Targeting HER1/EGFR in cancer therapy: experience with erlotinib

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Research into the role of the human epidermal receptor growth factor receptor 1/epidermal growth factor receptor (HER1/EGFR) in tumorigenesis has generated a new class of anticancer drugs. One such agent, erlotinib (Tarceva℠), is a potent, selective and reversible inhibitor of HER1/EGFR tyrosine kinase activity. Erlotinib has demonstrated the clinical activity in a variety of solid tumors, and has recently demonstrated improvements in survival in large Phase III trials, in non-small-cell lung cancer and pancreatic cancer.

Keywords: chemotherapy, erlotinib, human epidermal growth factor receptor/epidermal growth factor receptor (HER1/EGFR), lung cancer, non-small-cell lung carcinoma

In the year 2000, of the 6.2 million cancer-related deaths worldwide, the majority (1.2 million) were due to lung cancer [1]. Non-small-cell lung cancer (NSCLC) accounts for 75–80% of new lung cancer cases, most patients presenting with advanced disease (Stage IIIb or IV) [2]. The prognosis for such patients is poor, with 5-year survival rates of less than 10% [3]. Compared with monotherapy, combination chemotherapy is more effective in terms of tumor response, but leads to increased toxicity [4]. For first-line treatment of patients with unresectable advanced (Stage IIIb/IV) NSCLC, platinum-based doublets are the standard treatment [5,6]. The introduction of third generation cytotoxic agents (such as paclitaxel, docetaxel, gemcitabine, vinorelbine and irinotecan) achieved improvements in tumor response and tolerability [7,8], but only modest improvements in survival, and it may be that chemotherapy has reached its potential. Median survival remains around 8–10 months, irrespective of the chemotherapy doublet used [9–12], and adding a third cytotoxic drug has been demonstrated to be of little or no benefit [13]. Cytotoxic chemotherapy is nonspecific, nonselective and toxic, with common side effects including anemia, neutropenia and thrombocytopenia. The quality of life (QoL) of patients with lung cancer is often severely impaired by symptoms including shortness of breathe, cough and pain, loss of appetite, severe weakness, and fatigue and hemoptysis [14], and the toxic side effects of chemotherapy can also have a negative impact on QoL, especially in poor performance patients. Thus, new nontoxic therapies that prolong progression-free disease and overall survival, and improve QoL, are urgently needed.

Another tumor with a high mortality is carcinoma of the pancreas, which currently accounts for approximately 3% of cancer deaths worldwide, and is the fourth most common cause of death due to cancer in women in western Europe, and the fifth most common in men [15]. Cancer of the exocrine pancreas is rarely curable, and there has been no improvement in prognosis in the last 30 years. Most patients present with advanced, unresectable or metastatic disease, and the 5-year survival rate is still only 4% overall [15]. In the mid-1990s, gemcitabine replaced 5-fluorouracil (5-FU) as the standard first-line therapy for patients with metastatic pancreatic cancer [16]. The median survival of patients with advanced pancreatic cancer who are treated with gemcitabine, is approximately 6 months. Only approximately a fifth of patients will be alive after 1 year [16], so the need for improved therapeutic strategies is clear.

Molecular-targeted therapies

Identifying the DNA and protein abnormalities that lead to dysregulation of key cellular processes (e.g., control of the cell cycle, intracellular signaling, angiogenesis and programed cell death), and that underlie the growth and metastatic spread of tumor cells, has allowed the development of a new generation of molecular-targeted anticancer agents [2]. In contrast, to traditional chemotherapies, which have nonselective cytotoxic effects, the new agents offer the prospects of greater selectivity, more effective tumor control and reduced side effects [8]. Several agents have been developed, which targets various aspects of tumor cell biology. These include angiogenesis inhibitors, modulators of apoptosis, cyclooxygenase and lipoxygenase inhibitors and adenoviral therapies, and agents that act on intracellular signaling pathways [2]. The introduction of such agents into clinical practice represents an important paradigm shift in the approach to the treatment of cancer. One strategy at an advanced stage of clinical development is that of targeting the human epidermal growth factor

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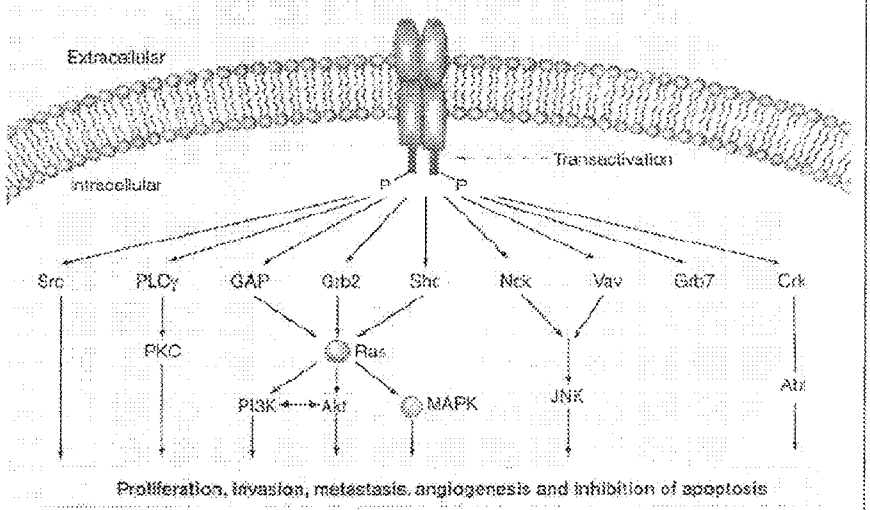
receptor 1/epidermal growth factor receptor (HER1/EGFR) [17], a cell membrane receptor that plays an important role in tumorigenesis [18].

HER1/EGFR: a target for cancer therapies

The human epidermal receptor (HER) family is a group of four transmembrane growth factor receptors (HER1–4), each with the same basic structure, consisting of three distinct domains (extracellular, transmembrane and intracellular). The intracellular domain of HER1, -2 and -4 has tyrosine kinase (TK) activity. HER1/EGFR is found on most normal cells, and is the receptor for several endogenous ligands, including epidermal growth factor [19]. Ligand binding induces the formation of a receptor dimer (a complex of two receptors), involving a structural change that promotes autophosphorylation (and activation) of the intracellular TK. The activated TK phosphorylates an intracellular protein, thus triggering a series of downstream changes in the activity of an intracellular signaling pathway [20,21]. Several such pathways regulated by HER1/EGFR are involved in control of cell proliferation, differentiation, migration, adhesion and invasion, regulation of cell death (apoptosis) and survival, and in regulating angiogenesis (Figure 1) [18]. HER1/EGFR activation, therefore, influences a variety of cellular functions that are essential for the regulation of normal cell growth. In normal adult cells, expression of HER1/EGFR is tightly controlled, and activation of the receptor stimulates cell proliferation [22,23] and inhibits apoptosis [24].

Overexpression or dysregulation of HER1/EGFR or its primary ligands (Figure 2), is characteristic of many solid human tumors, including lung, colorectal, ovarian, brain and head and neck cancers [25]. HER1/EGFR expression increases with disease stage or following onset of resistance to chemotherapy [17,25]. Many studies have demonstrated a relationship between HER1/EGFR dysregulation and poor clinical

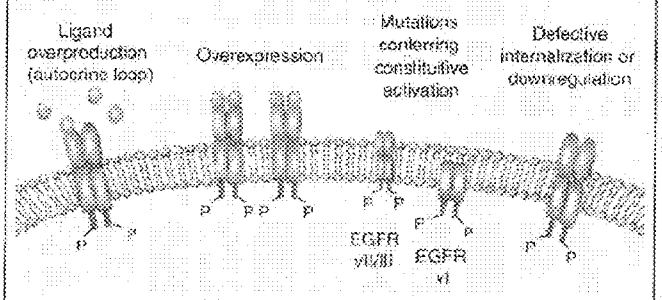
Figure 1. Effects of HER1/EGFR activation on downstream intracellular pathways.



Modulation of several of the molecules involved in activation of HER1/EGFR determine profound changes in the cell and tissue characteristics, with more proliferation, less apoptosis and more propensity for the tumor to invade, metastasize to other organs and form new vasculature.

Abl: Abelson murine leukemia; Akt: Protein kinase B; Crk: c-Abl tyrosine kinase; EGFR: Epidermal growth factor receptor; GAP: Growth associated protein; Grb: Growth factor receptor-bound protein; HER: Human epidermal growth factor receptor; JNK: c-Jun N-terminal kinase; MAPK: Mitogen-activated protein kinase; Nck: SH2/SH3 adaptor protein; P: Phosphate; PI3K: Phosphatidylinositol-3-kinase; PKC: Protein kinase C; PLC: Phospholipase C; Shc: Src-homology collagen; Src: Rous sarcoma virus; Vav: A family of proteins that among others act as guanosine exchange factors for Rac/Rho.

Figure 2. Examples of HER1/EGFR dysregulation in tumors.

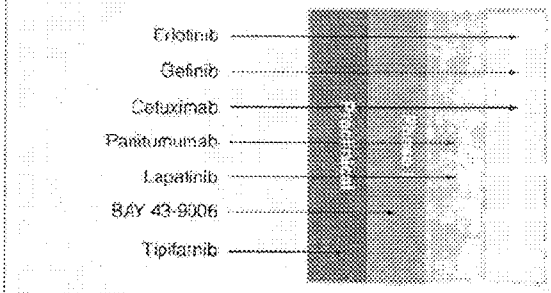


Several alterations have been described that dysregulate HER1/EGFR; among these are an overproduction of ligands that maintain the receptor constantly active, overexpression of the receptor, constitutive mutations in the receptor and defects in the processing of the receptor.
EGFR: Epidermal growth factor receptor; HER: Human epidermal growth factor receptor; P: Phosphate.

outcome, including poor response to treatment and short overall survival, although there are conflicting reports [26,27].

The specificity of action of HER1/EGFR-targeted agents has the potential for improved efficacy, tolerability and safety profiles compared with chemotherapy [28]. There are two main approaches, using monoclonal antibodies to target the extracellular domain, or small-molecule inhibitors of intracellular TK [4,5]. Several agents are at different stages of development (Figure 3), but erlotinib (Tarceva®) is one of the most extensively studied drugs, which has recently demonstrated improvements in survival in Phase III trials in both NSCLC [29] and pancreatic cancer [30]. The development of erlotinib in NSCLC and other cancer types shall be reviewed herein.

Figure 3. Development of HER1/EGFR-targeted agents in NSCLC.



Several molecules have already reached Phase II studies.
EGFR: Epidermal growth factor receptor; HER: Human epidermal growth factor receptor; NSCLC: Non-small cell lung carcinoma.

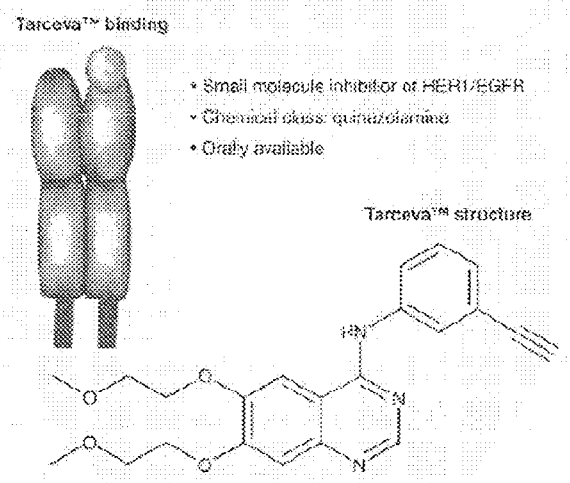
Preclinical development of erlotinib

Erlotinib is a small molecule of the quinazolinamine class (Figure 4). It is a potent, selective and reversible inhibitor of HER1/EGFR TK activity. The 50% inhibitory concentration (IC_{50}) of erlotinib for inhibition of HER1/EGFR TK activity *in vitro* is 2 nM, compared with 350, 600 and greater than 1000 nM for HER2, vascular endothelial growth factor receptor, and most other receptor TKs, respectively [31]. Erlotinib binds to the ATP-binding site in the intracellular domain of the HER1/EGFR, thereby blocking the binding of ATP, and preventing the activation of TK. This leads to changes in the activity of the intracellular pathways modulated by HER1/EGFR, resulting in cell-cycle arrest, inhibition of cell proliferation and an increase in apoptosis.

In *in vitro* studies, erlotinib has been demonstrated to be effective against several different types of tumor cells [31]. Erlotinib was found to inhibit cell-cycle progression and proliferation, and to initiate apoptosis at submicromolar concentrations, both in DiFi human colon tumor cells and HN5 head and neck tumor cells [32]. These effects appear to be due to the cell-cycle arrest in the G_1 phase [31]. In HC2 mice fibroblast cells, erlotinib was shown to inhibit both TK activity (IC_{50}: 1 μM) and cell proliferation (IC_{50}: 3–5 μM) [33]. Erlotinib has also been found to reduce the activity of the downstream components of intracellular signaling pathways, including mitogen-activated protein kinase [33]. Concentrations of erlotinib that reduced HER1/EGFR activity by 90% inhibited the activity of the downstream components by approximately 33% [33]. This indicates that almost complete inhibition of HER1/EGFR activity is required to achieve control of intracellular signaling although (Figure 5), as erlotinib is highly selective for HER1/EGFR, this might be achievable at concentrations that do not have effects on other TKs.

The anti-tumor effects of erlotinib have been examined *in vivo* in several human tumor xenograft models, including head and neck cancer [34], NSCLC [35–38], breast cancer [33,39], vulval and colorectal cancer [39]. In HN5 tumor xenografts, erlotinib was shown to be active within

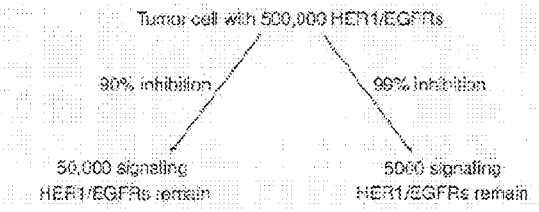
Figure 4. Structure of erlotinib and its binding to HER1/EGFR.



EGFR: Epidermal growth factor receptor; HER: Human epidermal growth factor receptor.

1 h of oral dosing, and inhibited HER1/EGFR phosphorylation in a dose-dependent manner, with an 50% effective dose of 9.9 mg/kg [35]. In both the HN5 and NSCLC tumor models, the effect of erlotinib on tumor growth was demonstrated to be dose dependent and correlated with plasma level [34,35]. In the HN5 model, 100% inhibition of tumor growth was achieved at a dose of 12.5 mg/kg/day orally [36]. At higher doses, tumor regression was observed [36], and it has been suggested that this effect is due to induction of apoptosis by erlotinib [35].

Figure 5. Hypothetical effect of extent of exposure on target inhibition.



High exposure (enabling complete receptor inhibition) may be necessary to adequately control downstream signaling).
EGFR: Epidermal growth factor receptor; HER: Human epidermal growth factor receptor.

The effect of combining erlotinib with chemotherapy agents commonly used in NSCLC and other cancers, has been investigated in human tumor xenograft models [33,35]. The data indicate that the use of erlotinib in combination with several different chemotherapy agents, including cisplatin and gemcitabine, has additive effects on anti-tumor activity, with no increase in toxicity.

Clinical experience with erlotinib in NSCLC

The maximum tolerated dose (MTD) of erlotinib was determined in a Phase I, dose-escalation study involving 40 patients with solid malignancies, refractory to conventional therapy [40]. Erlotinib was generally well tolerated, with diarrhea and rash being the most common treatment-related side effects. Dose limiting toxicities (including grade 3 and 4 diarrhea, and grade 2 rash) were observed with erlotinib 200 mg/day, and the MTD was confirmed as 150 mg/day. The study also provided encouraging preliminary evidence of clinical efficacy. One patient with renal cell carcinoma achieved complete remission of nodes and metastases, and a second patient with colorectal cancer had a 30% reduction in liver metastasis, lasting more than 11 months [39].

Subsequently, the efficacy and tolerability of erlotinib monotherapy was investigated in a Phase II study involving 57 patients with advanced, treatment-refractory HER1/EGFR-positive NSCLC [41]. Patients who had failed previous therapy received erlotinib 150 mg/day for 52 weeks, or until clinical deterioration or progression. A total of seven patients (12%) responded to treatment, two with complete responses of 18 and 80 weeks, and five with partial responses (12 and 56 weeks). A further 22 patients (39%) had stable disease. The median survival period was 8.4 months, and the survival rate at 12 months was 40%. These results were considered encouraging, in particular as 93% of patients had previously received two or more chemotherapy regimens [41]. Erlotinib was generally well tolerated, with mild-to-moderate rash and diarrhea being the most commonly reported side effects.

Three Phase III studies with erlotinib in patients with NSCLC have since been completed. Two of these examined the effects of erlotinib as a first-line treatment in combination with chemotherapy [42,43]. Both were multicenter, randomized, double-blind, placebo-controlled trials involving patients with unresectable advanced (Stage IIIb/IV) NSCLC who had not previously received chemotherapy, with an Eastern

Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. In the first trial (TArceva Lung CancEr INvesTigation [TALENT]), 1172 patients from centers in Europe and Asia received erlotinib 150 mg/day or placebo, plus concurrent cycles of gemcitabine and cisplatin [42]. There were no significant differences between the erlotinib and placebo groups in terms of tumor response, overall survival, time-to-progression and time-to-symptomatic progression. The toxicity profile of erlotinib plus chemotherapy was similar to that of placebo plus chemotherapy, except there was a greater incidence of grade 3/4 diarrhea and grade 3/4 skin rash with erlotinib [42]. The second trial (Tarceva responses in conjunction with paclitaxel and carboplatin [TRIBUTE]) involved 1059 patients from US centers [43]. Patients received erlotinib 150 mg/day or placebo, with up to six concurrent cycles of carboplatin and paclitaxel. As in the TALENT study, there were no overall differences (in the overall population) in objective response, median overall survival, or median time-to-progression, between patients on erlotinib plus chemotherapy and those on chemotherapy alone. However, in patients who had never smoked, treatment with erlotinib achieved a marked and significant improvement in survival (22.5 vs 10.1 months for placebo; hazard ratio [HR] = 0.49) [44]. Adverse events with erlotinib were similar in incidence and severity to those with placebo, apart from a greater incidence of rash and diarrhea [45].

Two recent Phase III trials (Iressa® NSCLC Trial Assessing Combination Therapy [INTACT]-1 and -2) of first-line treatment with another TK inhibitor (TKI), gefitinib, in combination with chemotherapy, also failed to demonstrate a survival benefit compared with chemotherapy alone [45,46]. The reason for the lack of effect on survival in these trials is unclear. There are no significant pharmacokinetic interactions between the TKIs and any of the commonly used cytotoxic drugs. Other interactions have been postulated. For example, as erlotinib causes cell-cycle arrest at the G_1 phase [81], this might reduce tumor sensitivity to cytotoxic agents, many of which cause cell-cycle arrest at a later stage. More sophisticated dosing schedules could minimize such effects. However, the fact that in TRIBUTE there was a substantial improvement in survival in patients who had never smoked, indicates that such interactions do not preclude the use of combination therapy with erlotinib, which seems to be highly effective in some circumstances.

The Phase III BR.21 study examined the use of erlotinib monotherapy in 731 patients with NSCLC who had failed first- or second-line chemotherapy for advanced or metastatic disease [29,47]. Patients were randomized to receive erlotinib 150 mg/day or placebo until deterioration or disease progression. Most of the patients were men, and in late-middle age (median: 61.4 years). Almost 70% had a PS of 0 or 1, and 50% had received one previous chemotherapy regimen. There was a statistically significant improvement in overall survival with erlotinib compared with placebo (median survival: 6.7 vs 4.7 months; HR: 0.71; $p < 0.001$). The clinical benefit of erlotinib was apparent in all patient subgroups [47]. Disease progression was also significantly delayed by erlotinib compared with placebo (median time-to-progression: 2.2 vs 1.8 months; HR 0.61; $p < 0.001$). Time to deterioration of patient reported symptoms (QoL) was significantly longer with erlotinib [48]. Erlotinib was well tolerated and, as expected, rash and diarrhea were the most common adverse events. These were generally mild or moderate and easily managed [29,47]. This is the first and only controlled study to date to demonstrate an improvement in overall survival with a single-agent HER1/EGFR TKI in advanced NSCLC. In a similar Phase III trial of second- or third-line therapy, gefitinib did not significantly improve survival in patients with advanced NSCLC (Iressa® Survival Evaluation in Lung cancer [ISEL] trial [48]).

Exploring new therapeutic options with erlotinib

Given the negative outcomes of the first-line combination therapy studies, more research is needed on the potential role of agents such as erlotinib in first-line therapy for unselected patient populations. A Phase II trial is ongoing with erlotinib as a first- or second-line monotherapy for bronchioloalveolar carcinoma, a subtype of adenocarcinoma in which the TKIs have demonstrated somewhat greater activity. The interim analysis based on 39 patients, demonstrated favorable tolerability, with partial responses in 15 patients (25%). Patients who had never smoked were most likely to respond [49]. The effect of first-line treatment with erlotinib in elderly patients (>70 years of age) with advanced NSCLC is also being investigated in a Phase II study. Preliminary results indicate that erlotinib is well tolerated in this population, and show encouraging therapeutic activity. Among the 30 patients evaluated, there were four partial responses and 14 with stable disease [50].

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