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Advantages and Disadvantages of Targeting the C-erbB Family of Receptors in Cancer Treatment: A Review

Panagiotis Papanastasopoulos*

Imperial College, NHS Trust, Charing Cross Hospital, Fulham Palace Rd, London W6 8RF, UK

***Corresponding author:** Panagiotis Papanastasopoulos, Imperia l College, NHS Trust, Charing Cross Hospital, Fulham Palace Rd, London W6 8RF, UK, Tel: +44 20 3311 1423; E-mail: PPapanastasopoulos@nhs.net

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Abstract

C-erbB (EGFR) signaling is well known to promote cancer invasiveness and metastasis. Several pharmacologic approaches have been used aiming to inhibit its activity, ie monoclonal antibodies, antibody-like molecules (peptidomimetics) and receptor tyrosine kinase inhibitors. Several C-erbB signaling 'inhibitors', such as Trastuzumab, Cetuximab, gefitinib, erlotinib and lapatinib are now widely used in clinical practice, having revolutionized the management of certain malignancies, such as HER-2 positive breast cancer. In this review, we present an overview of the mechanism of action, pharmacokinetic properties, mechanism of resistance as well as the relative cost of administration for each group of EGFR inhibitors separately.

Keywords: C-erbB; Signaling; Monoclonal antibodies; TKI; Peptidomimetics

Introduction

The C-erbB family of receptors consists of tyrosine kinase receptors (TKR) with a physiological role in cellular proliferation, survival and differentiation. The family consists of 4 members, also known as the epidermal growth factor receptors (EGFR): ErbB1 (HER1), ErbB2 (HER2 or Neu), ErbB3 (HER3), and ErbB4 (HER4) [1]. They are structurally related and consist of an extracellular ligand-binding domain, a trans membane domain, and a cytoplasmic domain with a catalytic kinase activity. ErbB1 is primarily activated by EGF and TFG-a, whereas ErbB3 and ErbB4 are the receptors for the neuregulins. So far no ligand has been identified for HER2 [1].

As a general rule, ligand binding promotes the formation of homo and heterodimers between different receptors, which leads to the activation of the cytoplasmic domain kinase activity, resulting in trans-phosphorylation of the latter in tyrosine residues [1]. HER2 appears to be the preferred partner for the rest of EGFR [2]. The phosphorylated cytoplasmic domain functions as a docking site for downstream molecules with phosphotyrosine-binding domains, which mediate the signal through the activation of downstream molecular pathways: 1) the mitogen-activated protein kinase (MAPK), 2) the Akt/ phosphoinositide 3-kinase (PI3-kinase) and 3) the mammalian target of rapamycin (mTOR) pathway [1,3]. Ultimately, the signal will be transduced to the nucleus via secondary mediators, where specific up regulation and/ or down regulation of several gene groups, involved in cellular proliferation, survival, differentiation, angiogenesis and motility will take place [1]. Any dys regulation of the fine balance maintained between the cellular processes mentioned above can easily trigger malignant transformation to the cell.

EGFR are known to play a significant role in the pathophysiology of several cancer types in human. Gene amplifications and numerous mutations which may increase the transcription and stability of the receptors have been identified. As a consequence, an increased number of receptors are available each time on the cell surface, resulting in dimerization and activation of the kinase domain, without necessarily the presence of a ligand. A classic example is the overexpression of HER2 by 25% of invasive breast cancer cases, relating to poor prognosis. Other tumors where EGFR signaling is involved are non-small cell lung cancer and colorectal cancer [4-6].

Several therapeutic strategies are currently utilized to selectively target EGFR signaling in cancer cells; 1) monoclonal antibodies or antibody-like molecules (mab), 2) development of small molecules, tyrosine kinase inhibitors (TKI), 3) attachment of toxins to EGFR antibodies or ligands, 4) anti-sense therapies, 5) gene therapies.

Monoclonal Antibodies (MAb)

One of the first approaches to inactivate EGFR signaling was the development of monoclonal antibodies. EGFR-specific murine-derived mab were found to substantially reduce the expression of the receptor on the membrane of cancer cells, reversing their malignant transformation [6]. Similarly, treatment with monoclonal antibodies inhibited the growth of tumors expressing EGFR in xenograft models [7]. Mab show a high affinity for the extracellular receptor domain, competitively preventing the binding of activating ligands. They are also known to induce receptor internalisation and degradation [7-9]. An antibody-dependent cellular cytotoxicity (ADCC), driven by natural killer cells and macrophages which bind to the mab-EGFR complex, was also identified [10].

Two of the main initial problems were to overcome the human anti-mouse antibody immune response which limited their activity in humans, and also their reduced affinity for the human homolog receptor. The solution was given with the development of chimeric (human-mouse) monoclonal antibodies, and later on, fully humanized mab.

Cetuximab is a chimeric mab targeting ErbB1, with a 10-fold greater affinity compared to its physiological ligands [11]. It induces apoptosis via the up-regulation of p27Kip1, therefore arresting cancer cells in G1 phase [12]. There is also evidence that cetuximab sensitizes

cancer cells to the cytotoxic effects of chemotherapy and radiotherapy; In chemotherapy-refractory xenograft models, combined treatment induced a more extensive tumour regression as opposed to chemotherapy alone [13]. Furthermore, cetuximab-treated cancer cells demonstrated an inhibition in their DNA repair mechanisms, increasing their sensitivity to radiation [12].

In clinical studies, cetuximab was found to have a half-life (t1/2) of 7 days [8], demonstrating a benefit in response rate and progression free survival [14]. In colorectal cancer, it is only effective in KRAS-wild type patients [15]. KRAS is a downstream mediator of EGFR signaling, and when mutated and constitutively activated, the MAPK-pathway activation is independent of the EGFR status [16]. Finally, the addition of Cetuximab to platinum-based chemotherapy and radiotherapy in recurrent/metastatic head and neck SCC patients demonstrated significant efficacy [17].

Panitumumab is a fully humanized mab which binds with greater affinity (compared to cetuximab) to $ErbB_1$, causing no immunogenicity. In xenograft models, it achieved to completely eradicate tumours as monotherapy, as opposed to cetuximab [7,18]. In clinical trials of metastatic colorectal cancer, the combination of panitumumab and chemotherapy was found to confer a PFS advantage [19]. For both cetuximab and panitumumab, the main side effects consist of an acneiform rash, gastrointestinal toxicity and hypomagnesemia. They are intravenously administered on a 2-3 weekly basis, and the cost for eight weeks of treatment with cetuximab is approximately $30,000 per patient.

In breast cancer, the recombinant humanized anti-HER2 mab, Trastuzumab, revolutionalized breast cancer management, with significant clinical response rates in the metastatic setting, and an important reduction in the recurrence rate when used adjuvantly [20]. Mechanisms of resistance to trastuzumab have been described, such as the loss of phosphatase and tensin homolog (PTEN), the presence of the ectodomain-missing p95her2/neu receptor and insulin-growth factor 1 overexpression [21-23]. Clinical trials investigating the combined use of Trastuzumab and Pertuzumab (blocking receptor dimerization) to maximize EGFR inhibition are on-going. Trastuzumab side effects consist of mainly allergic reactions and cardio toxicity, requiring close cardiac function monitoring. It is given intravenously on a 3-weekly basis. A full one-year course of Trastuzumab treatment costs approximately $70,000 per patient.

Antbody-like Molecules/Peptidomimetics

Monoclonal antibodies face certain limitations, such as their size, preventing them from crossing the blood-brain barrier (BBB) where disease is often found, and also achieving rather low concentrations into solid tumors. Several laboratories have developed smaller molecules that usually consist of or resemble a specific part of the initial mab that is complementary to the targeted receptor. They can be potentially used to deliver drugs specifically to the cancer cells or prevent receptor dimerization. The main disadvantages are their low affinity, short half-life and their inability to induce ADCC. Such molecules are found in early experimental phases currently [5,24].

Receptor Tyrosine Kinase Inhibitors

Small molecules functioning as tyrosine kinase inhibitors are used to block EGFR signaling. They bind to the hydrophobic pocket of the cytoplasmic ATP-binding domain of EGFR, with high specificity, resulting in inhibition of the downstream signaling pathways. Reversible TKI compete with ATP for the binding site, whereas irreversible inhibitors alkylate a cysteine residue within the ATP-pocket, causing a permanent inhibition [5,25]. Some TKI can also indirectly inhibit more than one of the EGFR family members, possibly via blocking receptor dimerization [26]. They are administered orally and their half-life is much shorter compared to mab (i.e., lapatinib t1/2: 24 hours). Finally they can pass through the BBB and have been incorporated in treatments for CNS metastatic disease [27].

Reversible TKI

Erlotinib and Gefitinib are selective inhibitors of HER1, whereas Lapatinib can inhibit both HER1 and HER2. All three TKI have been incorporated in the management of several tumors, primarily including breast and non-smal cell lung cancer (NSCLC), based on their efficacy from pre-clinical and clinical trials [27-29]. NSCLC patients bearing certain mutations, increasing the affinity of the receptor for TKI, were found to benefit more from erlotinib or gefitinib [30]. Similarly, lapatinib was found to be effective against the trastuzumab-resistant ectodomain-missing p95her2/neu receptor [23]. A percentage of NSCLC patients with progression after continuous treatment with Gefitinib, develop a single point mutation which increases ATP affinity for EGFR, therefore bypassing inhibition [31]. Resistance can also develop via the up-regulation of other existing pathways that cross-talk to EGFR signaling, and compensate for its lost activity (i.e., up-regulation of Met gene), as well as altered receptor internalization [32]. More surprisingly, there is evidence that despite continuous treatment with TKI, HER1 and HER2 blockage is not durable, and results in the overexpression of HER3 which is preferentially signaling via the PI3-kinase/Akt pathway, conferring resistance to TKI [33].

Irreversible TKI

Irreversible TKI were designed to overcome the problem of incomplete inhibition caused by the reversible group. They were also found to be effective against cancer cells bearing in sensitizing mutations to reversible TKI. As they permanently deactivate EGFR kinase activity, intermittent treatment may be feasible, reducing toxicity. Irreversible TKI inhibit all EGFR family members and are currently investigated within clinical trials [5,8,34].

The main side effects from anti-EGFR TKI consist of fatigue, gastrointestinal toxicity, rash, cardio toxicity, impaired liver function tests, pneumonitis and infections. The cost of a year's treatment with Erlotinib and Lapatinib is approximately £18,000 and £20,000, respectively.

Conclusions

Various anti-EGFR agents are currently being used in current practice with promising efficacy, and overall limited toxicity compared to conventional chemotherapy. Increasing the affinity of designed drugs to EGFR, and modifying their chemical structure to achieve adequate and selective uptake by cancer cells can potentially reverse resistance. As resistance usually develops either through mutations/up-regulation of downstream signaling molecules, or the compensatory activation of other existing signaling pathways, combined treatment with different classes of EGFR inhibitors or inhibitors of different pathways may provide a more successful approach. Concomitant targeting of downstream molecules, such as

survivin or MAPK, integrating signals from different cellular pathways may increase treatment efficacy. Identifying in sensitizing ss mutations and designing molecules that specifically target them is another potential strategy. Finally, anti-sense treatments and gene therapies, even though currently in very early phase research, consist of approaches that may prove extremely useful tools in the future.

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