Epidermal growth factor receptor (EGFR) inhibitors and derived treatments

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Epidermal growth factor receptor inhibitors are used to treat advanced lung cancer patients for almost a decade. Current knowledge on their role in the first or subsequent lines of therapy serves as a model for other targeted therapies in development. Several molecular predictors of outcomes were successfully identified in preclinical and clinical studies. Evaluation of EGFR-activating mutations is currently used to define biologically distinct patient subsets with important consequences for prognosis and therapy. Ongoing translational and clinical research exploring EGFR inhibition in lung cancer focuses on better understanding of biology of EGFR-driven disease, efficacy of novel irreversible EGFR inhibitors and monoclonal antibodies, efficacy of combination strategies, and attempts to move EGFR inhibitors into therapy portfolio for early-stage disease.

Key words: afatinib, cetuximab, dacomitinib, erlotinib, gefitinib, neratinib

introduction

Understanding the importance of EGFR signaling pathway in cancer has led to the development of several anti-EGFR therapeutics in the late 1990s, including reversible first-generation tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib, as well as monoclonal antibodies such as cetuximab and panitumumab. These agents were subsequently tested in several tumor types in phase I–III clinical trials in pretreated patient populations. Results of the trials performed in non-small-cell lung cancer (NSCLC) indicated intriguingly high activity of TKIs given as monotherapy in a proportion of NSCLC patients and lack of their efficacy in combination with cytotoxic therapies. Contrary to the above, monoclonal antibodies appeared to enhance the efficacy of chemotherapy and had very modest single-agent activity. The associations of benefit from EGFR TKIs and molecular tumor characteristics became apparent after discovery of somatic activating EGFR gene mutations [1, 2]. These mutations occur in approximately 10%–20% of Western NSCLC patient populations, typically in those diagnosed with adenocarcinoma and with never/light smoking history, and indicate less aggressive course of the disease. Subset analyses of two important phase III trials evaluating the efficacy of single-agent gefitinib or erlotinib versus best supportive care in second- or third-line treatment of advanced NSCLC indicated the benefit for patients with tumors showing high EGFR gene copy number determined by in situ hybridization techniques (approximately 20%–40% of advanced NSCLC) [3, 4]. Based on the positive results of BR.21 trial, erlotinib was the first EGFR TKI registered in Europe for the treatment of advanced NSCLC patients whose treatment failed at least one line of chemotherapy irrespective of histology [5]. Gefitinib was registered in several Asian countries based on phase II and III data indicating its particularly high activity in the Far-East patient populations.

Next generation of clinical trials compared EGFR TKIs with chemotherapy in the second-line setting in unselected NSCLC patients [6] or in the first-line setting in molecularly defined subsets [7–10]. Phase III data indicated that in chemonaïve patients with tumors harboring EGFR mutations, the response rate to EGFR TKIs is in the range of 60%–70% and progression-free survival is in the range of 9–13 months, both figures substantially superior to those achieved with chemotherapy [7–11]. Important improvements in the quality of life were also observed. Patients with tumors showing wild-type EGFR derive greater benefit from chemotherapy than from EGFR TKIs in the front-line setting [11]. At the same time, it was noted that EGFR gene copy gain was no longer a reliable predictor for the differential benefit from EGFR TKI versus chemotherapy [11, 12], suggesting that this molecular feature may be of importance only in heavily pretreated patients in clinical trials using placebo in a comparator arm. Based on the above data, both gefitinib and erlotinib are now registered in Europe for front-line treatment of advanced NSCLC patients with tumors harboring EGFR-activating mutations. The reversible EGFR inhibitors erlotinib [13] and gefitinib [14] have also been investigated as a ‘switch maintenance’ after first-line chemotherapy. SATURN trial with erlotinib demonstrated statistically significant but clinically modest survival improvement in all patients. The benefit from erlotinib was particularly pronounced in patients with tumors having EGFR-activating mutations [15].

Results from a clinical trial testing the addition of cetuximab to cisplatin—vinorelbine in patients with EGFR
immunohistochemistry-positive tumors (First-line Erbitux Trial, FLEX)—indicated a modest survival benefit in favor of the experimental arm (difference in median survival of 1.2 months, corresponding to a hazard ratio [HR] of 0.87; P = 0.044) [16]. In an extensive biomarker study program based on immunohistochemical and genomic analyses of tumor tissue samples [17, 18], highly positive EGFR immunostaining (hybrid score ≥200 on a scale 0–300) was associated with a 2.4-month survival improvement [HR = 0.73], whereas there was no survival benefit for patients with low EGFR immunostaining [HR = 0.99; interaction test P = 0.044]. Another phase III trial with paclitaxel (Taxol, Bristol-Myers Squibb) and carboplatin with or without cetuximab (BMS099), performed in unselected advanced NSCLC patients, did not show the survival advantage in overall or biomarker-defined study groups [19].

Building on more than a decade of experience in basic, translational and clinical experience with EGFR inhibitors in lung cancer, how should we move forward with this important therapeutic strategy? The progress, briefly discussed in this review, includes better understanding of biology of EGFR-driven tumors, novel irreversible EGFR TKIs, novel anti-EGFR monoclonal antibodies and research strategies testing EGFR inhibitors in early-stage NSCLC.

understanding the biology of EGFR-driven tumors

Tumors harboring EGFR-activating mutations constitute a unique subset of biologically distinct diseases, in which EGFR activation is a driving molecular event, fulfilling ‘oncogene addiction’ criteria. Other EGFR abnormalities (gene copy gain, high EGFR protein expression) constitute mechanisms of tumor progression, and are probably insufficient to indicate long-term benefit from the target inhibition. High-level EGFR gene amplification, occurring in wild-type tumors, may be an exception to this rule, although it is extremely rare. In patients with EGFR-mutated tumors showing acquired resistance to EGFR TKIs, mechanisms of progression are partially understood and include exon 20 T790M mutations (arising through a clonal selection during continuous exposure to EGFR TKIs), MET amplification (gene coding a receptor for hepatocyte growth factor), emergence of other mutations such as those located in PIK3CA and histological transformation to small-cell lung cancer through unknown molecular mechanisms [20]. Multiple mechanisms of resistance were described in the same patient. It was also observed that resistance events may occasionally be reversed after subsequent cytotoxic treatment, providing rationale for repeated testing and re-challenge with EGFR inhibitors in selected cases [20].

irreversible EGFR inhibitors

Several novel, irreversible pan-HER TKIs were developed with hopes to overcome some of the above-mentioned resistance mechanisms, particularly the most common T790M mutations. Three most extensively studied compounds in advanced NSCLC, both in patients with mutated and wild-type EGFR, include neratinib (HKI-272), afatinib (BIBW2992) and dacomitinib (PF00299804). These agents share a 4-anilinoquinazoline structure with the ability to form covalent bonds with Cys979 residue located directly at the ATP-binding cleft of EGFR protein, and thus potentially preventing T790M mutation-related resistance. While neratinib phase II data were disappointing [21], other two agents are currently evaluated in a number of phase II and III trials with hopes for a better efficacy in patients with EGFR mutation positive or negative tumors [22]. Interestingly, the neratinib phase II trial showed high activity of the drug in a rare subset of patients with tumors having exon 18 G719X mutations, which could be predicted based on low inhibiting concentrations of the drug in the cells harboring this aberration [21]. Some (but not all) clinical data with reversible EGFR inhibitors (erlotinib and gefitinib) indicate their better efficacy in patients with tumors harboring common exon 19 deletions when compared with exon 21 point mutations (L858R) [23, 24]. This association should be closely investigated in clinical trials with novel irreversible EGFR TKIs, expected to be more potent against L858R mutations than reversible agents. Contrary to structural and in vitro models, there are reports on limited activity of irreversible inhibitors in association with acquired resistance through EGFR T790M mutations [25, 26]. This may be due to relatively low achievable steady-state drug concentrations, insufficient for effective EGFR T790M inhibition, particularly when T790M allele is selectively amplified [27]. Development of mutant-selective EGFR inhibitors, currently at the preclinical stage, appears to be a promising strategy to improve therapeutic ratio with these agents [28].

EGFR inhibitors have also been combined with other targeted therapies directed at the same pathway. Phase Ib/II data of afatinib combined with cetuximab in patients with acquired resistance to reversible EGFR inhibitors showed promising 36% response rate with an acceptable toxicity profile [29]. Preclinical models demonstrate encouraging activity of combined EGFR and mTOR inhibition [30], a strategy that is currently explored in phase I trials. Based on promising phase II data, erlotinib is being evaluated with anti-MET agents (tivantinib and METMab) in two large phase III studies, results of which should be available in the near future. The combination of MET inhibitors with irreversible EGFR inhibitors has not reached the clinical phase.

Taken together, the role of irreversible EGFR inhibitors in clinical practice is yet undefined and should be better understood after the reports from key clinical trials are available (some are expected in 2012). Ongoing clinical trials should mandate tissue collection at the time of initial biopsy and strongly encourage tissue and circulating tumor cell acquisition at the study entry.

anti-EGFR monoclonal antibodies

The role of anti-EGFR monoclonal antibodies in addition to front-line chemotherapy remains unproven. Although the survival benefit from cetuximab in patients with tumors showing high EGFR protein expression was impressive in the FLEX trial, the difference was found in a post-hoc analysis with exploratory cut-off point that needs a prospective validation. A
novel fully human IgG1 anti-EGFR monoclonal antibody, necitumumab, is evaluated in two large phase III randomized trials: INSPIRE—in combination with cisplatin/pemetrexed for non-squamous histologies—stopped prematurely due to safety concerns, and SQUIRE—in combination with cisplatin–gemcitabine for squamous histologies—closed to patient accrual. EGFR protein expression will hopefully be analyzed in tumor samples from participants of these trials and should provide additional information on this promising strategy.

**use of EGFR inhibitors in early-stage NSCLC**

Despite high activity of EGFR TKIs in advanced NSCLC with EGFR mutations, the strategy of moving these drugs to early-stage disease has been unsuccessful so far. Two randomized clinical trials with adjuvant gefitinib in unselected patients, National Cancer Institute of Canada BR.19 trial and a Japanese trial, were closed prematurely due to lack of efficacy of gefitinib in the phase III ISEL study and toxicity concerns (interstitial lung disease), respectively. Data from BR.19 trial were subsequently analyzed according to the EGFR mutation status in primary tumor and showed trends toward inferior survival in overall and mutation-positive study populations [31]. Maintenance gefitinib after definitive radiochemotherapy and docetaxel consolidation was significantly detrimental in a phase III SWOG S0023 trial (unselected patients) [32]. The results of RADIANT, an adjuvant erlotinib phase III trial in patients with tumors positive for EGFR protein or with high EGFR gene copy number, should be available in the near future.

Concurrent administration of EGFR TKIs or cetuximab with definitive radiotherapy has been assessed in locally advanced unresectable NSCLC. Data from head and neck cancer and from *in vivo* models indicate a possible synergistic activity, particularly for the latter combination. Two phase II trials conducted in the United States (RTOG 0324, weekly cetuximab, carboplatin and paclitaxel concurrent with radiotherapy followed by two cycles of chemotherapy consolidation with cetuximab [33] and CALGB 30407, carboplatin plus pemetrexed with or without cetuximab concurrent with radiotherapy followed by single-agent pemetrexed [34]) showed acceptable toxicity profiles and survival compatible with that seen in modern chemoradiotherapy series. RTOG 0617 phase III trial compared two doses of radiotherapy (74Gy versus 60Gy) in combination with carboplatin and paclitaxel with or without cetuximab followed by two cycles of chemotherapy consolidation with or without cetuximab (factorial design). The study was closed to patient accrual, with early termination of the high-dose radiotherapy arms due to futility analysis. Mature results with regard to cetuximab comparison should define the role of this agent in unresectable NSCLC.

Currently, the management of patients with locally advanced lung adenocarcinoma harboring activating EGFR mutations remains the same as that for patients with wild-type tumors. Although *in vitro* data support higher sensitivity of EGFR mutant cells through defective DNA damage repair after radiation [35], clinical reports supporting this observation are scarce [36]. The addition of EGFR TKI either as an induction treatment and/or concurrently with radiochemotherapy needs to be explored in the future studies. A possible cell cycle antagonistic mechanism of G1 arrest caused by EGFR TKI needs to be taken into account if concurrent treatment is planned.

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**references**


