

Current Molecularly Targeted Therapies against EGFR for Cancer

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Introduction

Epidermal Growth Factor Receptor (EGFR) is a Tyrosine Kinase cell surface receptor (RTK) that is expressed in more than 60% of Non-Small Cell Lung Carcinomas (NSCLC) [1], 60-80% of metastatic colorectal cancers (mCRC) [2] and 80-90% of head and neck squamous cell cancer (HNSCC) [3]. EGFR overexpression activates multiple downstream pathways such as PI3K-AKT-mTOR and RAS-RAF-MEK-ERK which are involved in cell differentiation, proliferation, angiogenesis, and apoptosis [4]. Mutations in EGFR Tyrosine Kinase (TK) domain are seen in the mCRC patients, [5] and in HNSCC [6] but their role in prognosis and therapy is currently being evaluated. mCRC patients expressing EGFR with wild type K-ras are treated with anti-EGFR Monoclonal Antibodies (MAB's) [7]. However, mutations such as BRAF and KRAS which inhibits the action of anti-EGFR MAB's have typically been observed in mCRC [8]. Anti-EGFR MAB's are also being used as a first line chemotherapy for recurrent and metastatic HNSCC patients [9].

In NSCLC, mutations in EGFR at exons 18-21, are responsible for increased kinase receptor activity and are associated with tumorigenicity [10]. The L858R point mutation in exon 21 and exon 19 deletion are the most common mutations accounting for 90% of EGFR activating mutations [11]. Other mutations in this domain include G719X mutation in exon 18, exon 19 insertion/deletion mutations, and exon 20 insertion mutations [10]. NSCLC patients with EGFR TK mutations are treated with EGFR Tyrosine Kinase Inhibitors (TKI's) as a first line therapy. Several secondary mutations in the EGFR TK domain such as T790M mutation in exon 20 and L861Q mutation in exon 21 are developed after treatment with EGFR TKI's [4]. Present existing therapies have often been associated with drug resistance, limiting their use. Hence, clinical trials for their improved efficacy are presently being carried out. Moreover, several new inhibitors/antibodies have recently been discovered and are currently in Phase I, II and III clinical trials.

Current Therapies

Anti-EGFR MAB's bind to the EGFR extracellular ligand binding domain and function as competitive antagonists, thereby inhibiting intracellular phosphorylation, preventing downstream signalling and leading to the arrest of cell growth and induction of apoptosis. The first anti-EGFR MAB to get FDA approval was Cetuximab, which is a chimeric, human/murine IgG1 MAB that is used for the treatment of lung, mCRC, and HNSCC patients. Recently, another anti-EGFR MAB, Panitumumab, a fully humanized IgG2 MAB, has been approved for the treatment of progressing mCRC in combination with or following standard chemotherapy [12].

While anti-EGFR MAB's have been used for the treatment of mCRC with limited success, they are ineffective in 40% of mCRC patients that have mutations in the KRAS and BRAF genes. The KRAS mutation leads to the activation of RAS/MAPK pathway by inducing cyclin D1 synthesis, because of which the EGFR pathway cannot be inhibited by an anti-EGFR MAB that acts upstream of the K-ras protein. The single missense BRAF mutation, V600E, is also downstream of EGFR and is located within the kinase domain of BRAF. The amino acid

change in V600E, results in constitutive activation of the BRAF kinase, promoting tumorigenicity, which reduces the efficacy of anti-EGFR MAB's. The PIK3CA mutation, which is not as frequent as KRAS and BRAF mutations, is also a cause for resistance against anti-EGFR MAB's [8]. Hence, several other MAB's are currently in clinical trials such as matuzumab, zalutumumab, MDX-447, nimotuzumab and Mab806, to achieve better efficacy against these mutations [12].

EGFR TKI's act by binding to the intracellular EGFR TK domain, and inhibit receptor phosphorylation and downstream signalling. The first generation of EGFR TKI's bind reversibly to the ATP binding site of the EGFR TK domain, and have higher binding affinity for EGFR with activating mutations, resulting in inhibition of RTK activity [12]. Erlotinib and Gefitinib have already been approved for the treatment of NSCLC [4]. Lapatinib and AE788 are dual kinase inhibitors, which in addition to EGFR, inhibit HER2 and VEGF receptors respectively [12].

However, prolonged use of EGFR-TKI's can lead to drug resistance that is often caused by the common secondary mutation, T790M, where substitution of threonine with methionine occurs on codon 790. The T790M mutation induces resistance by decreasing the binding of TKI's to the ATP binding domain. Other secondary mutations causing resistance include D761Y, T854A and L747S, which arise subsequent to the EGFR TKI sensitizing L858R mutation [4]. Recent studies indicate that resistance may be due to activation of alternative signalling pathways [13].

Acquired resistance due to the mutations described above can be overcome by irreversible EGFR TKI's, such as Afatinib and Dacomitinib, which are second generation irreversible EGFR TKI's. Dacomitinib is in late stages of clinical development and Afatinib has been approved for clinical use for NSCLC. The second generation irreversible TKI's have some advantages over the first generation TKI's, such as higher affinity for the EGFR TK domain and longer suppression of ErbB signalling due to irreversible binding. Additionally, these agents are also effective against the T790M mutation, as well as other mutations mentioned above that cause resistance against first generation drugs [14]. Several other second generation TKI's such as PK1166, EKB569, Canertinib, HKI-272, HKI-357, CL-387.785 and BIBW 2992 are currently under investigation [12].

Afatinib is a highly selective anilinoquinazol derivative and a first

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line irreversible ErbB inhibitor, which blocks the TK domain of EGFR in patients with EGFR and HER2 gene mutations. Dacomitinib is also an irreversible TKI for HER1, HER2, and HER4, and is effective in gefitinib resistant tumor cells and in patients with T790M or HER2 mutations, but has limited activity against KRAS mutations [14].

Clinical Trials

There are multiple ongoing clinical trials for new anti-EGFR MAB's, such as panitumumab and matuzumab, and new irreversible TKI's such as dacomitinib. The purpose of these clinical trials is to demonstrate improved efficacy and safety, in comparison to the therapies already in the market. Additionally, clinical trials are also being conducted to investigate the efficacy of previously approved drugs, such as erlotinib and gefitinib, in combination with other drugs, radiation therapy and adjuvants in an attempt to overcome the secondary EGFR mutation resistance and achieve increased efficacy.

Since targeting multiple pathways is more effective in preventing drug resistance and reducing tumorigenicity, current clinical studies also include drugs that target multiple signalling pathways, such as ZD6474 (vandetanib), which inhibits EGFR and VEGFR activity, and BMS-690514, which is an inhibitor of EGFR, HER-2 and VEGFR [4]. In a study of 60 patients with NSCLC, BMS-690514 administration resulted in disease control in 39% of erlotinib naïve patients and 22% of erlotinib failures. BMS-690514 was also observed to be efficient in patients with wild-type EGFR, T790M-EGFR, and KRAS mutations [4].

Clinical trials involving combinatorial therapies of gefitinib with BKM-120, PF-02341066 with PF-00299804, and afatinib with nimotuzumab, all of which are currently in Phase I trials, are also ongoing for treatment against EGFR TKI resistance. Pemetrexed Disodium and Carboplatin/Cisplatin with or without Erlotinib Hydrochloride are in Phase II clinical trials [15].

Clinical trials with monotherapy using Icotinib or PF-00299804 (dacomitinib) are currently in Phase II and Phase III clinical trials. Clinical trials with dacomitinib, in which 188 patients were randomly assigned and received 45mg dacomitinib once daily, showed good results. Median progression free survival (PFS) was improved in patients having KRAS wild type tumors or KRAS wild type/EGFR wild type tumors in comparison to patients treated with erlotinib. Median overall survival (OS) was 9.53 months, which is improved when compared to erlotinib treated patients which has median OS of 7.44 months [15].

Combination therapies using anti-EGFR MAB's and EGFR TKI's have received more attention in recent trials, and an estimated 200 studies are currently being carried out. Many studies also include the combination of these drugs with standard chemotherapy. Some of the current clinical trials involve anti-EGFR MAB's, such as cetuximab, followed by adjuvant treatment with chemoradiation or combinatorial therapy of cetuximab with Imprime PGG/ Regorafenib/ Afatinib/tivantinib. Phase II/III trials have shown promising activity of cetuximab in HNSCC, generating significantly improved survival in combination with radiotherapy over radiotherapy alone in locally advanced disease. Significantly improved response rates, with little enhancement of toxicity profiles, were also observed in these studies with combination of cetuximab and chemotherapy, when compared to chemotherapy alone, in recurrent/metastatic disease [16,17].

Of interest, a study is currently ongoing to determine the

correlation between c-Met expression and EGFR gene mutation with erlotinib response. In this study, 200 NSCLC patients with histologically or cytologically confirmed stage IV or recurrent NSCLC, who experienced progressive disease after first line chemotherapy, are being recruited. In these patients, c-Met expression will be studied by immunohistochemistry, and c-Met amplification by Silver In-Situ Hybridization and EGFR mutations by real time PCR. This phase IV study, when completed, may provide data for a patient profile responsive to new combinatorial therapy involving c-Met and EGFR inhibitors (Clinicaltrial.gov Identifier: NCT01523340).

Conclusion

Anti-EGFR drugs are rapidly evolving and this editorial attempts to summarize the most recent advances, with emphasis on new developments and future possibilities. Molecularly targeted therapies against EGFR demonstrate efficacy in NSCLC, mCRC and HNSCC, however, the hurdle of drug resistance due to development of new EGFR mutations and mutations in downstream signalling pathways currently limits their effectiveness. First generation EGFR TKI's, which reversibly bind to kinases, have had limited success as, after prolonged use patients have developed TKI resistance, often due to secondary mutations. To overcome this resistance, second generation drugs, which irreversibly bind to RTK, were developed and are currently being investigated. Additional therapeutic agents such as anti-EGFR MAB's have also been developed to target EGFR and increase the PFS of cancer patients. However, these MAB's are often ineffective in patients with mutations in KRAS and BRAF genes. Thus, new MAB's such as panitumumab and matuzumab are currently under investigation.

New clinical trials have revealed that combinatorial therapy improves efficacy of MAB's and TKI's, and further delays the development of resistance. Hence, the combination of MAB's with TKI's/radiation/adjuvant or TKI's with MAB's/chemotherapy/adjuvant/other TKI's are presently under investigation. Further research is also required to determine the optimal dose and duration of combination therapy to minimize adverse side effects.

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