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Preclinical and clinical studies on afatinib in monotherapy and in combination regimens: Potential impact in colorectal cancer

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ABSTRACT

Targeting the epidermal growth factor receptor (EGFR) with monoclonal antibodies (mAbs) or tyrosine kinase inhibitors (TKI) has been an interesting therapeutic strategy because aberrant activation of this receptor plays an important role in the tumorgenesis of many cancer types, including colorectal cancer (CRC). After the initial promising results of EGFR-targeted therapies, therapeutic resistance is a major clinical problem. In order to overcome resistance to these EGFR-targeted therapies, new treatment options are necessary. In contrast to first generation EGFR inhibitors, afatinib (BIBW2992) is a second-generation irreversible ErbB family blocker that inhibits EGFR as well as HER2 and HER4. Consequently, treatment with afatinib may result in a distinct and more pronounced therapeutic benefit. Preclinical studies have reported promising results for afatinib in monotherapy as well as in combination with other drugs in CRC model systems. Furthermore, clinical studies examining afatinib as single agent and in combination therapy demonstrated manageable safety profile. Nevertheless, only limited antitumor activity has been observed in CRC patients. Although several combination treatments with afatinib have already been investigated, no optimal combination has been identified for CRC patients yet. As molecular tumor characteristics have gained increased importance in the choice of treatment, additional studies with biomarker-driven patient recruitment are required to further explore afatinib efficacy in CRC.

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1. Introduction

Colorectal cancer (CRC) is a one of the most prevalent types of cancer worldwide with an incidence that is on the rise, and still with poor prognosis once recurred and/or metastasized. Although surgery remains the cornerstone in treatment of this devastating disease and chemotherapy and irradiation can improve survival rates, almost 50% of all CRC patients will relapse mainly due to the presence of unrecognized microscopic disease at the time of surgery. Therefore, it is imperative to integrate alternative strategies to improve outcome of patients with advanced CRC (Cunningham et al., 2010).

The introduction of targeted therapies is now at the forefront of personalized medicine in cancer treatment. Thanks to our rapidly expanding understanding of the molecular biology of cancer, an increasing number of patients are currently considered as candidates for treatment with molecular targeted pharmaceuticals. Interestingly, aberrant signaling of the epidermal growth factor receptor (EGFR) plays an integral role in the tumorgenesis of many cancer types, including CRC, making it a compelling drug target (Mahipal et al., 2014).

EGFR is a cell surface receptor that belongs to the ErbB tyrosine kinases family. Besides EGFR, also known as HER1 or ErbB1, other members of the ErbB family include HER2 (ErbB2 or Neu), HER3 (ErbB3), and HER4 (ErbB4). Binding of a ligand to the extracellular domain of these receptors leads to receptor homo- and hetero-dimerization that activates intrinsic TK activity resulting in transphosphorylation of specific tyrosine residues within the intracellular domain. As a result, downstream signal transduction pathways, such as the Ras/Raf, the PI3K/Akt, and the Jak2/Stat3 pathways controlling cellular proliferation, differentiation, survival, migration and motility, are activated (Hynes & Lane, 2005).

Abbreviations: AE, adverse events; CLX, cell line xenograft; CR, complete response; (m)CRC, (metastatic) colorectal cancer; EGFR, epidermal growth factor receptor; GI, gastrointestinal; HNSCC, head and neck squamous cell carcinoma; mAbs, monoclonal antibodies; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; OS, overall survival; PDX, patient-derived xenograft; PEGAuNPs, pegylated gold nanoparticles; Plk1, polo-like kinase 1; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; 5-FU, 5-fluorouracil.

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High expression of EGFR is frequently observed in CRC and several studies suggested that this overexpression of EGFR may be involved in metastasis and poor prognosis (McKay et al., 2002; Huang et al., 2013). Therefore, the inhibition of EGFR-mediated signaling pathways may be a specific therapeutic approach for metastatic CRC (mCRC).

So far, only the monoclonal antibodies (mAbs) cetuximab and panitumumab have been approved for reimbursement in patients with mCRC. Initially, these therapies were given to unselected patient populations, but novel insights suggested that these drugs would be effective only in wild type *RAS* populations (Allegra et al., 2009). However, even in wild type *RAS* disease, 40–60% of mCRC patients fail to respond (Amado et al., 2008; Van Cutsem et al., 2009; Fakih & Wong, 2010; Peeters et al., 2010; Bokemeyer et al., 2011; De Mattos-Arruda et al., 2011), possibly due to specific alterations in EGFR or other factors downstream of EGFR (De Mattos-Arruda et al., 2011; Montagut et al., 2012; Peeters et al., 2013).

After the initial promising results of EGFR-targeted therapies, drug resistance is a major clinical problem (Cohen, 2014). Therapeutic resistance to anti-EGFR therapy may arise from mechanisms that can compensate for reduced EGFR signaling and/or mechanisms that can modulate EGFR-dependent signaling. The precise mechanisms of intrinsic (primary) and extrinsic (acquired) resistance to EGFR inhibitors remain unclear. An improved understanding of the molecular mechanisms responsible for drug resistance will provide tools to increase the response to EGFR blockade and to establish new treatment options to overcome resistance (Boeckx et al., 2013; Leto & Trusolino, 2014). Despite the reported intrinsic and acquired resistance to EGFR-targeting agents, interest in targeting EGFR for the treatment of CRC remains high, with new strategies such as inhibitor combinations and irreversible or multi-targeting inhibitors, currently being evaluated.

In contrast to the first generation EGFR inhibitors cetuximab and panitumumab, afatinib (BIBW2992) is a second-generation irreversible ErbB family blocker that inhibits EGFR as well as HER2 and HER4. Consequently, treatment with afatinib may result in a distinct and more pronounced therapeutic benefit. In this review, we will focus on this second-generation tyrosine kinase inhibitor (TKI) afatinib (BIBW2992) in CRC. Since 2013, afatinib has been approved by the FDA for the first line treatment of metastatic non-small cell lung cancer (NSCLC) patients with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. Currently, preclinical and clinical studies with afatinib focus mainly on two tumor types, i.e. NSCLC and head and neck squamous cell carcinoma (HNSCC). As preclinical research has already demonstrated that combined inhibition of EGFR and HER2 induced tumor regression in CRC models (Bertotti et al., 2011), it is also interesting to further investigate the efficacy of afatinib, inhibiting EGFR, HER2 and HER4, in CRC. Preclinical results reported for afatinib have been encouraging in CRC model systems and therefore exploring its clinical activity in CRC patients might be of interest too. In the following paragraphs, we will present the preclinical and clinical findings of afatinib, with focus on its potential impact in CRC.

2. Pharmacologic characteristics of afatinib

Afatinib is a small molecule orally administered that irreversibly inhibits enzymatically active ErbB family receptors including EGFR, HER2 and HER4 as well as mutant forms such as $EGFR^{L858R}$ and $EGFR^{L858R/T790M}$. It is a second-generation ATP-competitive anilinoquinazoline derivate harboring a reactive acrylamide group that binds covalently to specific cysteine residues within the ATP binding domain of different ErbB family receptors. Due to its irreversible binding, the ATP binding site is permanently blocked and downstream signaling cascades remain inhibited (Li et al., 2008; Solca et al., 2012). Preclinical studies have demonstrated that the half-maximal inhibitory concentration (IC_{50}-value) of afatinib for EGFR, HER2 and HER4 kinases is respectively 0.5 nM, 14 nM and 1 nM (Eskens et al., 2008; Li et al., 2008). The irreversible binding of afatinib to HER2 inactivates this preferred dimerization partner of EGFR, thus preventing the formation of the dimer that promotes the receptor's tyrosine kinase activity (Ou, 2012; Giordano et al., 2016). Furthermore, irreversible, covalent binding of afatinib induces prolonged suppression of the receptor-kinase activity as kinase activity is inhibited until new receptors are synthesized (Spicer & Rudman, 2010).

Since CRC tumors are generally not depending on a single oncogenic signaling pathway for their survival and growth, single inhibition of the EGFR pathway is unlikely to be as effective as blocking signaling mediated through the ErbB family (Hickish et al., 2014). Consequently, given its potent activity against multiple ErbB family receptors, afatinib may provide advantages over other EGFR-targeting agents in CRC.

3. Preclinical studies of afatinib in colorectal cancer

3.1. Studies on afatinib monotherapy

Preclinical studies have demonstrated that afatinib displays antiproliferative activity in several human CRC cell lines (Khelwatty et al., 2011; Poindessous et al., 2011; Gamba et al., 2015; Kavuri et al., 2015; Kloth et al., 2015; Leto et al., 2015). Similarly to cell lines from other tumor types, afatinib caused an increased induction of apoptotic cell death in a panel of CRC cell lines. In these CRC cells, apoptotic cell death by afatinib was described to be associated with induction of mitochondrial toxicity, which could cause permeabilization of the mitochondrial outer membrane and hence cytochrome c release for induction of apoptosis (Guan et al., 2014). Furthermore, treatment of the CRC cell lines with afatinib leads to an arrest in the sub-G_0/G_1 phase of the cell cycle, which was followed by a reduction in the proportion of cells in the G_1, S and G_2/M phase. This was attributed to blocking of the constitutive activation of the PI3K/Akt and MAPK/ERK signaling pathways by afatinib (Schutze et al., 2007; Khelwatty et al., 2011; Gamba et al., 2015). In addition, the cell cycle arrest of afatinib-treated CRC cells was also associated with upregulation of the cyclin-dependent kinase inhibitor $p27^{KIP1}$, due to interruption of constitutively active PI3K function (Busse et al., 2000).

Similarly, afatinib monotherapy also induced apoptosis and inhibited cell growth in in vivo studies using human tumor xenograft mouse models of CRC (Poindessous et al., 2011; Guan et al., 2014; Leto et al., 2015), which was in line with studies in xenograft mouse models of other cancer types such as HNSCC and NSCLC (Schutze et al., 2007; Perera et al., 2009; Takezawa et al., 2010, 2012). Of particular interest was that Leto et al. observed reduced tumor growth in a HER2-amplified mCRC patient-derived xenograft model (Leto et al., 2015), which was also seen in a HER2-overexpressing cell line xenograft model (Guan et al., 2014). These findings led to the hypothesis that HER2 expression might play an important role in response to afatinib treatment in CRC, which will be discussed in more detail below.

3.2. Studies on afatinib in combination therapy

3.2.1. Afatinib plus chemotherapeutic agents

Due to differences in the mode of action, superior growth inhibition may be achieved when cells are treated with a combination of afatinib plus chemotherapeutic agents. Besides increased efficacy, therapeutic resistance to single agent treatment can be hampered by combination therapy. As a result, different combination therapy regimens have been investigated in a preclinical setting and are listed in Table 1.

3.2.1.1. Afatinib plus antimitotic drugs. Targeting mitosis is an important and validated approach for cancer therapy. For instance, taxanes and vinca alkaloids are currently used to treat a broad variety of cancer types. Both exert their antitumor activity by disrupting microtubule polymerization, which leads to mitotic arrest and cell death (Rowinsky, 1997). However, these drugs are ineffective in certain cancer types, including CRC. Therefore, combining afatinib with taxanes (such as

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