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EGFR Targeting in Oesophageal Squamous Cell Carcinoma: Potential Role and Rationale

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Abstract

Oesophageal cancer remains a highly lethal malignancy in spite of advances in multimodal approaches that have been adopted in its management during the last two decades. Squamous cell carcinoma of the oesophagus poses an even more difficult entity to treat than adenocarcinoma, on account of its stage at presentation, location and greater propensity for loco-regional recurrence. Oesophageal squamous cell carcinoma shows a relatively high expression of EGFR expression 33-77%. EGFR (Epidermal Growth Factor Receptor) over expression has been shown to be associated with higher pathological tumour stages, lymph node metastasis as well as poorer disease free survival and overall survival. This review article explores the rationale of Epidermal Growth Factor Receptor targeting in Squamous cell carcinoma of Oesophagus and current clinical data/experience in therapeutically addressing the Epidermal Growth Factor Receptor pathway.

Keywords: EGFR (Epidermal growth factor receptor); Oesophageal squamous cell carcinoma; Radiation Sensitizer; Targeted therapy

Introduction

Oesophageal cancer is the sixth most frequent cause of cancer worldwide [1] and squamous cell carcinoma remains the most common histology in the Asian population where its incidence is higher [2]. The highest risk area, stretching from Northern Iran, through the central Asian Republics to North central China i.e., the Oesophageal cancer belt, squamous cell carcinoma forms 90% of the cases. Prognosis of oesophageal squamous cell carcinoma in advanced stages remains dismal in spite of the survival benefit contributed by using chemotherapy as a radiosensitizer. Strategies aimed towards treatment intensification through dose escalation have not met with favourable results. The results from Intergroup 0123 clearly showed the limitations in terms of toxicity and treatment related deaths by treating this site with doses exceeding 50Gy [3]. The RTOG 92-07 trial tried to address this issue with increasing the total dose through brachytherapy. However even this was associated with an unacceptable increased toxicity from treatment related fistulas nearly 12% [4]. In recent years a greater understanding of the mechanisms of carcinogenesis and the biology of site specific cancers have revealed the potential of targeting pathogenic pathways with molecular agents. In this article we would like to give an overview of the rationale and potential of targeting the EGFR pathway. Research is ongoing to establish predictive/prognostic factors for EGFR therapy. Some of the available data on the subject will be reviewed. Expression of Epidermal Growth Factor Receptor: A prognostic and predictive biomarker the Epidermal Growth Factor Receptor (EGFR, ERB-1) is a member of the Erb B family of receptor tyrosine kinases. Both erb B2/Her 2 neu and Erb B1 or EGFR are both associated with multiple pathogenic signalling cascade and serve as potential therapeutic targets. EGFR activation is associated with angiogenesis, cell cycle progression, development of metastasis and induction of anti-apoptotic pathways. EGFR expression has been shown in several studies to represent a poor prognostic marker especially in squamous cell carcinoma where its incidence is relatively higher [5-8]. A well designed retrospective analysis by Q Feng Wang et al. [9] in 243 patients of oesophageal squamous cell carcinoma provides significant clinical evidence of the value of EGFR expression as a poor prognostic biomarker. Currently this is one of the largest series that has analysed the issue. Their data has shown that EGFR protein was over expressed in 187 patients (77%). Over expression was also correlated with other known poor prognostic markers namely higher pathologic tumour stage ($p = 0.001$), lymphnode metastasis ($p = 0.002$) and higher Union for International Cancer Control (UICC) stage ($p < 0.00010$. A multivariate analysis also established EGFR over expression to be independently associated with poorer disease free survival ($p = 0.003$) and overall survival ($p = 0.001$). The 5 year OS and DFS rates of patients with EGFR expression was 15% and 14.4 % , with the median survival times of 16 months and 11.6 months.

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Whereas the 5 year OS and DFS of the patients found to have no or low EGFR expression was 39.3% and 37.5% and the median survival were also better being 31.7 and 25.7 months. EGFR: A Clinical Target EGFR is the cell surface receptor for members of the Epidermal Growth Factor family. The binding of its specific ligands like Epidermal Growth Factor (EGF) and Transforming Growth Factor (TGF_{α}) can activate downstream gene pathways. Activation of Mitogen Associated Protein Kinase (MAPK) protein kinase B (AKT) and c-Jun N-terminal kinase (JNK) pathways are associated with DNA synthesis, cell proliferation, migration and invasion [10].

Efgr Inhibition and Radiosensitisation: Lessons Learnt

There are a number of postulated mechanisms evidenced in vitro and in vivo experiments that account for the potentiation of radiation effect. Application of the mAbC225 (Cetuximab) before single dose irradiation of tumors enhanced the tumour control. It was also observed that continuation of C225 after radiation increased the tumour control [11]. As the maximal benefit was derived from the combination and subsequent treatment rather than combination alone. It is safe to assume that c225 may have individual activity against clonogenic cell lines in addition to its radiation enhancing properties. In FaDutumour, application of c225 before single dose irradiation also significantly improved the local control versus irradiation alone [12]. On the other hand similar experiments using TKI inhibitors showed the tumour control benefit was improved when the treatment was continued after irradiation. This implies that TKI inhibitors may not have an independent cytotoxic effect and may be clinically less efficacious than monoclonal antibodies.

Mechanisms of Radiosensitization

EGFR inhibition by mAB C225 or by TKI inhibitors repress DNA repair in irradiated cells. Anti EGFR treatment blocks nuclear EGFR-DNA-PKCS interaction which leads to compromised DNA double stranded break repair and enhances the radiation damage.

Another postulated mechanism of radio sensitization is indirectly by overcoming radio resistance [13,14]. EGFR over expressing tumour cells on being subjected to radiation activate proliferation through stimulated signalling via PBK-AK7 and RAS –MAPK pathways. Inhibition of these pathways through EFGR blockade results in improved cell cycle progression [15-17]. Research is ongoing to establish predictive /prognostic factors for anti EGFR therapy response. Preclinical studies (transgenic cells) indicate that type III EGFR variant (EGFRVIII) confers significant radio resistance to tumours while negative tumour cells are radioresistant [18]. The proportion of patients with treatment failure at 24 weeks was lower in arm A (CRT+CTX) 67.4% *vs.* 76.9%. However median overall survival was better in arm B with CRT alone 24.5 months *vs.* 22.1 months and that is why the trial did not proceed to phase III. Although this trial failed to achieve its primary endpoint it did show that addition of monoclonal antibody could reduce local failure and did not compromise quality of life (comparable in both cohorts). The 2 year follow up of these patients showed lower survival in the (CRT+CTX) arm, however this would be difficult to interpret as patients had non selective salvage intervention.

Role of Genetic Variants of EGFR as a Prognostic Marker

Genetic variants of EGFR have played an important role in many different types of cancer including non-small cell lung cancer [19], metastatic colorectal cancer [20] and pancreatic cancer. The studies on the role of such variants in squamous cell carcinoma are limited although there is supportive data to suggest the poor prognosis of selective variants in gastro-oesophageal and gastric adenocarcinomas [21]. One large study by Per Wang et al has addressed this issue [22]. A total of 334 patients with advanced squamous cell carcinoma were enrolled, the response to treatment which involved concurrent chemo irradiation followed by surgery or best supportive care was evaluated. The authors identified 2 major unfavourable genotypes i.e. EGF:rs4444903 and EGF:rs2237051 as having independent cumulative prognostic value to patients containing all of the unfavourable genes and had a higher associated risk of death compared with patients having none. Median survival time was (MST= 17.51 VS 5.21 MONTHS) in EGF rs 4444903 containing subset and (MST=14.72 VS 5.21) in EGF rs2237051 containing set.

The progression free survival was also significantly worse in EGF: rs4444903 containing subset (p=0.034) and borderline significant in the EGF: rs 2237051 containing subset. The results of this study suggest that there may be a subset of patients with EGFR over expression with poorer outcome. The next step would be to analyse if these same prognostic variants were responsive to anti -EGFR interventions. Two categories of anti EGFR targeting agents are being evaluated in the clinical setting; small molecule tyrosine kinase inhibitors (TKI's) such as Geftinib, Erlotinib and Lapatinib and humanized MABs like Cetuximab and Nimotuzumab.

Role of TKI's

TKI's are small molecules that cross the plasma membrane and block the cytoplasmic portion of cellular receptors. The EGFR TKI that has been evaluated in both the locally advanced and metastatic setting is Erlotinib. Initial studies have been focussed on the response and comparative toxicity profile. However evaluation / interpretation of results is difficult and may not be representative. Mainly because adenocarcinoma cases were also included and EGFR evaluation was retrospective. In the second line and metastatic setting TKI's show a moderate response of 9-12%. However notably have a favourably low toxicity profile limited to grade I / II skin reactions and diarrhoea.

Erlotinib is currently being evaluated in the definitive management of locally advanced Oesophageal Cancer integrated into the standard chemo irradiation protocol. A phase I trial by [23] evaluated the best efficacious dose of Erlotinib in this setting. The results of this study suggested that 150mg of the drug could provide a good response with tolerable toxicities. Erlotinib was administered concurrently with cisplatinum and 5 FU and thoracic irradiation to a dose of 50.4 Gy. The few toxicities of grade 1 skin rash, nausea and diarrhoea were non dose limiting [23].

One such phase II trial Li et al. [24] evaluated 24 patients treated radically with concurrent cisplatinum, paclitaxel and radiotherapy. The study showed promising results with 2 yr local control 87.5% and 2 yr survival of 57.4%. Again no dose limiting toxicity that could be attributable to erlotinib. The reported incidence of skin rash was 4%. In the background of promising results in small studies, a large randomised phase III trial was initiated-" The Cancer Oesophagus Geftinib (COG)" trial recruited 450 patients from 51 centres through UK. Patients with metastatic oesophageal cancer that had failed the first line chemotherapy were randomised to geftinib *vs.* placebo till progression. The primary end point of improved survival was not superior in the geftinib arm. However there was an improvement in

progression free survival and Quality of life which would practically be of more importance in this category of patients. Patients in the Geftinib arm also had a longer period of stable disease with symptom palliation p (0.014). The results might have been more promising if it had concentrated on squamous cell type which formed only 24% of the trial cohort. A follow up study TRANSCOG aims to identify predictive biomarkers including EGFR and hopes to identify the subset of patients who will achieve the maximum benefit [25]. A follow up study (TRANS-COG) was conducted to identify predictive biomarkers for EGFR response. It was hypothesized that Epidermal growth factor receptor copy number gain (EGFR CNG) may be correlated to the beneficial subgroup of patients receiving geftinib. EGFR-FISH results were available in 295 patients. In (EGFR-CNG) patients overall survival was 71% for those receiving geftinib *vs.*64 % in placebo arm at 3 months and 25% *vs.*5% at 9 months, 13% *vs.* 6% at 12 months (p = 0.42). More importantly the disease control rates (DCR) i.e., RECIST (CR+PR+SD) which would be more representative of benefit in the palliative set up were significantly improved. In patient receiving with EGFR-CNG *vs.* those without EGFR-CNG 24% *vs.* 14% p = 0.05, EGFR amplification (6%) patients had the greatest benefit by being treated with geftinib. This probably indicates that EGFR-CNG may be a potential predictive marker for response to TKI treatment in oesophageal cancer.

Role of Monoclonal Antibodies

Monoclonal antibodies are currently preceding TKI's in the clinical scenario. Cetuximab a monoclonal I_gG1 antibody has been used in many cancers, notably with significant benefit in head and neck squamous cell carcinoma [15]. Monoclonal antibodies targeting EGFR are directed against the extracellular domain and thought to induce G1 cell cycle arrest, inhibit radiation induced DNA damage repair and promote radiation induced apoptosis. The latter two effects are of special consideration when considering the potential of this molecule as a radiosensitizer in addition to its independent actions. However among the available antibodies, Cetuximab appears to have a less favourable toxicity profile which probably accounts for the mixed results in oesophageal trials.

The safety and efficacy of Cetuximab in the setting of concurrent chemoradiation with carboplatin and paclitaxel has been evaluated by M.Suntharalingam et al. [26], in a phase II trial involving 60 patients of esophagogastric cancer. These results showed promising response rates with 49 patients who were eligible for surgery showing a pathological CR of 27% and 70% evidenced clinical response. Notably 30% of the study cohort who achieved CR were squamous cell carcinomas. The grade 3 ooesophagitis was limited to 12% and only 3 patients enrolled had hypersensitivity reaction related to cetuximab [26]. However in a larger study RTOG 0436 enrolling 328 patients of which 125 were squamous cell carcinoma of oesophagus the results did not favour the addition of cetuximab into the treatment protocol in terms of survival. In this trial both cohorts i.e., the one receiving 3 drugs vizcisplatinum, paclitaxel and cetuximab had similar responses and survival to the control receiving chemotherapy without the targeting agent. The toxicity profile in both cohorts was comparable with the exceptions of dermatologic events which was higher in the study cohort [27]. Another phase III trial with a significant proportion of squamous cell carcinoma among treatment groups was the (SCOPE-1) trial [28]. This was a multicentre phase 2/3 randomized trial conducted in UK in which patients with nonmetastaticoesophageal cancer were randomized to receive definitive chemoradiation with Cetuximab, cisplatinum and capecitabine versus chemo irradiation without monoclonal antibodies. Both cohorts received 2 cycles of neoadjuvant chemotherapy followed by concurrent chemo irradiation with cycle 3 and 4. This study had 129 patients in both cohorts with nearly 71% of squamous cell carcinomas in cohort A concurrent chemo irradiation + Cetuximab (CRT+CTX) and 74% in cohort B (CRT).

Role of Newer Targeting Agents

A lot of interest is currently being generated by Nimotuzumab (h-R3) a humanised monoclonal antibody targeting the extracellular domain of the Epidermal Growth Factor Receptor (EGFR). Its clinical efficacy has been evaluated and proven in squamous cell carcinoma of the head and neck and is currently being assessed concomitantly with chemoradiotherapy in patients with locally advanced oesophageal cancer. A phase II trial involving 42 patients with locally advanced squamous cell carcinoma of the oesophagus was conducted by Jun Wang et al to evaluate the safety and therapeutic effects of Nimotuzumab (h-R3) in combination with standard conformal radiotherapy.

Some interesting and promising facts and results have been evidenced in this study. This study exclusively looked into squamous cell carcinoma of the oesophagus which forms the larger cohort of patients in the Asian population. The over expression of EGFR was 95.2% which highlights how significant this clinical target may be. The 2 year and 3 year survival was a favourable 33.3% and 26.2% respectively. An interesting observation that was observed was a more favourable median survival and overall survival in patients having (+++) EGFR expression *vs.* those having (++) EGFR expression. This suggests that there may be a predictive element in choosing patients who may maximally benefit from targeted therapy. In addition to this Nimotuzumab has a significantly less documented hypersensitivity and dermatological toxicities compared to Cetuximab which would improve its tolerance in the concomitant set up with combination chemotherapy and also may provide an alternative to chemotherapy in patients with a poorer performance status. Ongoing trials are evaluating Nimotuzumab in this setting [29].

Discussion

EGFR expression is an established prognostic and predictive biomarker in advanced squamous cell carcinoma of the oesophagus. This histological subtype has shown a relatively stable incidence worldwide and forms the predominant cohort in the Asian population. The problems of improving survival in patients with locally advanced oesophageal cancer includes, inoperability at presentation, lack of scope for dose escalation of radiotherapy because of proximity of critical normal structures, poor performance status at presentation and hence limiting the benefit of concurrent chemotherapy. In this review the authors have concentrated on evaluating the role of EGFR targeting in squamous cell carcinoma of the oesophagus without focussing on other histological subtypes or molecular targets. As elaborated in the text EGFR is a proven clinical target that can be benefitted with the addition of molecular therapy both in the form of TKI's and monoclonal antibodies. The clinical impact of this addition to standard management would include radiosensitization, better response rates that should carry over to survival benefits and predictive subtype treatments. They also may provide a clinically efficacious addition to radiotherapy in patients with poor tolerance to standard chemotherapy. Comparative toxicity profiles and subtype predictive benefits of degree of EGFR expression may in the future direct the selection of type of targeting agent that may provide the best benefit.

Conclusion

EGFR has proven to be an important prognostic and predictive biomarker in advanced squamous cell carcinoma of the oesophagus and targeting it with molecular therapy has the potential to improve current survival rates. The good response rates and the low toxicity profile gives it an added role in poor performance status patients, second and third line treatment as well as palliation. Ongoing studies should be able to define, the impact of its addition to standard chemoirradiation and potential role in other clinical settings including neoadjuvant, adjuvant and palliative scenarios.

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