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Anti-Tumour Treatment

Oral epidermal growth factor receptor tyrosine kinase inhibitors for the treatment of non-small cell lung cancer: Comparative pharmacokinetics and drug–drug interactions

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ABSTRACT

The development of orally active small molecule inhibitors of the epidermal growth factor receptor (EGFR) has led to new treatment options for non-small cell lung cancer (NSCLC). Patients with activating mutations of the *EGFR gene* show sensitivity to, and clinical benefit from, treatment with EGFR tyrosine kinase inhibitors (EGFR-TKIs). First generation reversible ATP-competitive EGFR-TKIs, gefitinib and erlotinib, are effective as first, second-line or maintenance therapy. Despite initial benefit, most patients develop resistance within a year, 50–60% of cases being related to the appearance of a T790M gatekeeper mutation. Newer, irreversible EGFR-TKIs – afatinib and dacomitinib – covalently bind to and inhibit multiple receptors in the ErbB family (EGFR, HER2 and HER4). These agents have been mainly evaluated for first-line treatment but also in the setting of acquired resistance to first-generation EGFR-TKIs. Afatinib is the first ErbB family blocker approved for patients with NSCLC with activating EGFR mutations; dacomitinib is in late stage clinical development. Mutant-selective EGFR inhibitors (AZD9291, CO-1686, HM61713) that specifically target the T790M resistance mutation are in early development. The EGFR-TKIs differ in their spectrum of target kinases, reversibility of binding to EGFR receptor, pharmacokinetics and potential for drug–drug interactions, as discussed in this review. For the clinician, these differences are relevant in the setting of polymedicated patients with NSCLC, as well as from the perspective of innovative anticancer drug combination strategies.

Introduction

Identification of different driver mutations that define new molecular subsets of non-small cell lung cancer (NSCLC) has been critical in defining novel targeted therapeutic approaches [1]. One of the most well-known examples is epidermal growth factor receptor (EGFR), a cell-surface receptor that is activated in more than half of NSCLC patients [2]. The EGFR receptor belongs to the ErbB family of transmembrane tyrosine kinase receptors, which includes EGFR (also known as ErbB1 or HER1), ErbB2 (HER2 or neu), ErbB3 (HER3) and ErbB4 (HER4) [3]. With the exception of HER3, all have tyrosine kinase activity. The EGFR/ErbB family tyrosine kinase receptors play an integral role in cell proliferation, differentiation and apoptosis, and therefore represent a valid target for preventing tumour growth and metastasis.

The development of small-molecule tyrosine kinase inhibitors (TKIs) that target EGFR has revolutionised the management of NSCLC. The so-called "first generation" EGFR-TKIs, erlotinib and gefitinib, compete reversibly with adenosine triphosphate (ATP) for binding to the intracellular catalytic domain of EGFR tyrosine kinase and thus inhibit EGFR autophosphorylation and downstream signalling [4]. Erlotinib and gefitinib are especially effective in tumours with activating *EGFR* mutations, evident in 10–15% of Caucasians and 40% of Asians with NSCLC [5]. In 90% of cases, these mutations are exon 19 deletions or exon 21 L858R substitutions [5].

Reversible EGFR-TKIs

Clinical trials have demonstrated that treatment with gefitinib or erlotinib significantly improves progression-free survival (PFS) and quality-of-life compared with chemotherapy as first-line

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therapy in advanced *EGFR* mutation-positive NSCLC [6–10]. Gefitinib was approved in the US for third-line treatment of advanced NSCLC in 2003; however, its marketing application for use in new patients was withdrawn in 2005, after failure to show a benefit on overall survival (OS) in the Iressa Survival Evaluation in Lung Cancer (ISEL) trial [11]. In Europe, gefitinib was approved in 2009 for all lines of treatment in patients with advanced NSCLC with *EGFR* mutations. Erlotinib was approved in 2004 (USA) and 2005 (Europe) for second- and third-line treatment of chemotherapy-resistant, advanced NSCLC. In 2010 its use was expanded to include maintenance therapy after platinum-based chemotherapy, followed by approval in 2012 (Europe) and 2013 (USA) for use as first-line treatment of NSCLC with EGFR activating mutations (exon 19 deletions or exon 21 L858R substitution) [12,13].

As erlotinib and gefitinib bind reversibly to the tyrosine kinase domain of EGFR, they are susceptible to mutations that affect the binding affinity of ATP or the kinase inhibitor itself. Thus, despite excellent tumour response to initial targeted therapy, *EGFR* mutation-positive patients eventually develop resistance to erlotinib or gefitinib after 9–12 months of treatment [6–10]. One important mechanism of acquired resistance is the T790M gatekeeper *EGFR* mutation in exon 20, which is found in about 50–60% of patients [14,15]. This mutation increases the affinity of the kinase for ATP, and thus reduces the inhibitor efficacy [15–17]. In addition, c-*MET* amplification, *HER2* amplification, small cell transformation, and *PIK3CA* mutations have been associated with the development of EGFR-TKI resistance [14,15]. Consequently, an unmet need exists for the development of novel targeted agents that are effective in this setting.

Irreversible ErbB family blockers

Agents that bind irreversibly to the EGFR receptor, and also target multiple ErbB-family members, including HER2 which plays a key role in ErbB activation, also described as "second-generation EGFR-TKIs", may overcome the acquired resistance observed with erlotinib and gefitinib [18]. Irreversible EGFR-TKIs, including afatinib, dacomitinib and neratinib, have demonstrated a higher affinity for the ATP-binding domain and form an irreversible covalent bond to the ATP-binding site, they also inhibit HER2, and some also inhibit HER4 (see below).

Afatinib is the first irreversible ErbB family blocker approved for first-line treatment of metastatic NSCLC with EGFR mutations [19,20]. The LUX-Lung clinical trial programme investigated afatinib in the settings of second- or third-line treatment of patients with acquired resistance to gefitinib or erlotinib (LUX-Lung 1, 4 and 5) [21–23] as well as first-line treatment in patients with EGFR-activating mutations (LUX-Lung 2, 3 and 6) [24–26]. The phase IIb/III LUX-Lung 1 showed that treatment with afatinib prolonged PFS – but not OS – in patients refractory to both chemotherapy and either erlotinib or gefitinib [21]. The phase III LUX-Lung 3 and 6 trials showed that PFS was significantly prolonged with afatinib versus pemetrexed plus cisplatin (LUX-Lung 3) or gemcitabine plus cisplatin (LUX-Lung 6) in treatment naïve patients with advanced lung adenocarcinoma and activating *EGFR* mutations and improved tumour-related symptoms and global health status [25,26]. LUX-Lung 3 [25] provided the basis for approval of afatinib in the US, Taiwan and Europe in 2013, in the setting of first-line treatment of metastatic NSCLC with *EGFR*-activating mutations [19,20]. Preliminary results of a pooled analysis of these two trials show a significant improvement in OS (27.3 to 24.3 months; HR = 0.81, $p = 0.037$) with afatinib in patients with common *EGFR* mutations (Del19/L858R) compared with standard chemotherapy [27]. This was even more pronounced in patients whose tumours harbour a deletion in exon 19 (33.3 versus 21.1 months in LUX-Lung 3 [HR 0.54]; and 31.4 versus 18.4 months in LUX-Lung 6 [HR 0.64]). In addition, phase II trials have demonstrated benefit with another irreversible EGFR-TKI, dacomitinib (PF-00299804), in a number of settings including after failure of one or two chemotherapy regimens and failure on erlotinib [28,29] first-line treatment of patients with *EGFR*-mutant tumours or known T790M mutations [30] as well patients refractory to chemotherapy and TKIs [31]. Preliminary results for phase III trials comparing dacomitinib with erlotinib (ARCHER 1009) in advanced NSCLC previously treated with chemotherapy (second/third line); or with placebo after failure of TKI and chemotherapy (BR.26) were recently reported [32,33]. The ARCHER 1009 trial did not meet its objective of significant improvement in PFS versus erlotinib; the BR.26 trial also failed to show significant prolongation of OS versus placebo. A further phase III trial versus gefitinib in treatment-naïve patients with *EGFR*-mutation mutated tumours (ARCHER 1050, NCT01774721) is ongoing with results expected in 2015. Additionally, neratinib has been tested in patients with NSCLC and prior response to first-generation EGFR-TKIs and in TKI-naïve patients [34] but due to low response rates and dose-limiting diarrhoea, monotherapy treatment evaluation was discontinued. Benefit with the combination of neratinib and temsirolimus, an mTOR inhibitor, has been seen in patients with solid tumours [35]. Consequently, neratinib is now being evaluated in combination with weekly temsirolimus in patients with HER2-mutant NSCLC [36]. In view of the lack of benefit and future clinical development with neratinib monotherapy, further discussion about this drug is not included in this review.

Mutant-selective EGFR-TKIs

Newer, so called "third-generation" EGFR-TKIs targeting activating EGFR mutations and T790M but sparing wild-type EGFR are also in development as first-line or following resistance to treatment.

Three such compounds, AZD9291, CO-1686 and HM61713, are oral, irreversible, selective inhibitors of both *EGFR*-activating and resistance (T790M) mutations, while sparing wild-type EGFR [37–40]. Ongoing phase I dose-escalation trials show significant tumour shrinkage (by RECIST criteria) in patients with *EGFR*-mutant NSCLC tumours (mainly harbouring T790M) and acquired resistance to prior EGFR-TKI treatment [41–43]. Sparing of wild-type EGFR present in normal skin and gut cells is thought to be associated with an improved therapeutic index. An extensive phase II/III development program with CO-1686 (TIGER I–V trials) as second-line therapy for NSCLC patients with acquired resistance to EGFR-directed therapy due to T790M mutations and as a first-line treatment for *EGFR*-mutated tumours is planned from 2014. Further development of AZD9291 and HM61713 is yet to be officially announced.

In contrast to platinum-based systemic chemotherapy, oral EGFR-TKIs offer potential for extended first-line therapy, given evidence of good tolerability, and increased duration of PFS. Relevant to considerations for their clinical use, are the pharmacokinetic characteristics and potential for drug–drug interactions with the first and second-generation EGFR-TKIs, which is the focus of this review.

Profile of receptor activity

All of the EGFR-TKIs show a similar high affinity for the EGFR receptor (see Supplementary Table 1); [44–47] afatinib and dacomitinib also show high affinity for HER2 and HER4 receptors. Afatinib also inhibits transphosphorylation of HER3, thereby blocking signalling of all ErbB family members [45]. Compared with gefitinib and erlotinib, afatinib has shown superior *in vitro* activity in