Conference paper
UDC: 616-006:615-085:632.938



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# EGF receptor as a therapeutic target in oncology

**KEYWORDS: Epidermal Growth Factor; Neoplasms; Antineoplastic Agents**

Epidermal growth factor (EGF) was discovered more than 40 years ago and nearly 20 years later, its receptor (EGFR) was identified and cloned. These discoveries led to the awarding of the Nobel Prize in 1986. EGFR and its ligands play a critical role in over 70% of all cancers. The enhanced activity of this receptor is a hallmark of many human malignancies - breast, lung, prostate, head and neck, ovary, stomach, kidney, brain, pancreas (1). In many of these tumor types, EGF receptor is expressed 100-times higher than on the surface of the normal cells. EGFR belongs to subfamily of four closely related receptors (erbB1-HER1, erbB2-HER2, erbB3-HER3 and erbB4-HER4). Structurally, each receptor is composed of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain. The receptors exist as inactive monomers. Upon binding to ligands such as EGF and transforming growth factor alpha, the receptors undergo conformational changes that facilitate homo- or heterodimerization (2). EGFR-dimerization activates the intrinsic protein tyrosine kinase activity of the receptor leading to activation of intracellular signal trunsduction pathways involved in tumor progression, proliferation, cell survival, angiogenesis and metastatic disease (3). Overexpression of at least two of these receptors (EGFR and closely related ErbB2) has been associated with a more aggressive clinical behavior (4). Because that EGFR was identified early as an important target for drug development. Now a number of therapeutic strategies specifically target either the inside- or the outside of the EGF receptor and its family members are available.

The enhanced activity of the EGFR is due to molecular events, which can lead to the persistent activation of the kinase activity of the receptor (receptor overexpression, gene amplification, activating mutations, overexpression of receptor ligands, and/or loss of their negative regulatory mechanisms) (2). Activation of the EGFR pathway is not limited to members of its family only. Also it can occur by the cross co-operation with other signaling pathways (G protein coupled receptors, platelet-derived growth factor (PDGF) receptor, Jak-2 and PTEN) (1).

Next categories of compounds have been developed with aim to target the EGF receptor:

1) ligand antagonists (have not met success)
2) monoclonal antibodies (Table 1)
3) tyrosine kinase inhibitors (TKIs) (Table 2).

**Table 1.** Monoclonal antibodies designed to target the EGFR family

| Agent | Characteristic | Target | Tumor Type |
|---|---|---|---|
| Cetuximab | Chimeric | HER-1 | Colon, head and neck, NSCLC, pancreas |
| ABX-EGF | Human | HER-1 | Colon, renal |
| EMD-7200 | Humanized | HER-1 | Head and neck, ovarian, colon, cervix |
| h-R3 | Humanized | HER-1 | Head and neck |
| Pertuzumab | Humanized | HER-2 | Breast, ovarian, prostate, NSCLC |
| Trastuzumab | Humanized | HER-2 | Breast |

**Table 2.** Tyrosine kinase inhibitors designed to target the EGFR family

| Agent | Irreversible | Target | Tumor Type |
|---|---|---|---|
| Gefitinib | No | HER-1 | NSCLC |
| Erlotinib | No | HER-1 | NSCLC, pancreas |
| Lapatinib | No | HER-1/2 | Breast |
| CI-1033 | Yes | Pan HER | Squamous cell carcinoma, skin |
| EKB-569 | Yes | HER-1 | Colon |
| BMS-599626 | No | HER-1/2 | — |
| AEE788 | No | HER-1/2 Anti-VEGFR | — |

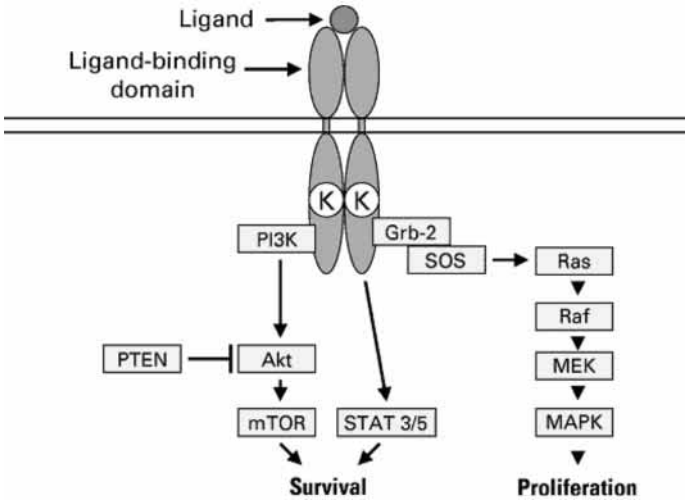


**Figure 1.** EGFR signaling patway

Figure 1 shows the network of EGFR signaling. There is a theoretical possibility of combining a few signal transduction inhibitors in order to achieve better efficacy (e.g. an inhibitor of Ras pathway can be added to the EGFR agent or targeting PKB/Akt pathway in conjunction with the targeting of EGFR). The fact that Iressa(r) in combination with cisplatin was not effective awaits more experimentation and better understanding of tumor cell signaling network. Also it is not known whether targeting of EGFR pathway could be better achieved by blocking the receptor itself or by blocking of its downstream elements (3).

EGFR expression, generally measured by immunohistochemistry (IHC), has long been associated with a poor prognosis (4). It had been hoped that there would also be a clear association between EGFR expression, as measured by IHC or amplification by fluorescence in situ hybradization (FISH), and the activity of targeted EGFR inhibitors. This has not been the case in most studies of targeted EGFR inhibitors, whether they be small molecules or antibodies. Some of monoclonal antibodies and TKIs that showed success in clinical practice and come broadly to market will be described in this article with more details.

## HERCEPTIN

Overexpression or amplification of HER2 occurs in approximately 15% to 25% of patients with metastatic breast cancer (MBC). It is associated with aggressive disease and decreased survival (4) and represents an early event in breast cancer pathogenesis. These facts led to the interest in HER2 as a target for therapy and developing of trastuzumab - a recombinant, DNA-derived,

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The manuscript was received: 30.09.2005.

Accepted for publication: 15.10.2005.

humanized monoclonal antibody that specifically target the extracellular domain of HER2. HER2-positive status by IHC is defined at the 3+ level. In case of 2+ level, HER2 gene amplification by FISH should be performed. HER2 testing could be performed on a sample of the primary tumor or a biopsy of a metastatic site. Trastuzumab has been extensively investigated in the clinical setting, both as monotherapy (5) and in combination with standard chemotherapeutic drugs (6). In combination with doxorubicine/cyclophosphamide or paclitaxel, it has been shown that trastuzumab prolong survival in women with HER2-positive MBC (6). Further, detailed preclinical studies that have shown synergy of trastuzumab with platinum salts and vinka alkaloids have been correlated with very promising clinical activity with these combinations (7, 8). The current clinical indication for the use of trastuzumab is in the treatment of MBC patients with HER2 overexpressing tumors. In the trials that led to the approval of trastuzumab as treatment for patients with HER-2 positive MBC, trastuzumab was administered as a loading dose of 4 mg/kg intravenously followed by a weekly dose of 2 mg/kg, which is now the standard schedule. The most common adverse effects of trastuzumab are mild to moderate infusion-related reactions, which are usually noted with the first infusion and decrease in frequency thereafter. The most clinically significant adverse event is symptomatic cardiac dysfunction, which occurred in 2% to 4,7% of patients in trials of trastuzumab monotherapy (5). In the pivotal trastuzumab combination trial (H0648g) trastuzumab was associated with cardiotoxicity, especially when given with anthracyclines (28% of patients) (6). Trastuzumab trials since then have included cardiac eligibility criteria and prospective cardiac monitoring. The incidence of congestive heart failure in a pooled analysis of six recent trials was 2,7%. Cardiotoxicity is usually reversible and manageable even with continued trastuzumab therapy. News of this receptor-based strategy in different breast cancer setting (adjuvant use) should be a part of another presentation at this meeting.

**GEFITINIB**

Gefitinib is a synthetic anilinoquinazoline capable of inhibiting EGFR tyrosine kinase. Following completion of phase I study and observation of good tolerability and surprisingly objective response in patients with previously treated non-small cell lung cancer (NSCLC), a series of phase II and III trials were initiated. Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL) studies were multicenter: patients enrolled in IDEAL-1 were required to have failed one prior platinum-containing regimen whereas patients enrolled in IDEAL-2 were required to have failed two prior chemotherapy regimens including a platinum-containing and docetaxel. Patients were randomized between 250 or 500 mg of gefitinib per day. Among the approximately 40% of patients who reported improvement in symptoms, the median time to symptomatic improvement was rapid with averaging less than 10 days. Grade 3 and 4 toxicities were relatively uncommon with acne like rash and diarrhea, the only noted side effects. No cases of interstitial pneumonitis were reported (9). Iressa NSCLC Trial Assessing Combination Treatment (INTACT) were undertaken, in which chemotherapy (cisplatin and gemcitabine - INTACT-1, carboplatin and paclitaxel - INTACT-2) plus gefitinib was compared to chemotherapy alone in chemotherapy naive patients with advanced NSCLC. Unfortunately, neither INTACT-1 nor INTACT-2 revealed an improvement in overall survival. The higher dose of gefitinib produced somewhat greater toxicity than the 250 mg per day dose. Data of Iressa(r) Survival Evaluation in Lung Cancer (ISEL) study were presented this year at the Annual Meeting of the American Association of Cancer Research. Gefitinib did not significantly prolong survival in the overall study population or in patients with adenocarcinoma. Subsequently, manufacturer withdrew application from the EMEA. Gefitinib-treated patients survived longer than placebo-treated patients in two specific patients subsets: patients of Asian origin and never-smokers (10). In June 2005, U.S. Food and Drug Administration Agency issued a New Labeling and Distribution Program for gefitinib, limiting its administration.

**ERLOTINIB**

Pre-clinical studies showed that erlotinib, which is a quinazoline, is a capable of inhibiting phosphorylation of EGFR. This effect is related to erlotinib's ability to specifically inhibit the tyrosine kinase activity of the intracellular portion of HER1/EGFR. A phase I trial established maximal tolerated dose of erlotinib, on a protracted daily schedule, at 150 mg/day. The dose-limiting toxicities were diarrhea and skin rush. A subsequent phase II NSCLC included patients who had progressive disease following platinum based chemotherapy. Overall response rate was 12%, stable disease was recorded among 35% of patients, and 1-year survival rate was 48%. These results led to phase III trials. A trial of National Cancer Institute of Canada - Clinical Trials Group compared orally administered erlotinib with placebo for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. A total of 731 patients was randomized using a 2:1 randomization schema. EGFR status was determined for 33% of patients who had tissue samples available prior to the study (either at diagnosis or at relapse). Survival was significantly longer in the erlotinib arm. In the EGFR-positive subset, erlotinib produced a longer survival duration than placebo. No apparent erlotinib survival effect was observed in the EGFR-negative subset. However, the confidence intervals for the EGFR-positive and EGFR-negative subsets were wide and overlapped. Thus, an erlotinib survival effect in the EGFR-negative subset cannot be excluded (10). A subset analysis according to smoking status showed that the erlotinib survival benefit was greater in patients who had never smoked. Progression-free survival (PFS) was significantly longer in the erlotinib arm (in the EGFR-positive subgroup). Tumor responses were observed in all EGFR subgroups. At the moment erlotinib remains the only EGFR inhibitor approved for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen (11).

Tyrosine kinases (there are more than 90 known protein kinase genes in human genome) and their receptors, when mutated or altered structurally and become potent oncogenes, have shown great progress in our understanding of malignant transformation. We will digress at this part of lecture dedicated to EGFR with aim to present imatinib, which was the first successful signal transduction inhibitor in oncology.

**IMATINIB**

KIT gene encodes for a transmembrane tyrosine kinase growth factor receptor belonging to the platelet-derived growth factor (PDGF) family. Imatinib Mesylate (STI571) is a small molecule and a selective inhibitor of the chimeric Bcr-Abl fusion protein, the PDGF receptors alpha and beta and the KIT tyrosine kinase receptor.

Imatinib has shown significant activity in patients with chronic myeloid leukemia (CML), in whom the consistent molecular abnormality is the Bcr-Abl fusion gene. Imatinib Mesylate produces complete hematologic and cytogenetic responses in 24 and 17% of CML patients in chronic phase. Imatinib is also active in accelerated phase and blast crisis of CML (12,13), with lower response rate in patients with more advanced disease. Several smaller studies have suggested a benefit for doses higher than the standard 400 mg daily, prompting the initiation of the larger multicenter Rationale and Insight for Gleevec High Dose Therapy trial in which all responses occurred early during the treatment. Three-log or greater reduction in Bcr-Abl observed in 40% of patients and undetectable levels of Bcr-Abl reported in 30% of patients by 3 months. By comparison, in the International Randomized study of Interferon plus Ara-C vs. STI571 in Chronic Myeloid Leukemia trial, a three-log reduction in Bcr-Abl was achieved in approximately 35% of patients after 12 months. Fluid retention has been observed in majority of patients, but has not generally required intervention. The real issue is determining whether high-dose imatinib improve survival rates. To confirm such benefit, we require a large-scale trial with 10 to 20 years of follow-up. Imatinib resistance occurs

in 16% of patients with newly diagnosed CML and in 25% of patients previously treated with imatinib. Imatinib binds only to the inactive confirmation of Bcr-Abl. New agents with possibility to inhibit multiple tyrosine kinases are required.

Activating mutations of the KIT tyrosine kinase are found in the majority of patients with gastrointestinal stromal tumors (GIST). Patients operated on for GIST commonly relapse. Chemotherapy and radiotherapy have been ineffective for patients with metastatic or non-resectable disease. Such patients treated by Gleevec(r) have a response rate of approximately 60% and stable disease in another 25% of patients. The drug is also recommended for patients with resectable disease medically unfit for surgery or for whom surgery would be debilitating. A European Organization for Research and Treatment of Cancer phase I study identified the highest feasible dose of imatinib to be 400 mg bid (14). Phase II studies showed activity at all doses tested (400 to 800 mg). Two large, randomized, phase III studies comparing doses of 400 mg once a day to 400 mg bid have confirmed the activity of imatinib in terms of PFS and overall survival (15). One of these studies has also documented a small but significant benefit with the high-dose regimen (400 mg bid) in terms of PFS (16). A randomized trial from the French Sarcoma Group has demonstrated that imatinib therapy should be continued indefinitely, even after complete response. Response of GIST to imatinib does not always result in an immediate decrease in size of the lesions - some of responses have been first documented more than 1 year after start of therapy (17). Recent studies showed that imatinib mesylate is most active in GISTs with KIT exon 11 mutations. The phase II adjuvant trial studied patients considered to be high risk, specifically those who had undergone complete gross resection of a primary GIST that expressed KIT and whose tumors were 10 cm or larger. A daily regimen of 400 mg of imatinib mesylate for 12 months was well tolerated. Because this study focused exclusively on the safety, benefit of adjuvant imatinib for patients at high risk has not yet been defined. A phase III adjuvant trial is currently underway.

## INSTEAD CONCLUSION

In recent years, the field of cancer therapy has witnessed the emergence of novel targeted strategies that inhibit specific cancer pathways and key molecules in tumor growth and progression. Important work needs to be done in the areas of patients selection (complementing and going beyond receptor mutations), selection of appropriate dose and schedules with new agents entering the clinic and implementation of strategies to study the appropriate combination both with conventional therapies as well as with other antisignaling agents.

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