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Review Article

Epidermal growth factor receptor tyrosine kinase inhibitors in cancer therapy*

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Summary

Receptor tyrosine kinases are transmembrane proteins involved in signal transduction. They propagate growth factor signals from the cell surface to intracellular processes that control critical functions such as growth, differentiation, angiogenesis and inhibition of apoptosis. In malignancies, these signaling pathways are often exploited to optimize tumor growth and metastasis. One such family of receptor tyrosine kinases is the epidermal growth factor receptor (EGFR) tyrosine kinase. These receptors are overexpressed in a wide variety of epithelial cancers and have been implicated in tumor aggressiveness. Thus, targeting the EGFR tyrosine kinase has attracted considerable attention. This review will summarize current preclinical and clinical knowledge of the small-molecule oral inhibitors of the EGFR tyrosine kinase, which include ZD-1839, OSI-774, CI-1033, EKB-569, PKI-166, GW-2016 and BIBX-1382.

Introduction

Malignant neoplasms demonstrate the properties of autonomous cell growth, invasion of surrounding tissues and metastasis. This malignant phenotype is controlled partly by dysregulated cell signaling that leads to cell proliferation and/or inhibition of apoptosis (1, 2). One class of signaling proteins that is often targeted through mutation or overexpression is the receptor tyrosine kinases. Currently, approximately 60 genes encoding transmembrane receptor protein tyrosine kinases, distributed in 20 subfamilies, have been identified in the human genome. These genes are part of the approximately 500 identified protein kinase genes (1).

Signaling by receptor tyrosine kinases proceeds through ligand-induced receptor oligomerization, resulting in cytoplasmic tyrosine autophosphorylation. This process generates phosphorylated tyrosine residues that mediate specific binding of adaptor proteins and activates an intracellular cascade (Fig. 1). One member of the receptor tyrosine kinase family that has been widely targeted for anticancer therapy is the epidermal growth factor receptor (EGFR).

The EGFR family

The epidermal growth factor (EGF) is the prototype of a large family of closely related growth factors, which includes transforming growth factor (TGF), amphiregulin, heparin binding EGF and β-cellulin. TGF has been well-characterized as a key modulator of both normal and malignant cell proliferation. TGF binds to its specific cell membrane receptor, the EGFR, with subsequent activation of the EGFR tyrosine kinase catalytic activity that activates cytoplasmic and nuclear signaling leading to cell proliferation and survival.

EGFR (HER1, erbB1) was originally cloned in 1984 (3) and belongs to a family of transmembrane receptor tyrosine kinases involved in cell growth and differentiation. EGFR differs from the other receptor tyrosine kinases in that there is a single isoform, from a single 26 exon gene located across 110kb on chromosome 7p11-13. Besides a single kinase domain, EGFR has two cysteine-rich extracellular regions. The ligand binding domain contains the two cysteine-rich regions which allow binding of the ligands described above (EGF, TGF-alpha, amphiregulin, heparin binding EGF) and a number of virally encoded ligands (4). Other known members of the EGFR family include HER2 (human epidermal growth factor-like receptor type 2), HER3 and HER4 (also known

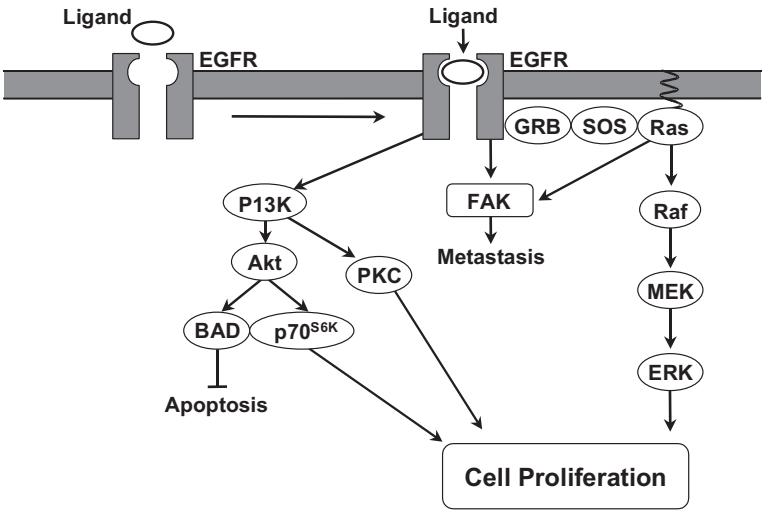

Fig. 1. A simplified schematic diagram of known pathways of EGFR signaling. The well-characterized Ras-Raf-MAPK pathway is activated downstream of EGFR activation. Cross-talk, however, exists and there is concurrent activation of the PI_3-kinase/Akt survival pathway. PI_3K = phosphoinositide-3-kinase; PKC = protein kinase C; FAK = focal adhesion kinase; MEK = mitogen-activated protein kinase kinase; ERK = extracellular signal-regulated kinase.

as erbB2, erbB3 and erbB4). Subtypes erbB3 and erbB4 serve as heregulin receptors, while the ligand for erbB2 is unknown. Although erbB2 has no known ligand, it can form dimers with ligand-bound members of this HER family and participate in cell signaling. In addition, oncogenic mutations in erbB2 lead to a constitutively activated receptor, which transduces signals without receptor binding. EGFR interacts with HER2 and HER3 but not HER4, which pairs with HER2. It is noteworthy that HER3 lacks a functional tyrosine kinase catalytic domain, but serves as a noncatalytic partner to recruit a broader spectrum of downstream effectors after phosphorylation by EGFR or HER2 (4).

In eukaryotes, EGFR plays a critical role in wound healing. This function involves stimulation of mitogenesis, apoptosis, cell migration, differentiation and angiogenesis (4-6). These processes are also important in tumorigenesis. For example, coexpression of TGF-α and EGFR in invasive breast cancer strongly correlates with microvessel density (7).

Members of the EGF receptor family and their ligands are overexpressed or expressed as an autocrine loop in a number of tumor types, including pancreatic, lung, ovarian, renal cell, gastric, hepatocellular and breast cancers (8-10). Such overexpression often correlates with advanced disease and poor prognosis (11). For example, EGFR overexpression is associated with increased tumor grade, increased metastatic potential and a poor prognosis in bladder, breast and gastric cancers. Also, amphiregulin and EGF have been found to be coexpressed in pancreatic and ovarian carcinomas. In a study of primary breast tumors, 59% of samples expressed the EGFR receptor and correlated with poor response to hormonal therapy. HER2 is overexpressed in bladder, breast, colorectal, endometrial, esophageal, gastric, non-small cell lung, ovarian, prostate, renal, salivary gland, uterine, cervical, glioblastoma and melanoma cancers. In particular, HER2 is overexpressed in 30% of breast and ovarian cancers. Its overexpression is associated with poor prognosis in breast, colorectal, gastric, non-small cell lung, ovarian, prostate, salivary and uterine cancers. HER3 is also overexpressed in a wide variety of cancers including bladder, breast, gastric, non-small cell lung, ovarian, prostate and melanoma. Its overexpression has been correlated with advanced tumor grade, increased metastatic potential and poor prognosis. Its overexpression in non-small cell lung cancer is associated with poor prognosis (12-14).

The biochemical pathways involved in EGFR signaling have been elucidated. Catalytic activity is initiated after ligand binds to the receptor. As previously mentioned, erbB2 has no known ligand, but participates in receptor signaling by heterodimerization with other ligand-bound family members. Dimerization results in a conformational change, activation of the kinase domain, autophosphorylation and initiation of cytoplasmic signaling (15). Downstream effectors include the proliferative Ras/Raf/MEK/ERK pathway (16) and the antiapoptotic phosphoinositol 3-kinase/Akt pathway (17). Thus, EGFR signaling appears to be important for the maintenance of the neoplastic phenotype and is a rational target for anticancer therapy.

EGFR tyrosine kinase inhibitors

The EGFR tyrosine kinase inhibitors are the most widely studied oral small-molecule inhibitors of receptor tyrosine kinases to date (18). Phase III clinical trials of at least one of these agents has been completed with

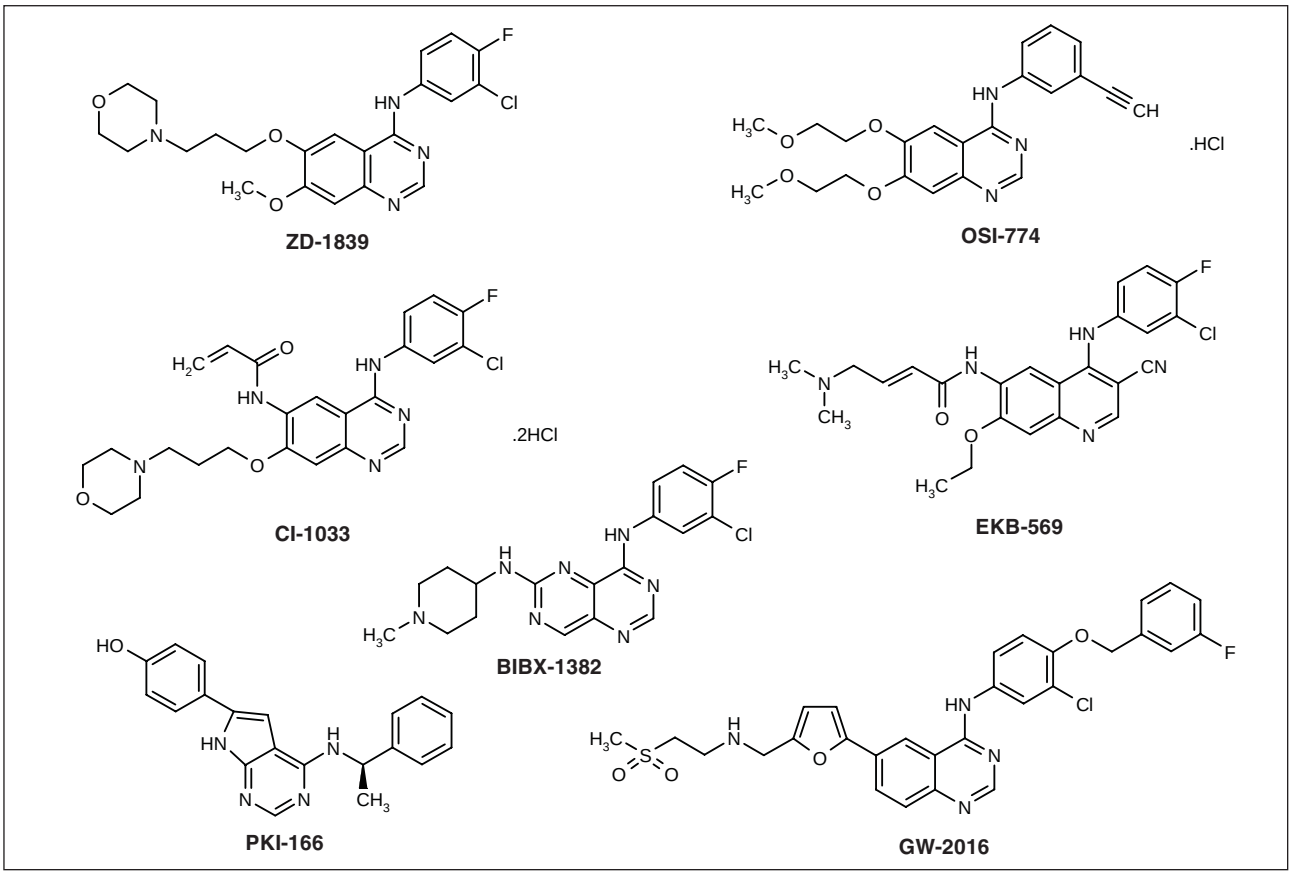

Fig. 2. Structures of some epidermal growth factor receptor tyrosine kinase inhibitors.

interim results expected within a year. At least 6 members in this class of agents are in clinical trials. All of these EGFR tyrosine kinase inhibitors are orally administered and exhibit only mild to moderate toxicities. They inhibit EGFR function by binding to its ATP-binding pocket, hence inhibiting autophosphorylation. The most common and sometimes severe toxicity seen with these agents is an acneiform skin rash (19, 20). The pathogenesis of this rash undoubtedly is related to the inhibition of EGFR in skin, since the basal layer of the epidermis has high levels of EGFR. This hypothesis is supported by the fact that skin rash has so far been seen with all the oral EGFR tyrosine kinase inhibitors, as well as with antibodies that target EGFR such as C225 (cetuximab) (21). Anecdotal evidence suggests that this acneiform rash may be a predictive marker of response to these agents. Another mechanism-based toxicity appears to be diarrhea.

The chemical structures of of some EGFR tyrosine kinase inhibitors are shown in Figure 2.

ZD-1839

ZD-1839 (Iressa®) is a selective quinazoline inhibitor of EGFR (HER1) *in vitro* and *in vivo.* The IC_{50} of EGFR tyrosine kinase inhibition is 0.023 μM, while the IC_{50} for inhibition of HER2 tyrosine kinase is 1.2-3.7 μM (5, 19, 20). ZD-1839 is one of the first agents in this class to be tested in clinical trials. This agent appears to be mainly cytostatic, although a 2- to 4-fold increase in apoptosis has been observed with higher doses in preclinical studies (22). Synergistic cytotoxicity has been demonstrated for combinations of ZD-1839 and taxanes, gemcitabine and platinum agents in a number of human cell lines (22, 23). Interestingly, the observed synergy is independent of the level of EGFR expression in the tumor models used (23). ZD-1839 has significant antiangiogenic effects that are further enhanced by combination with paclitaxel (22).

Objective clinical responses have been observed in phase I studies, with the efficacy highest among NSCLC patients. In the first phase I study, 64 patients were treated with a daily oral dose of ZD-1839 given for 14 days followed by 14 days observation. Antitumor activity was seen in 4 patients, 2 with partial responses and 2 with significant disease regression. (20). An acneiform rash and diarrhea were the most common toxicities. The second study was a phase I/II trial utilizing continuous once-daily dosing. Data on 127 patients have been reported. The most common toxicities were rash, diarrhea, nausea,

vomiting and elevation in transaminases. Clinical activity was seen in NSCLC and prostate cancer (19). As a result of these early studies, ZD-1839 doses of 250 mg and 500 mg daily have been selected for further testing. Single-agent phase II studies are ongoing in third-line NSCLC, in prostate cancer, head and neck cancer, glioma and renal cell carcinoma.

Three large phase III studies in NSCLC have completed accrual and results are awaited with interest. These studies evaluated ZD-1839 in the first-line setting in combination with chemotherapy. After 6 cycles of the standard chemotherapy, patients continue therapy with the investigational agent. Patients are randomized to receive placebo, 250 mg or 500 mg ZD-1839. Two identical studies are being run using gemcitabine/cisplatin (Europe) or paclitaxel/carboplatin (U.S.) as the chemotherapy regimen. The third study utilizes the two doses of ZD-1839 in patients who have failed one or two prior chemotherapy regimens. Results are awaited with interest.

OSI-774

OSI-774 (Tarceva®) is a selective quinazoline inhibitor of human EGFR tyrosine kinase with an IC_{50} of 2 nM and selectively reduces EGFR autophosphorylation in intact tumor cells with an IC_{50} of 20 nM. It competes with adenosine triphosphate (ATP) and may be influenced by intracellular ATP concentration. OSI-774 also inhibits the recombinant intracellular (kinase) domain of the EGFR, indicating that the inhibitor binding site is in this domain. A reduction of EGFR by autophosphorylation in intact tumor cells has been observed. This agent blocks cell cycle progression at the G_1 phase resulting from $p27^{KIP1}$ accumulation in treated cells. Consequent to this, apoptosis is induced, as determined by DNA fragmentation (24). Significant *in vitro* activity was demonstrated in clonogenic assays that utilized tumor cells obtained from patients. OSI-774 (10 μM) inhibited 63% of breast cancer, 75% of NSCLC and 83% of ovarian cancer cells (25).

Preliminary results from three phase II trials have been reported. In the first study, 113 patients with previously treated squamous cell carcinoma of the head and neck received treatment with 150 mg of OSI-774 daily. Objective responses have been documented in 10 out of 78 evaluable patients. The principal toxicity is an acneiform skin rash, which is often ameliorated by minocycline or topical silver sulfadiazine (26). The second study evaluated OSI-774 in patients with NSCLC progressing on platinum-based chemotherapy. OSI-774 (150 mg) was administered as a single oral daily dose for 1 year or until disease progression. Seven out of 56 patients achieved a partial response. The treatment was well tolerated with mild to moderate acneiform rash occurring in 79% of treatment courses (27). In the third study, 150 mg of OSI-774 was administered to patients with advanced ovarian cancer. Partial responses were documented in 3 of 34 patients. Disease stabilization over a period of 2-6 months was documented in 15 of these patients (28). A phase III study of OSI-774 in combination with paclitaxel and carboplatin is underway in patients with NSCLC.

CI-1033

CI-1033 is another quinazoline compound that differs from the other agents in this class. First, CI-1033 inhibits receptor tyrosine kinase activity irreversibly. Second, it inhibits all members of the EGF family of receptor tyrosine kinases. In the first reported phase I study of this agent, drug was administered orally daily for 7 days every 21 days (29). An acneiform rash, emesis and diarrhea have been the most common toxicities. Reversible moderate to severe thrombocytopenia has been observed, as well as 1 case of reversible severe hypersensitivity reaction. Of the 37 treated patients, there was a partial response in 1 patient with squamous cell carcinoma of the head and neck and disease stabilization in 10 patients. A second phase I study administered CI-1033 weekly for 3 weeks out of every 4 weeks. The toxicity pattern was similar to that described above, and 1 disease stabilization in a patient with osteosarcoma has been documented out of 34 patients (30).

A recently published study has provided some insight into the observation that synergistic cytotoxicity between this class of agents and standard cytotoxic agents may not be related to EGFR tyrosine kinase inhibition. Erlichman *et al*. demonstrated synergistic cytotoxicity between CI-1033 and a number of chemotherapy agents including mitoxantrone and the topoisomerase I inhibitors in different cell lines. Mechanistically, they demonstrated that CI-1033 enhances steady-state drug accumulation mediated by inhibition of the breast cancer resistance protein (BCRP) (31). Thus, synergistic cytotoxicity with systemic chemotherapy agents which are substrate for BCRP may depend on the tumor expression of BCRP and may not have any relationship to EGFR tyrosine kinase inhibition. CI-1033 also has synergistic effects when combined with radiotherapy (32).

EKB-569

EKB-569 is a cyanoquinoline that binds covalently to EGFR and potently inhibits recombinant EGFR tyrosine kinase *in vitro* (IC_{50} = 1.3 nM) and the phosphorylation of EGFR (IC_{50} = 15 nM) in cells that overexpress EGFR. Greater than 10-fold higher concentrations of EKB-569 are needed to inhibit other receptor tyrosine kinases, including HER2. Despite these differences, EKB-569 is equipotent in inhibiting the proliferation of cells expressing EGFR or HER2. These findings may be explained, in part, by the ability of HER2 to heterodimerize with EGFR upon stimulation. The specificity of these effects are demonstrated by the fact that 50-fold higher drug concentrations are needed to inhibit cells that do not

overexpress either receptor. Cell growth inhibition by EKB-569 is associated with reversible cell cycle inhibition in G_0/G_1 and occurred in rodent xenograft models (33). In a recently reported study, a combination of EKB-569 and the nonsteroidal antiinflammatory agent sulindac yielded a synergistic effect in prevention of intestinal neoplasia in a murine model of human familial adenomatous polyposis (34). This synergistic effect may be due to the convergence of EGFR and cyclooxygenase signaling and suggests a possible role for the EGFR tyrosine kinases in chemoprevention. Phase I studies of EKB-569 in patients with a variety of cancers known to overexpress EGFR are ongoing. Toxicity patterns appear to be similar to other agents in this class and include diarrhea and skin rash.

PKI-166

PKI-166 is a pyrrolo-pyrimidine compound that selectively and potently inhibits the EGFR tyrosine kinase *in vitro* (IC_{50} = I nM). EGF-mediated EGFR autophosphorylation, c-*fos* mRNA expression and cell proliferation were inhibited in the submicromolar range (35). At higher concentrations, the compound also inhibited cellular c-erbB2 autophosphorylation (IC_{50} = 0.1-1 μM). PKI-166 has shown potent and selective *in vivo* antitumor activity in several EGFR expressing xenograft tumor models in nude mice following oral administration of 10-100 mg/kg/day. Phase I studies of this compound are ongoing with no data reported to date.

Other agents

BIBX-1382 is a receptor tyrosine kinase inhibitor that potently blocks TGF-α-induced cell signaling (36). This agent is in phase I trials in Europe. GW-2016 is a 6-furylquinazoline derivative that selectively inhibits the catalytic domains of both the EGFR and the erbB2 tyrosine kinases (IC_{50} = 10 nM for both kinases *in vitro*) with equimolar potency (37). GW-2016 is in phase I clinical trials in the U.S.

Future directions

The results of preclinical studies and preliminary results from ongoing clinical trials indicate that EGFR is a valid target for anticancer therapy. All the small-molecule inhibitors discussed above demonstrate antitumor activity, either clinically, preclinically or in combination with standard cytotoxic agents. In addition to these 6 small-molecule inhibitors of EGFR tyrosine kinase, there are at least 6 monoclonal antibodies designed to target EGFR. The challenge, therefore, is to define which of these agents is the most promising based on efficacy, toxicity patterns and other intrinsic properties of the chemical molecule. The first question to be answered would be whether antibody approaches and small-molecule approaches are equally effective. Because of the recent discovery of a variant mutated receptor with a truncated extracellular domain (38), it had been hypothesized that chemical inhibitors of receptor tyrosine kinase function may be superior to monoclonal antibodies. However, a monoclonal antibody, Y10, that recognizes both human and murine mutated EGFRvIII has been engineered. Y10 inhibits cellular proliferation and induces cell-mediated cytotoxicity *in vitro*. Intratumoral administration to mice bearing human EGFRvIII glioma xenografts increased median survival by 3-fold with 25% of mice achieving long-term survival (39). Ongoing studies will elucidate the appropriate role(s) of antibodies *versus* chemical inhibitors.

A more pressing issue is the performance of correlative laboratory studies aimed at predicting which patients will respond to these agents. Currently it is unclear whether EGFR expression or EGFR phosphorylation status of tumors is predictive of response to therapy with EGFR tyrosine kinase inhibitors. One must be careful not to conclude that these proteins have no predictive value. The reason this question remains unsettled is that investigators have not consistently asked the important question of predictive markers in studies performed to date.

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