City, PO Box 9515, Jeddah 21423, Saudi Arabia

^{*}Author for correspondence: Tel.: +966 505 82 5953; Fax: +966 52 650 9141; ezzibrahim@imc.med.sa

cetuximab increased objective response rates and achieved approximately 10 and 13% improvement in PFS and overall survival, respectively. To date, no trial has shown a significant benefit of cetuximab in previously treated patients with advanced NSCLC.

The available data comparing cetuximab with other targeted agents in different lines of lung cancer therapy are scarce. A Phase II study compared first-line docetaxel and cetuximab against docetaxel plus the proteasome inhibitor bortezomib in advanced NSCLC. While the PFS was longer in the docetaxel and cetuximab arm, neither combination met the prespecified primary end point [6]. Likewise, data regarding combining cetuximab with other biological agents are limited. In the SWOG0536 study investigating carboplatin–paclitaxel plus cetuximab plus bevacizumab in patients with advanced NSCLC, the benefit was not clinically significant [7].

Molecular biomarkers & EGFR inhibitors

Biomarker analysis in NSCLC is a real challenge. Somatic mutations in the tyrosine kinase domain of EGFR exist in approximately 10% of specimens in the USA and 30–50% in Asia [8]. Activating mutations are limited to exons 18, 19, 21 and 24 and show great structural diversity [1].

In tyrosine kinase inhibitor studies, patients with NSCLC that harbor tumors that tested positive for EGFR by immunohistochemistry showed conflicting results [9–11], whereas the association between somatic mutations in the tyrosine kinase domain of EGFR and favorable outcome has been consistent [12]. It seems, therefore, that there are differences in outcome based on the type of EGFR mutations [8], while the T790M mutation seems to be responsible for approximately 50% of secondary resistance to EGFR inhibitors.

“...the clinical benefit of cetuximab in previously untreated advanced NSCLC is, at best, very modest.”

The predictive role of biomarkers with cetuximab, however, is not conclusive. The results of several retrospective analyses of randomized trials of platinum doublet chemotherapy with or without cetuximab suggested that *KRAS* mutational status, EGFR expression status, *EGFR* gene copy number, *EGFR* mutational status and PTEN expression were not predictive for

cetuximab benefit [13,14]. By contrast, in another study comparing sequential versus concurrent cetuximab in addition to carboplatin and paclitaxel chemotherapy, survival favored FISH-positive patients [15]. However, this result was not conclusive, since patients in both arms of the study received cetuximab. It appears from these results that the benefit from cetuximab in NSCLC is regardless of *EGFR* mutation status. Among clinical parameters, the development of early-onset skin rash appears to be associated with benefit from EGFR-directed therapies [16].

Resistance to EGFR inhibitors

It is well known that most tumors that initially respond to EGFR inhibitors will go on to progress despite continued EGFR inhibition. Cetuximab-resistant cells overexpress EGFR ligands, and overexpression of these ligands is associated with the nuclear translocation of EGFR mediated by the Src family kinase [17]. Other causes of resistance to EGFR inhibitors include MET amplification and loss of the tumor suppressor gene *PTEN* in a second pathway activated by EGFR, the PI3K/AKT/mTOR pathway [18]. It has also been postulated that anti-EGFR antibodies could inhibit EGFR-mediated VEGF production and may contribute to antibody resistance [19].

Cost-effectiveness of cetuximab in the management of advanced NSCLC

In light of the expense of targeted agents and limited resources in many institutions, it is necessary to evaluate the cost of these agents. In a Swiss study, adding cetuximab to cisplatin and vinorelbine in the first-line setting in advanced NSCLC was too costly, with an attained gain of 0.07 quality-adjusted life-years per patient and an incremental cost-effectiveness ratio of €376,205 [20].

We conclude that the clinical benefit of cetuximab in previously untreated advanced NSCLC is, at best, very modest. Increased understanding of the molecular pathology of NSCLC will facilitate the future identification of predictive biomarkers and provide key components for the personalization of therapy, allowing the tailoring of existing and novel treatment agents and regimens to patients who are most likely to benefit and avoiding toxicities for those who would not. By also considering the cost of these new therapies, such an individualized approach may improve the cost-effectiveness of a treatment.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes

employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

- Sharma PS, Sharma R, Tyagi T. Receptor tyrosine kinase inhibitors as potent weapons in war against cancers. *Curr. Pharm. Des.* 15(7), 758–776 (2009).
- Pirker R, Pereira JR, Szczesna A *et al.* Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised Phase III trial. *Lancet* 373(9674), 1525–1531 (2009).
- Lynch TJ, Patel T, Dreisbach L *et al.* Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter Phase III trial BMS099. *J. Clin. Oncol.* 28(6), 911–917 (2010).
- Ibrahim EM, Abouelkhair KM, Al-Masri OA, Chaudry NC, Kazkaz GA. Cetuximab-based therapy is effective in chemotherapy-naïve patients with advanced and metastatic non-small-cell lung cancer: a meta-analysis of randomized controlled trials. *Lung* 189(3), 193–198 (2011).
- Lin H, Jiang J, Liang X, Zhou X, Huang R. Chemotherapy with cetuximab or chemotherapy alone for untreated advanced non-small-cell lung cancer: a systematic review and meta-analysis. *Lung Cancer* 70(1), 57–62 (2010).
- Lilenbaum R, Wang X, Gu L, Kirshner J, Lerro K, Vokes E. Randomized Phase II trial of docetaxel plus cetuximab or docetaxel plus bortezomib in patients with advanced non-small-cell lung cancer and a performance status of 2: CALGB 30402. *J. Clin. Oncol.* 27(27), 4487–4491 (2009).
- Gandara D, Kim ES, Herbst RS *et al.* S0536: carboplatin, paclitaxel, cetuximab, and bevacizumab followed by cetuximab and bevacizumab maintenance in advanced non-small cell lung cancer (NSCLC): a SWOG Phase II study. *ASCO Meeting Abstracts* 27(15 Suppl.), 8015 (2009).
- Peled N, Yoshida K, Wynes MW, Hirsch FR. Predictive and prognostic markers for epidermal growth factor receptor inhibitor therapy in non-small cell lung cancer. *Ther. Adv. Med. Oncol.* 1(3), 137–144 (2009).
- Cappuzzo F, Finocchiaro G, Rossi E *et al.* EGFR FISH assay predicts for response to cetuximab in chemotherapy refractory colorectal cancer patients. *Ann. Oncol.* 19(4), 717–723 (2008).
- Tsao MS, Sakurada A, Cutz JC *et al.* Erlotinib in lung cancer – molecular and clinical predictors of outcome. *N. Engl. J. Med.* 353(2), 133–144 (2005).
- Hirsch FR, Varella-Garcia M, Bunn PA Jr *et al.* Molecular predictors of outcome with gefitinib in a Phase III placebo-controlled study in advanced non-small-cell lung cancer. *J. Clin. Oncol.* 24(31), 5034–5042 (2006).
- Rossi A, Galetta D, Gridelli C. Biological prognostic and predictive factors in lung cancer. *Oncology* 77(Suppl. 1), 90–96 (2009).
- O'Byrne KJ, Gatzemeier U, Bondarenko I *et al.* Molecular biomarkers in non-small-cell lung cancer: a retrospective analysis of data from the Phase 3 FLEX study. *Lancet Oncol.* 12(8), 795–805 (2011).
- Khambata-Ford S, Harbison CT, Hart LL *et al.* Analysis of potential predictive markers of cetuximab benefit in BMS099, a Phase III study of cetuximab and first-line taxane/carboplatin in advanced non-small-cell lung cancer. *J. Clin. Oncol.* 28(6), 918–927 (2010).
- Hirsch FR, Herbst RS, Olsen C *et al.* Increased *EGFR* gene copy number detected by fluorescent *in situ* hybridization predicts outcome in non-small-cell lung cancer patients treated with cetuximab and chemotherapy. *J. Clin. Oncol.* 26(20), 3351–3357 (2008).
- O'Byrne KJ, Von Pawel J, Vynnychenko I *et al.* First-cycle rash as a clinical marker in patients with advanced non-small cell lung cancer (NSCLC) receiving first-line chemotherapy (CT) plus cetuximab: efficacy by histology. *ASCO Meeting Abstracts* 28(15 Suppl.), 7556 (2010).
- Li C, Iida M, Dunn EF, Ghia AJ, Wheeler DL. Nuclear EGFR contributes to acquired resistance to cetuximab. *Oncogene* 28(43), 3801–3813 (2009).
- Tufman A, Huber RM. Biological markers in lung cancer: a clinician's perspective. *Cancer Biomark.* 6(3–4), 123–135 (2010).
- Viloria-Petit A, Crombet T, Jothy S *et al.* Acquired resistance to the antitumor effect of epidermal growth factor receptor-blocking antibodies *in vivo*: a role for altered tumor angiogenesis. *Cancer Res.* 61(13), 5090–5101 (2001).
- Joerger M, Matter-Walstra K, Fruh M *et al.* Addition of cetuximab to first-line chemotherapy in patients with advanced non-small-cell lung cancer: a cost–utility analysis. *Ann. Oncol.* 22(3), 567–574 (2011).