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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.

Contents

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 & Carpenter, 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

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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(Nishinaka & Yabe-Nishimura, 2001; Sebolt-Leopold & Herrera, 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 & Baselga, 2000). (See Table 1.)

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 & Tortora, 2001; Herbst & Bunn, 2003), head and neck (Grandis & Tweardy, 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, 1979; Bentzen et al., 2007; Shewach & Lawrence, 2007; Morgan et al., 2014; Morris & Harari, 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 epidermal growth factor receptor targeted therapies and radiation

2.1. 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 & Huang, 2002; Liang et al., 2003). In a

Table 1
Clinical Trials using an EGFR Inhibitor and Radiation.

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 mo chemoRT 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 2. Radiation with carboplatin/pemetrexed + cetuximab	101	18 mo OS: 58% chemoRT vs. 54% chemoRT + cetuximab	Grade 3+ toxicity: 76% ChemoRT vs. 85% ChemoRT + 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
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%