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EGFR Targeted Therapies and Radiation: Optimizing Efficacy by Appropriate Drug Scheduling and Patient Selection

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Abstract

The epidermal growth factor receptor (EGFR) plays an important role in tumor progression and treatment resistance for many types of malignancies including head and neck, colorectal, and nonsmall cell lung cancer. Several EGFR targeted therapies are efficacious as single agents or in combination with chemotherapy. Given the toxicity associated with chemoradiation and poor outcomes seen in several types of cancers, combinations of EGFR targeted agents with or without chemotherapy have been tested in patients receiving radiation. To date, the only FDA approved use of an anti-EGFR therapy in combination with radiation therapy is for locally advanced head and neck cancer. Given the important role EGFR plays in lung and colorectal cancer and the benefit of EGFR inhibition combined with chemotherapy in these disease sites, it is perplexing why EGFR targeted therapies in combination with radiation or chemoradiation have not been more successful. In this review we summarize the clinical findings of EGFR targeted therapies combined with radiation and chemoradiation regimens. We then discuss the interaction between EGFR and radiation including radiation induced EGFR signaling, the effect of EGFR on DNA damage repair, and potential mechanisms of radiosensitization. Finally, we examine the potential pitfalls with scheduling EGFR targeted therapies with chemoradiation and the use of predictive biomarkers to improve patient selection.

Keywords

Epidermal growth factor receptor; EGFR; chemoradiation; radiation; combined modality therapy; personalized medicine

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Conflicts of Interest Statement

Drs. Lawrence and Nyati hold a patent (application #20120190622) for “Inhbitors of the Epidermal Growth Factor Receptor-Heat Shock 90 Protein Interactions”. They also have a company named Pi Squared Therapeutics related to this patent. The authors have no other conflicts of interest to report.

1. Introduction

The epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase belonging to the ErbB family. EGFR consists of an extracellular domain, a single transmembrane region, and a cytoplasmic kinase domain (Gullick et al., 1985). There are several known ligands for EGFR including EGF, TGFα, HB-EGF, amphiregulin, betacellulin, epigen, and epiregulin (Linggi et al., 2006). Upon ligand binding, EGFR forms a dimer and specific tyrosine residues are phosphorylated promoting signal transduction (Uberall et al., 2008) through many pathways including PI3k/Akt (Hennessy et al., 2005), Ras-MAPK (Nishinaka et al., 2001, Sebolt-Leopold et al., 2004), STAT (Schmidt-Ullrich et al., 1997, Bowman et al., 2000), and PLCγ (Oliva et al., 2005). Activation of these pathways promotes several cellular processes including proliferation, migration and invasion, transformation, differentiation, and angiogenesis (Mendelsohn et al., 2000).

Due to its important role in cell proliferation and other cellular processes, EGFR is an attractive target for cancer therapy. Overexpression or upregulation of EGFR is seen in many types of malignancies including lung (Ciardiello et al., 2001, Herbst et al., 2003), head and neck (Grandis et al., 1993), esophageal (Mukaida et al., 1991), and colorectal cancers (Moroni et al., 2005). Several EGFR targeted drugs are FDA approved for clinical use including the antibodies cetuximab and panitumumab and small molecule inhibitors erlotinib and afatinib. The use of EGFR targeted therapies is standard of care in subsets of patients with metastatic colorectal cancer, metastatic nonsmall cell lung cancer, and locally advanced head and neck cancer.

Concurrent administration of chemotherapy with radiation therapy has been standard practice since the 1980's. Traditionally, cytotoxic agents such as cisplatin or 5-FU are combined with fractionated radiation therapy in the adjuvant and definitive treatment settings. Combined modality therapy has several potential advantages over radiation alone. These therapies may work synergistically to enhance cell kill through a number of mechanisms. Previous reports have reviewed the potential interactions between radiation and systemic therapy in detail (Steel et al., 1979, Bentzen et al., 2007, Shewach et al., 2007, Morgan et al., 2014, Morris et al., 2014). A consequence of the concurrent administration of chemotherapy with radiation therapy is increased toxicity. For this reason, the use of a systemic radiosensitizing drug targeting a specific pathway more active in cancer cells than normal tissues is an attractive strategy. In this article, we review the completed and ongoing clinical trials that combine EGFR targeted therapies with radiation. We then discuss the interaction between radiation and EGFR signaling and explore potential strategies for optimizing EGFR directed therapies with radiation.

2. Clinical trials with EGFR targeted therapies and radiation

Head and neck cancer

The most successful implementation of an EGFR inhibitor in combination with radiation therapy has been in locally advanced head and neck cancer. Head and neck cancers are frequently driven by EGFR signaling and high expression of EGFR is associated with a poor prognosis (Dassonville et al., 1993, Grandis et al., 1998, Gupta et al., 2002, Ang et al., 2004,

Eriksen et al., 2004) and radioresistance (Bonner et al., 1994, Ang et al., 2002, Harari et al., 2002, Liang et al., 2003). In a landmark study by Bonner et al., cetuximab improved local control and survival in patients with locally advanced head and neck cancer receiving definitive radiation therapy (Bonner et al., 2006, Bonner et al., 2010). On subset analysis, the survival benefit was predominately in younger patients with an oropharynx primary treated with an accelerated radiation course (Bonner et al., 2010). Interestingly, patients who experienced a prominent cetuximab-induced acneiform rash had better outcomes than patients not having this reaction.

Although the Bonner study found a benefit with cetuximab in locally advanced head and neck cancer, the results are difficult to interpret because patients on the control arm received radiation therapy alone. Current standard of care for locally advanced head and neck cancer is radiation therapy with concurrent chemotherapy (Pignon et al., 2000). To address this issue, several trials have been performed to study cetuximab in combination with chemoradiation. RTOG 0522 was a phase III study that randomized patients to cisplatin based chemoradiation with or without cetuximab (Ang et al., 2014). This trial found no improvement in progression free survival with the addition of cetuximab. Additionally, treatment with cetuximab plus chemoradiation resulted in more toxicity than chemoradiation alone.

Another question that has been explored is whether or not cetuximab can replace chemotherapy as a radiation sensitizer in a specific subset of patients. GORTEC (TREMPLIN, NCT00169247) published the results from a randomized phase II study where patients with cancer of the larynx or hypopharynx received induction chemotherapy followed by chemotherapy or cetuximab concurrent with radiation. There was no significant difference between the two arms suggesting cetuximab could replace chemotherapy in this setting; however, the outcomes of both arms were not better than that of a previous trial with induction chemotherapy followed by radiation alone in a similar patient population (Lefebvre et al., 2013). A recently completed four arm phase II/III study (2×2 factorial design) from Italy examined the role of induction chemotherapy and concurrent cetuximab or chemotherapy with radiation (NCT01086826). Results presented at ASCO 2012 and 2013 found a similar response rate in the patients who received cisplatin/5-FU or cetuximab with radiation therapy (complete response 36% versus 39%) and no difference in median overall survival (44.7 months in both groups) (Ghi et al., 2013). It should be noted that the primary endpoint for the chemoradiation versus cetuximab-radiation comparison was grade 3–4 in field toxicity and not response rate or survival. Surprisingly, toxicity was not different in patients receiving cetuximab with radiation compared to chemotherapy with radiation (Ghi et al., 2012).

Additional studies comparing chemoradiation to cetuximab with radiation are ongoing. RTOG 1016 is a phase III study that recently completed patient accrual. On this study, patients with locally advanced head and neck cancer are randomized to cetuximab or cisplatin with radiation therapy. This study only includes patients with HPV positive head and neck cancer, which is associated with a better prognosis and is potentially more sensitive to EGFR directed therapies (NCT01302834). Additionally, in Italy there is an ongoing randomized phase II clinical trial studying the use of cisplatin or cetuximab with

radiation (NCT01216020) and the Trans-Tasman Radiation Oncology Group is running a phase III study comparing weekly cisplatin to weekly cetuximab with radiation therapy in head and neck cancer patients (TROG 12.01 NCT01855451).

Several other phase III studies with cetuximab in head and neck cancer have recently opened. The ATSCANIII study (NCT01969877) from Sweden is a four arm phase III trial. It examines two different radiation fractionation schemes with concurrent cisplatin or cetuximab. Additionally, a study by the GORTEC (NCT01233843) group in France randomizes patients to concurrent carboplatin with radiation therapy versus induction chemotherapy with docetaxel, cisplatin, and 5-FU followed by concurrent cetuximab and radiation therapy. Additional studies with cetuximab and radiation therapy include RTOG 0920, a phase III study of post-operative radiation with or without cetuximab in locally advanced head and neck cancer patients, and RTOG 1216, (NCT01810913) a three arm phase II/III study of radiation with either docetaxel, docetaxel with cetuximab, or cisplatin in high risk post-operative patients.

In almost all of studies that include cetuximab with radiation therapy, cetuximab is administered with a loading dose of 400 mg/m^2 followed by weekly dosing at 250 mg/m^2. This dosing schedule is based off PK/PD studies and phase I dose escalation studies which show saturation of EGFR binding at 250 mg/m^2 (Robert et al., 2001, Fracasso et al., 2007). Given the complex role EGFR has on the cell cycle, DNA repair, and cell survival/ proliferation pathways, it is unclear if this is the optimal dosing schedule when combined with radiation therapy or chemoradiation therapy. This point is discussed in greater detail below.

In addition to cetuximab, results from studies using the fully humanized monoclonal anti-EGFR antibody panitumumab have recently been reported. CONCERT-1 was a randomized phase II study where patients with locally advanced head and neck cancer received chemoradiation therapy with or without panitumumab (Mesia et al., 2015). Local regional control was not significantly different between the two groups (2 year locoregional control 68% without panitumumab versus 61% with panitumumab) and there was higher toxicity with panitumumab (43% vs. 32%). CONCERT-2 was a randomized phase II study where patients with locally advanced head and neck cancer received chemotherapy or panitumumab with radiation (Giralt et al., 2015). The local regional control rate at 2 years was lower but not significantly different with panitumumab (51% panitumumab-RT vs. 61% chemoRT) and the rate of serious toxicity was similar (40% chemoRT vs. 34% panitumumab-RT). Several other trials with panitumumab in head and neck cancer are ongoing including a study by the NCIC that recently finished patient accrual. This phase III study compares cisplatin with standard fractionated radiation therapy and panitumumab with accelerated radiation therapy (NCT00820248).

Nonsmall cell lung cancer

EGFR targeted therapies have become standard of care in a subset of patients with advanced stage nonsmall cell lung cancer. In a landmark study, the small molecule EGFR inhibitor erlotinib improved overall survival in patients with advanced stage NSCLC who had failed chemotherapy (Shepherd et al., 2005). Additionally, the EGFR targeted antibody cetuximab

improved survival in patients with metastatic nonsmall cell lung cancer receiving cisplatin and vinorelbine (Pirker et al., 2009). Subset analyses from several studies demonstrate the benefit of small molecule EGFR inhibitors is limited to patients with tumors harboring specific EGFR mutations and wild type KRAS (Lynch et al., 2004, Paez et al., 2004, Pao et al., 2004, Eberhard et al., 2005). Interestingly, specific acquired EGFR mutations (T790M) also lead to erlotinib resistance (Pao et al., 2005).

Given the success of combining cetuximab with radiation in head and neck cancer and the benefit of EGFR targeted therapies in nonsmall cell lung cancer, several clinical trials have been designed to study the effect of adding erlotinib or cetuximab to chemoradiation in patients with locally advanced nonsmall cell lung cancer. The RTOG performed a phase II study (RTOG 0324) where patients with locally advanced nonsmall cell lung cancer received carboplatin, paclitaxel, and cetuximab with radiation. Two year survival was a very encouraging 49% (Blumenschein et al., 2011). The CALGB completed a randomized phase II study in patients with locally advanced nonsmall cell lung cancer receiving carboplatin, pemetrexed, and radiation therapy with or without cetuximab. There was no difference in 18 month overall survival (58% versus 54%) and increased toxicity was seen in the arm containing cetuximab (Govindan et al., 2011). Additionally, van den Heuvel et al. performed a randomized phase II study with cisplatin and radiation with or without cetuximab in 102 patients with locally advanced nonsmall cell lung cancer. Similar to the CALGB trial, use of cetuximab did not improve overall survival (van den Heuvel et al., 2014).

A very important trial with cetuximab and radiation in NSCLC was RTOG 0617. In this phase III study patients were randomized to radiation therapy and concurrent carboplatin and paclitaxel with or without cetuximab. Similar to the phase II studies, there was no survival benefit with cetuximab (median survival 25.0 versus 24.0 months, HR 1.07) and grade 3 or higher toxicity was increased (86% to 70%). However, on subset analysis patients with increased EGFR expression had improved overall survival with the addition of cetuximab (42 months versus 21 months) (Bradley et al., 2015). The RTOG currently has a phase II study open (RTOG 0839, NCT00979212) where patients are randomized to preoperative chemoradiation therapy with or without panitumumab. A second randomization of consolidative chemotherapy with or without cetuximab on RTOG 0839 was closed in 2010.

Many contemporary trials in nonsmall cell lung cancer have focused on patient selection and the use of small molecule inhibitors. Prior studies in locally advanced and metastatic lung cancer have identified subsets of patients that benefit the most from treatment with EGFR small molecule inhibitors. Massachusetts General Hospital is running a phase II study of afatinib followed by concurrent chemoradiation in EGFR mutant nonsmall cell lung cancer (NCT01553942). An ongoing phase II study from Beijing Cancer Hospital (NCT01391260) is studying the combination of gefitinib with radiation alone in patients with specific EGFR activating mutations. Another phase II study from China randomizes patients with exon 19 or 21 EGFR mutations to cisplatin and etoposide or erlotinib with radiation therapy (NCT01714908). With our evolving ability to properly select patients for EGFR targeted therapy in nonsmall cell lung cancer and the findings from RTOG 0617, the use of anti-EGFR therapies with radiation in lung cancer is still promising

Rectal cancer

EGFR plays a very important role in the progression and treatment of colorectal cancer. This protein is overexpressed in approximately 50–80% of colorectal tumors and EGFR targeted antibodies, such as cetuximab and panitumumab, are effective in advanced stage disease (Cunningham et al., 2004, Van Cutsem et al., 2007, Sorbero et al., 2008, Bokemeyer et al., 2009, Van Custem et al., 2009, Douillard et al., 2010). In rectal cancer, EGFR overexpression is associated with a lower pathologic complete response rate and a worse prognosis in patients receiving neoadjuvant chemoradiation (Azria et al., 2005, Giralt et al., 2005, Li et al., 2006, Kim et al., 2006, Bertolini et al., 2007, Zlobec et al., 2008). Interestingly, unlike nonsmall cell lung cancer, in colorectal cancer EGFR overexpression or specific EGFR activating mutations have not been found to be predictive of response to anti-EGFR therapies (Chung et al., 2005, Hebbar et al., 2006). Due to the clear benefit of preoperative chemoradiation in locally advanced rectal cancer, a number of studies have looked at the role of EGFR targeted therapies in combination with radiation therapy for this disease.

The early phase I and II trials using EGFR targeted therapies in combination with radiation therapy for rectal cancer seemed to produce promising results. These studies used pathological complete response rate (pCR) as a surrogate for outcome. A study by Valentini et al. found a 30% pathologic complete response rate with gefitinib and 5-FU based chemoradiation, which was much higher than what has been seen historically (Valentini et al., 2008). Pinto et al. examined the use of panitumumab with 5-FU and oxaliplatin. In this study the pCR rate was an encouraging 21% (Pinto et al., 2011). McCollum et al. also demonstrated a promising pCR rate of 28% in a phase II study of cetuximab and 5-FU based chemoradiation; however, this rate was not significantly different from the pCR rate of patients on the control arm not receiving cetuximab (McCollum et al., 2014).

Prior studies in patients with advanced stage colorectal cancer have demonstrated that anti-EGFR therapies are not as effective in patients with KRAS mutant tumors (Eberhard et al., 2005, Lievre et al., 2006, Amado et al., 2008, De Roock et al., 2008, Bokemeyer et al., 2009, Van Cutsem et al., 2009). It is possible the trials using chemoradiation discussed above found no benefit because they did not select for the patients most likely to respond to EGFR targeted drugs. Dewdney et al. performed a randomized phase IIB study where patients received capecitabine, oxaliplatin, and radiation therapy with or without cetuximab. The subset of patients with KRAS and BRAF wild type tumors had lower response rates to chemoradiation compared to the reports above and there was no statistically significant difference in the pCR rate (11% versus 9%) between the two treatment arms. However, the secondary end points of radiological response rate and overall survival were improved with cetuximab (Dewndey et al., 2012). More recently, a pooled analysis of two phase II studies (IRIX and ERBIRIX trials), which included patients treated with capecitabine, irinotecan, cetuximab and radiation was performed. Interestingly, this analysis found no benefit with the addition of cetuximab to chemoradiation in patients with KRAS wild type tumors (Kim et al., 2013).

Several ongoing studies are exploring the role of EGFR directed therapies in patients receiving preoperative chemoradiation therapy for rectal cancer. The Southwest Oncology

Group is running an 80 patient phase II study with preoperative capecitabine, oxaliplatin, cetuximab and radiation (S0713, NCT00686166). Also, the Zhejiang Cancer Hospital is performing a study with nimituzumab, capecitabine, oxaliplatin, and radiation (NCT01899118). Given the importance of patient selection in the advanced stage setting, proper patient selection may be necessary to demonstrate a benefit in patients with locally advanced rectal cancer receiving chemoradiation therapy.

Esophageal cancer

In esophageal cancer, EGFR overexpression is common and associated with a poor prognosis (Chen et al., 1991, Mukaida et al., 1991). Therefore, EGFR has been identified as a potential molecular target in this disease. A 65 patient phase II study from Brown University and the University of Maryland concluded that treatment with carboplatin, paclitaxel, and cetuximab was well tolerated. This study had a clinical complete response rate of 70%, which was very encouraging (Safran et al., 2008). ECOG 2205 was a phase II study of cetuximab, oxaliplatin, 5-FU and radiation in patients with resectable esophageal cancer. Unfortunately, in this study 4 of the 22 patients who underwent surgery died from complications (Gibson et al., 2010). The Southwest Oncology Group also completed a phase II study in patients with locally advanced, unresectable esophageal cancer receiving cetuximab, cisplatin, irinotecan, and radiation therapy. Similar to ECOG 2205, this combination was poorly tolerated with a treatment related mortality rate of 10% (Tomblyn et al., 2012). Conflicting with these findings, the SAKK 75/06 study concluded that adding cetuximab to cisplatin/docetaxel with radiation was not associated with increased postoperative mortality (Ruhstaller et al., 2011). Given the high rate of toxicity in many of these trials, less intensive regimens incorporating EGFR inhibitors need to be studied. The Hoosier Oncology Group completed a phase II study of cetuximab and radiation (without chemotherapy) in patients with resectable esophageal cancer. Pathological CR rates were promising at 37% and treatment was well tolerated (Becerra et al., 2013).

More recently, two randomized phase II studies with cetuximab and chemoradiation therapy for esophageal cancer have been reported. RTOG 0436 was a phase II study that evaluated the addition of cetuximab to cisplatin and paclitaxel in patients with locally advanced esophageal cancer treated without surgery (Suntharalingam et al., 2014). The addition of cetuximab did not improve overall survival at 2 years (44% versus 42%). Similarly, the SCOPE1 trial was a randomized phase II study were patients received definitive chemoradiation with 5-FU/cisplatin with or without cetuximab. Use of cetuximab was associated with increased treatment failure, decreased survival, and worse toxicity (Crosby et al., 2013).

Several other trials of EGFR inhibitors and radiation therapy in esophageal cancer are ongoing. A phase II study from Germany randomizes patients receiving chemoradiation to cisplatin and 5-FU with or without cetuximab (NCT01787006). The Swiss Group for Clinical Cancer Research has a phase III study open where patients receive cisplatin and docetaxel with or without cetuximab followed by surgery (NCT01107639). There is also an open phase III study in China where patients with esophageal cancer are randomized to cisplatin, paclitaxel, and radiation with or without erlotinib (NCT00686114). In summary,

the role of anti-EGFR targeted therapies in combination with chemoradiation for esophageal cancer is not well defined at this time. The phase II studies reported so far are concerning for high toxicity and a lack of efficacy.

Other disease sites

In addition to the disease sites discussed above, EGFR targeted therapies and radiation have been studied in cancers originating from the anal canal and cervix. Similar to head and neck cancer, in anal cancer overexpression of EGFR is common and KRAS mutations are rare (Paliga et al., 2012). Additionally, HPV is responsible for up to 90% of anal cancers (www.cdc.gov/cancer/hpv/statistics). Since HPV positive head and neck cancer patients may benefit from cetuximab, its use in anal cancer is promising. Several studies are ongoing in this disease site. The AIDS Malignancy Clinical Trials Consortium is running a phase II study with cisplatin, 5-FU, cetuximab, and radiation therapy in patients with HIV and anal cancer (NCT00324415). ECOG currently has a phase II study open with cetuximab and chemoradiation in patients with stage I–III anal cancer (NCT00316888). The FFCD also has an open phase I/II trial in anal cancer where patients receive 5-FU, mitomycin C, and panitumumab (NCT01581840). Another study from Switzerland is examining the use of capecitabine, 5-FU, and panitumumab in this patient population (NCT01843452). Given the role EGFR plays in anal cancer and the toxicities associated with mitomycin C and cisplatin, the use of EGFR targeted agents in this disease is promising.

Cervical cancer is another potential disease for the addition of EGFR targeted therapies to chemoradiation. Similar to head and neck cancer, in cervical cancer EGFR is commonly overexpressed and overexpression is associated with a worse prognosis (Soonthornthum et al., 2011). Additionally, HPV plays a very important role in this disease and chemoradiation is the primary treatment modality for many patients. The GOG recently completed a 64 patient phase I study with cetuximab, cisplatin, and radiation in stage I–III cervical cancer (GOG-9918, NCT00104910). Results from this study have not been reported. To date, the use of EGFR targeted therapies for cervical cancer remains an area of active research.

Multiple phase I studies and phase II studies with radiation therapy and an EGFR targeted agent have been completed or are underway in several other disease sites. A full summary of each of these trials and disease sites is beyond the scope of this review.

3. Interaction of EGFR with Radiation and Chemotherapy

Interaction of EGFR with radiation therapy

The interaction between EGFR signaling and radiation was first described over 20 years ago. Early studies demonstrated that prolonged exposure to EGF increases the cytotoxic effects of radiation (Kwok et al., 1989, Bonner et al., 1994). Additionally, the expression of EGFR increases after radiation therapy (Peter et al., 1993) and the cytotoxic effect of radiation is inversely correlated with EGFR expression (Sheridan et al., 1997, Akimoto et al., 1999, Lammering et al., 2001, Milas et al., 2003, Milas et al., 2004). Translational studies performed in the 1990’s further demonstrated that EGFR overexpression is associated with radioresistance in patients (Miyaguchi et al., 1991, Zhu et al., 1996). These

pioneering studies paved the way for the use of EGFR inhibitors with radiation therapy in the clinic.

The mechanism of radiosensitization with EGFR inhibitors is complex. Three distinct phases of EGFR's role in the radiation response have been elucidated. These phases include: EGFR's role in DNA repair, the activation of pro-survival pathways, and enhanced cell proliferation (Huang et al., 2000, Nyati et al., 2006, Chen et al., 2007). Given the observation that treatment with EGFR directed therapies leads to G1 arrest in most cell types (Peng et al., 1996, Di Gennaro et al., 2003), one explanation of radiosensitization is that the cytostatic effect of EGFR inhibition limits tumor repopulation during a course of fractionated radiation therapy. Other studies show the role behind radiosensitization may be more complex than the induction of cell cycle arrest. For example, studies by Huang and Harari found that cetuximab promoted radiation induced apoptosis (Huang et al., 1999, Harari et al., 2002), impaired sublethal DNA damage repair, and affected the nuclear translocation of DNA-PK (Huang et al., 2000). Interestingly, the effect of radiation on EGFR activation appears to be most pronounced in confluent or serum starved cells (Schmidt-Ullrich et al., 1997). More recent studies by Ahsan et al. found that quiescent and proliferating cell lines differ in their radiosensitivity and response to EGFR inhibition. Specifically, in quiescent cells radiation induces a brief period of EGFR activation leading to S phase progression, impaired DNA repair, and enhanced cell death (Ahsan et al., 2009). Thus, EGFR inhibition during the first few hours after radiation may actually protect cells, whereas 24 hours after inhibition, the combined effects of G1 arrest and inhibition of DNA repair might produce sensitization.

The majority of kinases have functions beyond their kinase activity (Rauch et al., 2011). Given the complex role EGFR plays in several cellular locations, inhibition alone may not be the optimal means to target this protein. In addition to forming a homodimer with itself, EGFR can dimerize with other receptor tyrosine kinases including Erb2, Erb3, and c-Met leading to downstream signal transduction (Mueller et al., 2010, Ahsan et al., 2014). Additionally, EGFR binds to the chaperone protein hsp90 promoting stability of the inactivated receptor (Ahsan et al., 2013). Recent studies suggest novel drugs that degrade EGFR are more effective than drugs that inhibit EGFR in preclinical models (Haglund et al., 2003, Zhuang et al., 2003, Feng et al., 2007, Kirisits et al., 2007, Ahsan et al., 2009, Ahsan et al., 2010). Due to the multiple functions of EGFR within a cell, blocking activation with antibodies or small molecules may not be the optimal means to target this protein.

Nuclear EGFR

Although EGFR is typically depicted as a cell surface receptor, this protein is involved in several nuclear processes. Nuclear EGFR is prognostic in several types of cancer including head and neck (Psyrri et al., 2005, Psyrri et al., 2008), breast (Lo et al., 2005, Hadzisejdic et al., 2010), esophageal (Hoshino et al., 2007), and ovarian cancer (Xia et al., 2009). Additionally, resistance to radiation therapy is related to nuclear EGFR expression (Chen et al., 2007). Nuclear EGFR signaling plays an important role in gene expression (Wang et al., 2009, Hadzisejdic et al., 2010, Huo et al., 2010). EGFR is a transcriptional co-activator for many cancer related genes including cyclin D1 (Lin et al., 2001), COX2 (Lo et al., 2010), c-

Myc (Jaganathan et al., 2011), aurora kinase A (Huang et al., 2008), and nitric oxide synthase (Lo et al., 2005).

In addition to gene regulation, nuclear EGFR plays an important role in DNA repair (Bandyopadhyay et al., 1998, Dittmann et al., 2005). Radiation promotes the internalization and transport of EGFR by caveolin-1 leading to the activation of DNA-PK in response to DNA damage (Dittmann et al., 2008, Dittmann et al., 2010, Liccardi et al., 2011). DNA-PK is a vital kinase for nonhomologous end joining repair. Interestingly, inhibition of EGFR with cetuximab attenuates EGFR nuclear import and suppresses DNA-PK activity (Dittmann et al., 2005). EGFR also affects the DNA repair proteins XRCC1 and ATM (Debucquoy et al., 2010) and interacts with the ribonuclease PNPase through DNA-PK mediated phosphorylation leading to increased radioresistance (Yu et al., 2012). Finally, nuclear EGFR phosphorylates PCNA which plays an important role in recruiting DNA polymerase, DNA ligase, and other DNA repair proteins (Wang et al., 2006, Stoimenov et al., 2009).

Interestingly, nuclear EGFR also plays a role in resistance to EGFR targeted therapies. Cell lines that develop cetuximab resistance after prolonged exposure are characterized by high levels of nuclear EGFR (Wheeler et al., 2008, Li et al., 2009). Additionally, nuclear EGFR is associated with resistance to gefitinib (Kwak et al., 2005, Nishimura et al., 2008) and this effect can be attenuated by AKT inhibition (Huang et al., 2011). Cells resistant to gefitinib also express high levels of BCRP and other ATP-binding cassette transporters associated with drug resistance (Nakamura et al., 2006, Shi et al., 2009)

Interaction of EGFR with chemotherapy

Extensive effort has been directed towards combining EGFR targeted therapies with chemotherapy. The interaction between chemotherapy and EGFR inhibitors involves several potential mechanisms including attenuation of EGFR signaling pathways, induction of cell cycle arrest, and impairment of DNA repair. Given that the focus of this article is on EGFR targeted agents with radiation and chemoradiation, we will briefly discuss the interaction between EGFR inhibitors and chemotherapy.

Similar to radiation therapy, EGFR signaling is activated in response to chemotherapeutic agents including 5-FU, gemcitabine (Chun et al., 2006), cisplatin (Benhar et al., 2002), and taxanes (Sumitomo et al., 2004). The mechanism behind chemotherapy induced EGFR phosphorylation is not fully understood and is possibly different for each drug class. For example, cisplatin induces nuclear translocation of EGFR (Dittmann et al., 2005). It is postulated that this action leads to chemoresistance through a DNA-PK mediated mechanism (Liccardi et al., 2011). Other reports have demonstrated that cisplatin induced EGFR activation is dependent on Src (Benhar et al., 2002). Also, gefitinib attenuates the repair of cisplatin induced DNA crosslinks (Friedmann et al., 2004, Friedmann et al., 2006) and reduces DNA-PK activity and expression (Magne et al., 2003, Friedmann et al., 2006).

4. Scheduling of EGFR inhibitors with radiation and patient selection

Importance of treatment schedule with EGFR targeted therapies

The optimal dosing schedules of EGFR targeted therapies with chemoradiation or radiation therapy are yet to be determined. The most successful implementation of an EGFR targeted drug and radiation has been in head and neck cancer. In the Bonner trial, cetuximab added to radiation alone improved survival (Bonner et al., 2010). Additionally, multiple studies have demonstrated a benefit when cetuximab or other EGFR targeted therapies are added to chemotherapy. Given these results, it is perplexing why the combination of EGFR inhibitors with chemoradiation has been a failure so far.

Similar to radiation, the effect of EGFR inhibition on the cell cycle plays an important role in the interaction between EGFR directed drugs and chemotherapy. Many chemotherapy agents are more effective in cells that are actively dividing. Given the G1 arrest seen after EGFR inhibition, it is possible EGFR inhibitors are antagonizing the effects of chemotherapy when administered simultaneously. Supporting this point are studies showing that treatment with gemcitabine followed by gefitinib is more cytotoxic than the reverse sequence (Chun et al., 2006). The sequence dependence of chemotherapy and EGFR inhibition has also been demonstrated with other chemotherapy agents including cisplatin and oxaliplatin (Xu et al., 2003, Azzariti et al., 2004, Morelli et al., 2005). Given the lack of efficacy in most of the clinical trials discussed above and the clear sequence dependence seen in preclinical studies, pilot studies using alternative schedules of chemoradiation therapy with EGFR directed therapies are greatly needed prior to investing large amounts of resources into phase II/III clinical trials.

To improve the effectiveness of EGFR directed therapies with chemoradiation both proper patient selection and proper drug scheduling are needed. As discussed above, preclinical studies demonstrate that the sequencing of EGFR inhibitors with chemotherapy and with radiation therapy affect sensitivity and synergy. Given the G1 arrest associated with EGFR inhibition, it would theoretically be more effective if EGFR targeted agents are sequenced after chemotherapy versus before (Morelli et al., 2005). There are several issues with proper scheduling of EGFR inhibitors. First off, the most commonly used drug with radiation, cetuximab, has a long half-life (approximately 97–114 hours). Drugs with shorter half-lives may be needed for proper sequencing with daily radiation treatments. Additionally, it is unclear if the standard dosing of cetuximab is appropriate when combined with concurrent chemoradiation therapy and if this dosing is optimal for each individual due to patient heterogeneity.

An effective biomarker of EGFR activity would be helpful to confirm appropriate target inhibition. In the Bonner study the development of an acneiform rash was associated with a more favorable response (Bonner et al., 2010). This finding suggests that variable patient factors alter cetuximab’s pharmacokinetics and pharmacodynamics. It is likely that some patients require a higher dose than others to achieve the optimal clinical effect. Potential variations on chemoradiation therapy regimens incorporating an EGFR inhibitor are described in figure 1.

Patient selection for EGFR targeted therapies in combination with chemoradiation

The Bonner Study, RTOG 0617, and the EXPERT-C study demonstrate the importance of patient selection when using EGFR targeted therapies with radiation. In the Bonner Study the benefit of cetuximab was limited to a subset of patients with an oropharynx primary (Bonner et al., 2010). In RTOG 0617 a benefit from cetuximab was only seen in the subset of patients expressing high levels of EGFR (Bradley et al., 2015). Additionally, in the EXPERT-C study patients with KRAS/BRAF wild type rectal cancers benefited from the addition of cetuximab to chemoradiation (Dewdney et al., 2012)

In the advanced stage setting, several predictive biomarkers related to EGFR inhibitors have been discovered. Interestingly, the criteria for predicting response is different for each disease site. In lung cancer, specific EGFR mutations determine sensitivity and resistance to small molecule inhibitors (Pao et al., 2004, Lynch et al., 2004, Paez et al., 2004, Pao et al., 2005). In colorectal cancer, increased EGFR gene copy number may be predictive of response to cetuximab (Moroni et al., 2005). Interestingly, increased gene copy number does not correlate with overexpression (Moroni et al., 2005, Cappuzzo et al., 2008) and neither EGFR mutations nor EGFR overexpression are predictive of response. In colorectal cancer and other malignancies, alterations of several downstream proteins are predictive of resistance to EGFR directed therapies. The most robust is KRAS mutational status (Eberhard et al., 2005, Lievre et al., 2006, De Roock et al., 2008, Amado et al., 2008); however, BRAF, PI3K, or PTEN mutations and c-Met or Her2 overexpression are also associated with anti-EGFR therapy resistance (reviewed in Misale et al., 2014). Almost all of the findings above are from trials with EGFR directed therapies in combination with chemotherapy. It is not clear if the same predictors of response apply in the radiation and chemoradiation settings. The table included in this report lists several of the known patient and tumor related factors associated with sensitivity and resistance to EGFR directed therapies.

Another challenge with EGFR inhibitors is that prolonged treatment with these drugs leads to resistance through several of the mechanisms described above. In nonsmall cell lung cancer, treatment with erlotinib is associated with the development of/selection for cells with a resistant T790M EGFR mutation (Pao et al., 2005). Recently, drugs have been developed to target cells harboring a T790M EGFR mutation. AZD9291 is an irreversible tyrosine kinase inhibitor with selectivity against mutant forms of EGFR (Cross et al., 2014, Finlay et al., 2014). This drug was found to be effective in patients with nonsmall cell lung cancer harboring the T790M EGFR mutation who had progressed on treatment with EGFR small molecule inhibitors (Janne et al., 2015). Interestingly, resistance to AZD9291 develops through another acquired EGFR mutation (C797S), illustrating the complexity and challenges associated with anti-EGFR therapy (Thress et al., 2015).

For EGFR targeted therapies to be successful, both proper patient selection and monitoring for early resistance are needed to optimize efficacy. The development of novel agents which target EGFR by different mechanisms such as receptor degradation and inhibition of dimerization may also be necessary to overcome resistance. Additionally, combinations of EGFR targeted therapies with other novel agents, such as drugs targeting hsp90, may improve the efficacy of these therapies (Ahsan et al. 2013).

Conclusions

Given the important role EGFR plays in several types of cancer and the well-defined role of EGFR in the response to radiation therapy, this receptor remains an important target for radio- and chemoradiosensitization. Next generation EGFR targeted therapies may allow for more control over proper sequencing with chemoradiation therapy. Additionally, agents that target EGFR by novel mechanisms may improve the effectiveness of these approaches. Lastly, discovery of predictive biomarkers related to EGFR targeted radiosensitization will allow for the selection of patients most likely to benefit from this strategy.

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Abbreviations

DM	distant metastasis
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
OS	overall survival
pCR	pathologic complete response
PFS	progression free survival

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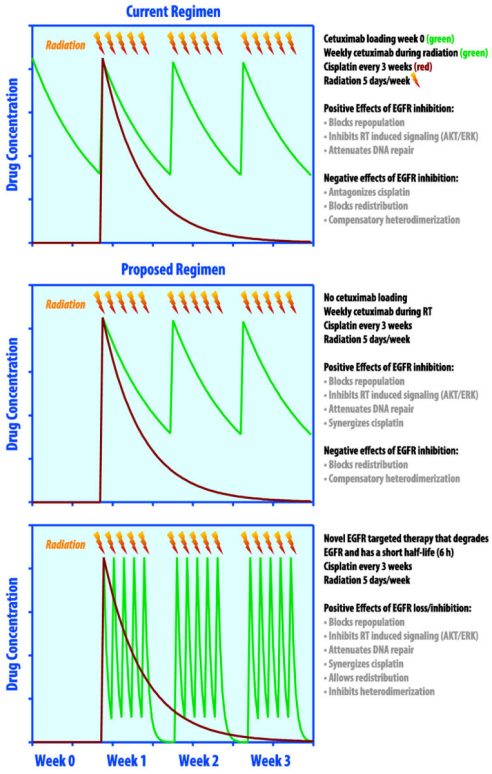

Figure 1.

Scheduling of EGFR targeted therapies with chemoradiation. EGFR inhibitors interact with radiation therapy through attenuation of DNA repair, inhibition of radiation induced pro-survival signaling pathways such as PI3k/AKT and MAPK/ERK, and by blocking tumor repopulation in between radiation fractions (Nyati et al., 2006, Chen et al., 2007, Huang et al., 2000). Top panel, treatment schedule used in RTOG 0522 (Ang et al., 2014). Shown are the concentrations of cetuximab (green) and cisplatin (red) as a function of time over the first 4 weeks of treatment. The loading dose of cetuximab theoretically antagonizes the effect of cisplatin (Morelli et al., 2005) and the long half-life of cetuximab potentially blocks redistribution of tumor cells to a more radiosensitive phase of the cell cycle (Peng et al., 1996, Di Gennaro et al., 2003). Additionally, compensatory heterodimerization of EGFR with another tyrosine kinase (e.g. c-Met, her2) can occur. Middle panel, by eliminating the loading dose of cetuximab the antagonistic effect of EGFR inhibition preceding cisplatin is mitigated. Bottom panel, by using a novel EGFR targeted agent that degrades rather than inhibits EGFR with a short half-life (6 hours) dosed daily after radiation, the negative effects of EGFR inhibition on cell cycle distribution can further be diminished while preserving the beneficial effects of these drugs.

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Table 1

Study	Disease	Treatment arms	N	Results (red indicates statistically significant result)	Toxicity/Notes
Alabama-Birmingham Bonner et al., 2006, 2010 Phase III	Head and neck cancer All sites	**1** Radiation alone **2** Radiation with cetuximab	424	3 y locoregional control: 34% RT vs. 47% RT + cetuximab Median OS: 2.4 y RT vs. 4.1 y RT + cetuximab 5 y OS: 36% RT vs. 46% RT + cetuximab	Grade 2+ rash: 61% with cetuximab No difference in QOL
RTOG 0522 Ang et al., 2014 Phase III	Head and neck cancer All sites	**1** Radiation with cisplatin **2** Radiation with cisplatin + cetuximab	895	3 y OS: 73% chemoRT vs. 76% chemoRT + cetuximab 3 y PFS: 61% chemoRT vs. 59% chemoRT + cetuximab 3 y DM: 13% chemoRT vs. 10% chemoRT + cetuximab	Grade 3–4 mucositis higher with cetuximab More skin toxicity with cetuximab
TREMPLIN Lefebvre et al., 2013 Randomized Phase II	Head and neck cancer Larynx Hypopharynx	Induction docetaxel/cisplatin, if response: **1** Radiation with cisplatin **2** Radiation with cetuximab	116	3 mo larynx preservation: 95% RT + cisplatin vs. 93% RT+ cetuximab 18 mo OS: 92% RT + cisplatin vs. 89% RT+ cetuximab	Treatment compliance higher in cetuximab arm Similar results with induction chemo followed by RT alone
Italian Study Group Ghi et al. 2012, 2013 Randomized Phase II	Head and neck cancer All sites	2×2 factorial design **A.** Plus or minus induction docetaxel/cisplatin/5-FU **B.** Radiation with cisplatin/5-FU or cetuximab	421	Complete response: 36% chemoRT vs. 39% cetuximab-RT Median PFS: 21.6 mochemoRT vs. 20.7 mo cetuximab-RT Median OS: 44.7 mo chemoRT vs. 44.7 mo cetuximab-RT	Primary endpoint was in field grade 3–4 toxicity: Mucositis 29% chemoRT vs. 23% cetuximab-RT Skin reaction: 11% chemoRT vs. 14% cetuximab-RT
CONCERT-1 Mesia et al., 2015 Randomized phase II	Head and neck cancer All sites	**1** Radiation with cisplatin **2** Radiation with cisplatin + panitumumab	153	2 y locoregional control; 68% chemoRT vs. 61% chemoRT+ panitumumab	Serious toxicity rate: 32% chemoRT vs. 43% chemoRT + panitumumab
CONCERT-2 Giralt et al., 2015 Randomized phase II	Head and neck cancer All sites	**1** Radiation with cisplatin **2** Radiation with panitumumab	152	2 y locoregional control: 61% chemoRT vs. 51% panitumumab-RT	Serious toxicity rate: 40% chemoRT vs. 34% panitumumab-RT
RTOG 0324 Blumenschein et al., 2011 Phase II	Nonsmall cell lung cancer	Radiation with carboplatin/paclitaxel + cetuximab	93	Response rate: 62% Median OS: 22.7 months 2 y OS: 49%	Grade 4 hematological toxicity: 22% Grade 3 esophagitis :8%; G3-4 pneumonitis: 7% 5 treatment related deaths
CALGB 30407 Govindan et al., 2011 Randomized Phase II	Nonsmall cell lung cancer	**1** Radiation with carboplatin/pemetrexed	101	18 mo OS: 58% chemoRT vs. 54% chemoRT + cetuximab	Grade 3+toxicity: 76% ChemoRT vs. 85% ChemoRT + cetuximab

Study	Disease	Treatment arms	N	Results (red indicates statistically significant result)	Toxicity/Notes
		2 Radiation with carboplatin/pemetrexed + cetuximab			
Netherlands Van den Heuvel et al., 2014 Randomized Phase II	Nonsmall cell lung cancer	**1** Radiation with cisplatin **2** Radiation with cisplatin + cetuximab	102	Local control: 84% chemoRT vs. 92% chemoRT + cetuximab 1 y OS:82% chemoRT vs. 71% chemoRT + cetuximab	Toxicity similar between groups
RTOG 0617 Bradley et al., 2015 Phase III	Nonsmall cell lung cancer	**1** Radiation with carboplatin/paclitaxel **2** Radiation with carboplatin/paclitaxel + cetuximab	544	Median OS: 24 mo chemoRT vs. 25 mo chemoRT + cetuximab High EGFR expression subset: Median OS: 21 mo chemoRT vs. 42 mo chemoRT + cetuximab	Grade 3+toxicity increased with cetuximab: 86% vs. 70%
StarPan/STAR-02 Pinto et al., 2011 Phase II	Rectal cancer	Preoperative radiation with 5-FU/ oxaliplatin + panitumumab	55	Pathological CR: 21% Pathological downstaging: 58%	Grade 3–4 diarrhea: 39%
US Oncology McCollum et al., 2014 Randomized Phase II	Rectal cancer	**1** Preoperative radiation with 5-FU **2** Preoperative radiation with 5-FU + cetuximab	139	Pathologic CR: 28% chemoRT vs. 27% chemoRT + cetuximab 5 y RFS: 61% chemoRT vs. 64% chemoRT + cetuximab	Higher grade 3–4 diarrhea with cetuximab: 16% vs. 22%
EXPERT-C Dewdney et al., 2012 Randomized Phase II	Rectal cancer KRAS and BRAF wild-type	Preoperative chemotherapy followed by: **1** Radiation with capecitabine/oxaliplatin **2** Radiation with capecitabine/oxaliplatin + cetuximab	90	Pathological CR: 9% chemoRT vs. 11% chemoRT + cetuximab Radiological response: 75% chemoRT vs. 93% chemoRT + cetuximab OS HR 0.27 (improved with cetuximab)	In the entire study population of 160 patients there were no significant differences in all endpoints. Benefit was only seen in KRAS/BRAF wild type tumors.
ECOG 2205 Gibson et al., 2010 Phase II	Esophageal cancer	Preoperative radiation with 5-FU/ oxaliplatin + cetuximab followed by postoperative docetaxel and cetuximab	22	Pathologic CR: 32%	Four post-operative deaths
SWOG 0414 Tomblyn et al., 2012 Phase II	Esophageal cancer	Definitive radiation with cisplatin/ irinotecan + cetuximab	21	2 y OS: 33% 2 y PFS: 24% Response rate: 18%	Grade 3 toxicity: 48%; Grade 4 toxicity: 29% Two treatment related deaths Non-operative patients
HOG G05-92 Becerra et al., 2013 Phase II	Esophageal cancer	Preoperative radiation + cetuximab	39	Pathological CR: 37%	Treatment well tolerated No chemotherapy

Study	Disease	Treatment arms	N	Results (red indicates statistically significant result)	Toxicity/Notes
SCOPE1 Crosby et al., 2013 Randomized Phase II/III	Esophageal cancer	**1** Definitive radiation with 5-FU/csiplatin **2** Definitive radiation with 5-FU/csiplatin + cetuximab	258	Failure free at 24 weeks: 77% chemoRT vs. 64% chemoRT + cetuximab Median OS: 25 months chemoRT vs. 21 months chemoRT + cetuximab	Increased grade 3–4 toxicity with cetuximab: 79% vs. 63%
RTOG 0436 Suntharalingam et al., 2014 Phase III	Esophageal cancer	**1** Definitive radiation with cisplatin/paclitaxel **2** Definitive radiation with cisplatin/paclitaxel + cetuximab	344	Clinical CR: 59% chemoRT vs. 56% chemoRT + cetuximab 2 *y* OS: 42% chemoRT vs. 44% chemoRT + cetuximab	Grade 4+ toxicity higher with cetuximab: 26% vs. 18%

Table 2

Disease	Factors Associated with Sensitivity	Factors Associated with Resistance
Head and neck cancer	Accelerated radiation fractionation Acneiform rash (cetuximab) Oropharynx primary	HPV negative tumor Smoker Non-oropharynx primary
Nonsmall cell lung cancer	EGFR mutation: exon 19 and 12 (L858R, L861), exon 18 (G719X, G719), exon 20 (S7681) KRAS wild type EGFR overexpression Non-squamous cell histology Non-smoker Asian heritage Female sex	EGFR T790M mutation EGFR exon 20 insertion KRAS mutation Squamous cell carcinoma MET amplification/overexpression Epithelial to mesenchymal transition
Colorectal cancer	RAS wild type BRAF wild type Increased EGFR gene copy number	KRAS mutation NRAS mutation BRAF mutation MET amplification/overexpression HER2 amplification/overexpression EGFR mutation in cetuximab binding domain (rare)