Integration of targeted agents in the neo-adjuvant treatment of gastro-esophageal cancers

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Abstract: Pre- and peri-operative strategies are becoming standard for the management of localized gastro-esophageal cancer. For localized gastric/gastro-esophageal junction (GEJ) cancer there are conflicting data that a peri-operative approach with cisplatin-based chemotherapy improves survival, with the benefits seen in esophageal cancer likely less than a 5–10% incremental improvement. Further trends toward improvement in local control and survival, when combined chemotherapy and radiation therapy are given pre-operatively, are suggested by recent phase III trials. In fit patients, a significant survival benefit with pre-operative chemoradiation is seen in those patients who achieve a pathologic complete response. In esophageal/GEJ cancer, definitive chemoradiation is now considered in medically inoperable patients. In squamous cell carcinoma of the esophagus, surgery after primary chemoradiation is not clearly associated with an improved overall survival, however, local control may be better. In localized gastric/GEJ cancer, the integration of bevacizumab with pre-operative chemotherapy is being explored in large randomized studies, and with chemoradiotherapy in pilot trials. The addition of anti-epidermal growth factor receptor and anti-human epidermal growth factor receptor-2 antibody treatment to pre-operative chemoradiation continues to be explored. Early results show the integration of targeted therapy is feasible. Metabolic imaging can predict early response to pre-operative chemotherapy and biomarkers may further predict response to pre-operative chemo-targeted therapy. A multimodality approach to localized gastro-esophageal cancer has resulted in better outcomes. For T3 or node-positive disease, surgery alone is no longer considered appropriate and neo-adjuvant therapy is recommended. The future of neo-adjuvant strategies in this disease will involve the individualization of therapy with the integration of molecular signatures, targeted therapy, metabolic imaging and predictive biomarkers.

Keywords: esophageal carcinoma, bevacizumab, trastuzumab, cetuximab, radiation, chemotherapy

Introduction

Globally both gastric and esophageal cancers are significant health problems and account for approximately 1.4 million new cases per year with 1.1 million cancer-related deaths [Parkin *et al.* 2005]. This annual mortality is higher than that for both breast and colorectal cancers combined. In the United States, in 2008, an estimated 16,470 patients will be diagnosed with esophageal cancer resulting in 14,280 deaths, making this disease the seventh leading cause of cancer death in men, and 21,500 cases of gastric cancer will be diagnosed resulting in 10,880 deaths [Jemal *et al.* 2008].

The last three decades have seen a dramatic epidemiologic shift in the location of both gastric and esophageal cancers as well as the histologic subtype of esophageal cancers. Tumors of the lower esophagus and proximal stomach are classified as gastro-esophageal junction (GEJ) cancers and this cancer has been increasing in incidence by 5–10% per year since the mid 1970s and is the most rapidly increasing cancer in many Western countries [Kamangar *et al.* 2006]. Distal esophageal and GEJ adenocarcinoma is now the predominant esophageal cancer subtype, and the majority of gastric cancers are now located in the proximal stomach [Pera *et al.* 1993].

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The 5-year survival of patients with gastro-esophageal cancers (distal esophagus, GEJ, and proximal stomach making up the majority of cases) has not changed significantly over the last 25–30 years. Approximately 50–60% of patients present with distant metastatic disease and median overall survival (OS) with systemic chemotherapy has remained at less than one year [Van Cutsem *et al.* 2008]. However, progress has been made in the treatment of localized disease. Combinations of pre-operative (neo-adjuvant) chemotherapy, peri-operative chemotherapy or pre-operative (neo-adjuvant) chemoradiotherapy with surgery have resulted in R0 resection rates between 40 and 80% and 5-year survival rates from 20 to 40%.

A variety of combination chemotherapeutic agents have been used in the treatment of gastro-esophageal cancers over the last 30 years. These include fluoropyrimidines, anthracyclines, platinum, taxanes and camptothecins. Combining different classes of drug exploits the different modes of action in the cancer cell and may allow lower doses of each individual drug to be given in the combination regimen thus reducing side effects. Work over the last decade has identified distinct molecular pathways leading to tumorigenesis, angiogenesis and metastasis. Drug development has led to direct treatment at specific molecular targets. This review will focus on the integration of targeted therapy into the neo-adjuvant treatment of gastro-esophageal cancers.

Rationale behind neo-adjuvant therapy

The optimal treatment for localized/early-stage disease, especially adenocarcinoma, is surgery. In squamous cell cancers, definitive chemoradiation without surgery is an acceptable option. However, even with R0 resection, the 5-year survival rate remains at less than 40%. This suggests that even at the time of resection, micrometastatic disease is present in the majority of cases and accounts for disease recurrence and high mortality. Neo-adjuvant chemotherapy, in the strictest sense of the word, is chemotherapy given prior to surgery on a tumor that is initially resectable. Pre-operative (definitive) therapy is given in the case where a tumor may, or may not, be resectable due to the locally advanced stage of the disease or to medical comorbidities of the patient. In this review we use the term 'neo-adjuvant' to mean both of the above

situations. Neo-adjuvant therapy is associated with many theoretical advantages [Harris and Mastrangelo, 1991] including the following:

- (1) The patient is better able to tolerate potential toxicities of treatment prior to surgery.
- (2) The primary tumor and distant micrometastatic disease is simultaneously attacked.
- (3) The primary tumor may regress thus improving local control and increasing R0 resection rates with subsequent surgery.
- (4) Baseline dysphagia may improve.
- (5) Patients who may benefit from post-operative therapy, or therapy in the metastatic setting are identified by assessing the response in the primary tumor.

Over the last decade many neo-adjuvant (pre-operative) strategies have been studied in gastro-esophageal cancers. It is increasingly apparent from clinical studies that surgery alone for localized disease, T3 or node-positive disease should not be the accepted standard of care, and the addition of neo-adjuvant or post-operative (adjuvant) therapy is of benefit. We will briefly highlight some of the key trials in order to provide an evidence base for the integration of targeted agents into such strategies.

Neo-adjuvant chemotherapy

The large North American Intergroup 113 trial randomized 440 patients with localized adenocarcinoma or squamous cell carcinoma of the esophagus to peri-operative (three cycles pre-operatively and two cycles postoperatively) cisplatin/5-fluorouracil (5FU) plus surgery *versus* surgery alone. There was no difference in median OS between the two arms, and 5-year OS with or without chemotherapy was 20% [Kelsen *et al.* 1998]. There was also no difference in outcomes by histology subtypes for pre-operative chemotherapy. The Medical Research Council Oesophageal Cancer Working Group randomized 802 patients to two cycles of pre-operative cisplatin/5FU plus surgery *versus* surgery alone [Group, 2002]. With 5-years follow-up, the OS benefit was 6% (23 *versus* 17% for the investigational and control arms respectively, $p=0.03$) with a surgical mortality of 10% [Allum *et al.* 2008]. Further work on chemotherapy combined with surgery was provided by the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial. This trial randomized 503 patients with gastric or GEJ cancer to

peri-operative epirubicin/cisplatin/5FU (ECF), three cycles pre-operatively and three cycles post-operatively, followed by surgery *versus* surgery alone. Pre-operative ECF improved median and 5 year OS by 4 months (24 *versus* 20 months) and 13% (36 *versus* 23%, $p < 0.001$), respectively [Cunningham *et al.* 2006]. A French trial of 224 patients treating esophageal and gastric adenocarcinoma also showed a benefit of pre-operative cisplatin/5FU followed by surgery *versus* surgery alone, 5-year OS was 38% for the investigational arm *versus* 24% for the surgery alone arm [Boige *et al.* 2007]. Finally, a randomized phase III trial (EORTC #40954) was recently presented in abstract form [Schuhmacher *et al.* 2009]. Although this trial was primarily for localized gastric cancer, around 50% of the 144 randomized patients had upper third gastric and cardia tumors (Sierwert II and III). After 4.4 years of follow up, there was no survival benefit with neo-adjuvant cisplatin/5FU followed by surgery compared with surgery alone. The authors noted that radical surgery with extended lymphadenectomy was associated with better outcome (median OS was greater than 36 months in both arms).

Despite inconsistencies in the above trials (see Table 1), for example, improvement in R0 resection rate and pathologic complete response rate (<5%), there appears to be a modest benefit to pre-operative (neo-adjuvant) chemotherapy in localized gastro-esophageal cancers. Meta-analyses have shown an absolute survival benefit of no more than 7%, however, and 5-year OS still remains at less than 40% [Gebbski *et al.* 2007;

Thirion *et al.* 2007]. There is a suggestion of a lesser benefit for squamous cell carcinoma (4%) compared with adenocarcinoma histology (7%) [Thirion *et al.* 2007]. Given the limited benefit achieved with conventional systemic chemotherapy, it is unlikely that newer agents will significantly improve the existing 5-year OS rates in localized disease. It is noteworthy in metastatic disease that the integration of taxanes has resulted in improved outcome [Van Cutsem *et al.* 2006]. There is therefore a clear role for the integration of novel targeted therapy into the pre-operative treatment paradigms for gastro-esophageal cancers.

Neo-adjuvant chemoradiotherapy

Pathologic complete response (pCR) after neo-adjuvant therapy is associated with an increased chance, approximately 50%, of cure, and has consistently shown survival rates of 50–60% at 5 years [Reynolds *et al.* 2007; Berger *et al.* 2005]. One of the weaknesses of neo-adjuvant chemotherapy alone is the failure to achieve meaningful rates of pCR (range 0 to less than 5%). Neo-adjuvant chemoradiation can result in pCRs in approximately 20–40% of patients. The addition of newer chemotherapeutic agents, e.g. taxanes and camptothecins, to the traditional cisplatin and 5FU has failed to increase these pCR rates.

Evidence for the superiority of combined chemoradiation over radiation alone in localized esophageal cancer was established by the phase III Radiation Therapy Oncology Group (RTOG)

Table 1. Phase III pre-operative chemotherapy trials in gastro-esophageal cancer.

Reference	Tumor type	Sample size	Regimen	R0 resection rate (%)	pCR rate (%)	Survival	
						Median months	Overall (%)
Kelsen [Kelsen <i>et al.</i> 1998]	SC [46%	213	Periop CF + Surgery	62	2.5	14.9	23 (3 year)
	AC [54%]	227	Surgery	59	N/A	16.1	26 (3 year)
MRC [Group, 2002]	SC [31%]	400	Periop CF + Surgery	60	N/A	16.8	23 (5 year)
	AC [66%]	402	Surgery	54	N/A	13.3	17 (5 year)
Cunningham [Cunningham <i>et al.</i> 2006]	AC	250	Periop ECF + Surgery	69	0	24	36 (5 year)
		253	Surgery	66	N/A	20	23 (5 year)
Boige [Boige <i>et al.</i> 2007]	AC	113	Periop CF + Surgery	87	3	N/A	38 (5 year)
		111	Surgery	74	N/A	N/A	24 (5 year)

AC, adenocarcinoma of gastric/gastro-esophageal junction/esophagus; CF, cisplatin/5-fluorouracil; ECF, epirubicin, cisplatin, 5-fluorouracil; N/A, not available; pCR, pathologic complete response; Periop, peri-operative; SC, squamous cell carcinoma of esophagus.

85-01 trial. This was a nonoperative study and compared daily-fractionation radiation of 64 Gy to radiation (50 Gy) plus concurrent cisplatin/5FU. At 5-years follow-up, the OS for the chemoradiotherapy arm was 26% compared to 0% in the radiation-alone arm. The survival rate in the chemoradiotherapy arm is similar to that seen with historic 5-year OS with surgery alone. It is noteworthy that the majority of patients in this trial had squamous histology. Local recurrences were reduced (44 *versus* 62%) and systemic recurrences were reduced (22 *versus* 38%) with the addition of chemotherapy to radiation compared with radiotherapy alone [Cooper *et al.* 1999; Herskovic *et al.* 1992]. The RTOG 94-05 (Intergroup 0123) showed that increasing the total radiation dose to 64.8 Gy combined with cisplatin/5FU was not superior to the standard 50.4 Gy [Minsky *et al.* 2002]. Thus, both the RTOG 85-01 and the INT 0123 established a standard of care for patients with locally advanced nonoperative esophageal cancer, although the majority of patients treated on these trials had squamous cancers.

Because chemoradiotherapy can achieve complete responses without surgery, recent trials have compared chemoradiotherapy with or without surgery in esophageal squamous cancers. Stahl and colleagues randomized 172 patients with operable squamous cell carcinoma of the esophagus to neo-adjuvant chemoradiotherapy followed by surgery or chemoradiotherapy alone. Both groups had induction cisplatin/5FU/etoposide. The median OS of 16 months and 3-year OS of 31.3% among patients receiving trimodality treatment were not significantly different than the 15 months and 24.4% achieved in the definitive chemoradiation arm, despite a trend favouring the addition of surgery. Local control was superior in the surgery arm, 2-year local progression free survival (PFS) was 64.3 *versus* 40.7% ($p=0.03$) for the surgery and chemoradiotherapy alone arms respectively, but this did not translate into an OS benefit [Stahl *et al.* 2005]. It is noteworthy that treatment-related mortality was significantly higher in the surgery arm, 12.8 *versus* 3.5%. Ten-year survival data for this trial has recently been presented in abstract form and no clear survival difference between the operative and nonoperative arms was confirmed [Stahl *et al.* 2008]. The French FFCD 9102 phase III study also reported no difference in OS comparing induction chemoradiation with cisplatin/5FU followed by surgery, with definitive

chemoradiation in 259 patients with squamous cell carcinoma of the esophagus. Of 444 patients involved in the study, 259 were randomized. Patients had to demonstrate a response to initial chemoradiation to proceed to subsequent randomization to surgery or additional chemoradiation; nonresponding patients were taken off the study. Median OS was 17.7 months for surgery *versus* 19.3 months for chemoradiotherapy alone, and 2-year OS was 34 *versus* 40%, respectively ($p=0.44$) [Bedenne *et al.* 2007]. Locoregional recurrence was higher in the chemoradiotherapy-only group (43 *versus* 34%) and 3-month mortality was significantly higher in the surgery group (9.3 *versus* 0.8%). From these two phase III trials, there is a clear role for definitive chemoradiotherapy in localized squamous cell carcinoma of esophageal/GEJ, and a subset of patients who respond to induction treatment have similar outcomes with or without surgery. Surgical salvage remains an option in patients who do not respond to chemoradiation [Jouve *et al.* 2008].

There are data to support the strategy of pre-operative chemoradiation prior to surgery. Of the modern phase III trials, only two indicated a survival benefit for pre-operative chemoradiation therapy compared to surgery alone (see Table 2) [Tepper *et al.* 2008; Burmeister *et al.* 2005; Urba *et al.* 2001; Bosset *et al.* 1997; Walsh *et al.* 1996]. Most of these trials report improved R0 resection rates up to 80% and pCR rates of up to 40% in the chemoradiation arms. Cisplatin/5FU is the chemotherapy used in most trials. A survival advantage of pre-operative chemoradiotherapy is suggested from these trials; however, it is not consistent across all studies. The Cancer and Leukemia Group B (CALGB) 9781 study is underpowered with only 56 patients enrolled, and if this trial is excluded from OS analyses, median OS with pre-operative chemoradiotherapy does not exceed 23 months. A recent meta-analysis reported on 10 randomized trials of pre-operative chemoradiotherapy *versus* surgery alone, including the five trials cited above, and reported a 13% absolute difference in mortality reduction at 2 years for the trimodality arms compared to 7% for pre-operative chemotherapy alone [Gebbski *et al.* 2007]. The benefit of trimodality treatment may be offset by increased treatment-related mortality as reported in a meta-analysis where the risk of postoperative mortality after pre-operative chemoradiotherapy followed by surgery group was significantly increased (OR = 2.01, $p=0.01$) [Fiorica *et al.* 2004].

Table 2. Phase III trials of neo-adjuvant chemoradiotherapy *versus* surgery in esophageal cancer.

Reference	Tumor type	Sample size	Regimen	R0 resection rate (%)	pCR rate (%)	Survival Med. months	Overall (%)
Walsh [Walsh <i>et al.</i> 1996]	AC	58 55	Preop. CRT Surgery	N/A N/A	25 N/A	16 11	32 (3 year) 6 (3 year)
Bosset [Bosset <i>et al.</i> 1997]	SC	143 139	Preop. CRT Surgery	81 69	26 N/A	18.6 18.6	26 (5 year) 26 (5 year)
Urba [Urba <i>et al.</i> 2001]	SC (24%) AC (76%)	50 250	Preop. CRT Surgery	45 45	28 SC 38% AC 24% N/A	16.9 17.6	30 (3 year) 16 (3 year)
Lee [Lee <i>et al.</i> 2004]	SC	51 50	Preop. CRT Surgery	100 87	43 N/A	28.2 27.3	55 (2 year) 57 (5 year)
B'meister [Burmeister <i>et al.</i> 2005]	SC (35%) AC (63%) Other (2%)	128 128	Preop. CRT Surgery	80 59	16 SC 27% AC 9% N/A	22.2 19.3	NS NS
Tepper [Tepper <i>et al.</i> 2008]	SC (25%) AC (75%)	30 26	Preop. Surgery	30 26	40 N/A	4.5 years 1.8 years	39 (5 years) 16(5 years)

AC, adenocarcinoma; CRT, chemoradiotherapy; N/A, not available; pCR, pathologic complete response; Preop., pre-operative; SC, squamous cell carcinoma.

Further benefit of a pre-operative chemoradiotherapy strategy was reported by Stahl and colleagues in a recent phase III trial in patients with locally advanced adenocarcinoma, comparing pre-operative chemotherapy with cisplatin/5FU followed by surgery with the same pre-operative chemotherapy follow by chemoradiation with cisplatin/etoposide and then surgery. In a population of 119 patients, R0 resections were similar in both arms, and the 3-year OS rate was improved from 27 to 47% in the chemoradiotherapy group, $p=0.07$ [Stahl *et al.* 2009]. This survival benefit is similar to that seen in meta-analyses [Gebbski *et al.* 2007; Thirion *et al.* 2007] and was achieved despite an increased rate of postoperative mortality with the addition of radiation (10.2 *versus* 3.8% for the chemoradiation and chemotherapy arms respectively). Local tumor progression also trended to favour chemoradiation. The rate of patients without local tumor progression at 3 years was 59 *versus* 76.5% for the chemotherapy and chemoradiotherapy arms respectively, $p=0.06$. There was no significant difference in postoperative mortality between the two arms.

Paclitaxel-based chemoradiation has been evaluated and multiple phase II trials report similar response rates and survival to cisplatin/5FU/radiation regimens. Phase II trials from Memorial Sloan Kettering (MSK) and Brown

University Oncology Group report that paclitaxel-based radiation is better tolerated with <5% grade 4 esophagitis and a potential lesser need for placement of enteral feeding tubes [Brenner *et al.* 2004; Safran *et al.* 2001]. The RTOG 0113 was a randomized phase II trial which evaluated the two-drug regimen of paclitaxel and cisplatin (with and without 5FU) with daily radiation based on data that paclitaxel is a potent radiosensitizer. The primary endpoint of $\geq 77.5\%$ 1-year survival rate was not met for either arm of this study (compared with the historical control in the RTOG 9405 trial which had a 1-year survival rate of 66%). The 5FU/paclitaxel arm was better tolerated than the paclitaxel/cisplatin arm [Ajani *et al.* 2008]. Three drug trials combining paclitaxel with cisplatin or carboplatin and 5FU with radiation have not consistently demonstrated superior results. Retrospective data from the Massachusetts General Hospital has shown similar pCR (46 *versus* 38%) and 3-year OS rates (43 *versus* 41%) compared with cisplatin/5FU and radiation [Roof *et al.* 2006]. Toxicity rates were similar in both arms ($\geq$ grade 3 toxicity rate of 80%).

Both docetaxel and oxaliplatin are undergoing study in combination with radiation and traditional agents, for example, cisplatin, cisplatin/5FU and 5FU [Schuller *et al.* 2008; O'Connor *et al.* 2007]. Toxicities from these new

combinations are acceptable and early results are promising. Induction docetaxel/cisplatin followed by the same regimen with radiation and then surgery reported a pCR (or near) rate of 47%, with survival data similar to other phase II studies [Ruhstaller *et al.* 2009; Schuller *et al.* 2008]. Combinations of infusional 5FU and oxaliplatin with radiation followed by surgery have reported pCR rates of 25–38% [Lorenzen *et al.* 2008; O'Connor *et al.* 2007; Khushalani *et al.* 2002]. The Southwest Oncology Group 0356 phase II study is evaluating oxaliplatin and protracted infusional 5FU combined with radiation in a multicenter setting (accrual is completed) [NCT00086996, www.clinicaltrials.gov]. This study was recently presented in abstract form and reported a pCR rate of 33% and *in situ* cancer in 10% of the 77 patients (86% of the total population) who underwent surgery [Leichman *et al.* 2009]. Survival data has not yet been reported.

Irinotecan has been studied in combination with cisplatin in localized gastro-esophageal cancer [Ilson *et al.* 1999]. Phase I–II data with cisplatin/irinotecan combined with radiation reported a pCR rate of 17–27% comparable to other chemoradiotherapy regimens [Ku *et al.* 2008; Ilson *et al.* 2003]. The CALGB 80302 trial is currently accruing a phase II study using this regimen [NCT00316862]. The relative absence of toxicity, ease of administration, and relief of dysphagia seen with cisplatin/irinotecan and radiation suggests that this is a promising regimen. The Eastern Cooperative Oncology Group (ECOG) trial 1201 recently reported results of a comparison between weekly cisplatin/irinotecan and weekly cisplatin/paclitaxel both combined with concurrent radiation as pre-operative chemoradiotherapy in esophageal adenocarcinoma. Median OS for the irinotecan arm was 34.9 months and for the paclitaxel arm was 21 months. The pCR rates, although relatively low at 15–16%, are in the range of 9–25% in previous studies reported studies for the adenocarcinoma subtype [Kleinberg *et al.* 2007].

Targeted therapy

Over the last decade many pathways in carcinogenesis have been studied at the molecular level. The role of the epidermal growth factor receptor (EGFR) tyrosine kinase (TK) pathway in tumorigenesis and vascular endothelial growth factor (VEGF) in angiogenesis have resulted in the development of targeted therapies that have now

become integrated into treatment paradigms of many malignancies (see Figure 1). In metastatic colorectal cancer, bevacizumab, a monoclonal antibody against VEGF, is now routinely used as first-line treatment in combination with chemotherapy [Hurwitz *et al.* 2004]. EGFR-blocking monoclonal antibodies, e.g. cetuximab, also appear to improve response and time-to-tumor progression when combined with first-line chemotherapy in metastatic colorectal cancer [Van Cutsem *et al.* 2009]. In gastro-esophageal cancer increased VEGF expression has been observed in both squamous and adenocarcinoma of the esophagus as well as in gastric cancer, and is associated with poor outcome [Kleespies *et al.* 2004; Karayiannakis *et al.* 2002; Maeda *et al.* 1996]. Bevacizumab in combination with cisplatin/irinotecan or docetaxel-based therapy has been shown to have activity in metastatic gastro-esophageal cancer [Enzinger *et al.* 2006; Shah *et al.* 2006]. The level of VEGF expression actually may increase in tumor and adventitial tissue during the course of chemoradiotherapy and may provide a rationale for combining VEGF inhibiting agents, for example, bevacizumab, with chemoradiotherapy regimens [Kulke *et al.* 2004]. EGFR is expressed in 50–90% of gastro-esophageal cancers and is also associated with poor prognosis, as are tumors that over-express human EGFR-2 (SynHER2, ERBB2) [Brien *et al.* 2000; Slesak *et al.* 1998; Mukaida *et al.* 1991]. Cetuximab, and the EGFR TK inhibitors (TKIs) gefitinib and erlotinib, have very limited activity in the metastatic setting with response rates of 0–10% [Gold *et al.* 2008; Pinto *et al.* 2007; Dragovich *et al.* 2006]. HER2 is overexpressed in 19–43% of gastro-esophageal cancers and is correlated with poor survival [Brien *et al.* 2000]. Trastuzumab was evaluated in combination with chemotherapy in HER2-positive metastatic gastric cancer in the recently completed ToGA (Trastuzumab with Chemotherapy in HER2-Positive Advanced Gastric Cancer) trial. Many other targets have been studied in metastatic gastro-esophageal cancer, for example, mammalian target of rapamycin (mTOR), cyclo-oxygenase 2 (COX2), platelet-derived growth factor receptor (PDGFR), and matrix metalloproteinase (MMP).

Encouraged by modest activity in the metastatic setting, investigators have integrated novel targeted agents into neo-adjuvant regimens. Most work has focused on anti-VEGF and

Figure 1. Molecular pathways involving epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2) and vascular endothelial growth factor (VEGF). Reproduced with permission Source: Hwang J, Marshall JL. Biology of tumor growth and molecular targets in metastatic colorectal cancer. Clinical Care Options; 2006. Available at <http://clinicaloptions.com/Oncology/Treatment%20Updates/CRC.aspx> Source: Cunningham D. EGFR-targeted antibodies: Clinical applications, treatment challenges, and ongoing scientific research. Clinical Care Options; 2008. Available at <http://www.clinicaloptions.com/Oncology/Treatment%20Updates/Targeted%20Therapies.aspx>. Reproduced with permission.

anti-EGFR/HER2 monoclonal antibody therapies and some of the studies are highlighted below.

Anti-EGFR therapy

Cetuximab has limited activity in metastatic gastro-esophageal cancers [Gold *et al.* 2008; Pinto *et al.* 2007]. However in localized disease, there may be a more defined role for this agent. Preclinical evidence has suggested synergy between cetuximab, paclitaxel, cisplatin, and radiation [Langer, 2004; Raben *et al.* 2004]. The binding of cetuximab to EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in the inhibition of cell growth, induction of apoptosis, and decreased MMP and VEGF production. Cetuximab may also have anti-tumor activity by inducing antibody-dependent cellular toxicity [Kawaguchi *et al.* 2007]. The efficacy and safety of cetuximab in combination with radiation therapy was studied in a randomized trial of 424 patients with locally or regionally advanced squamous cell carcinoma of the head and neck *versus* radiation therapy alone [Bonner *et al.* 2006]. Median duration of locoregional control was superior in the cetuximab arm, 24.4 *versus* 14.0 months, $p=0.005$. Median OS was also superior in the cetuximab arm, 49 *versus* 22.9 months, $p=0.03$. A rationale for combining cetuximab with chemotherapy and radiation is provided by preclinical evidence suggesting synergy between cetuximab, paclitaxel, cisplatin, and radiation [Raben *et al.* 2004]. The preclinical synergy between cetuximab, cisplatin and paclitaxel prompted The Brown University Oncology Group and the University of Maryland Cancer Center to pilot a study of carboplatin/paclitaxel and radiation in combination with cetuximab for localized gastro-esophageal cancer. Patients received cetuximab 400 mg/m² in week 1, then 250 mg/m²/week for 5 weeks; paclitaxel 50 mg/m²/week; and carboplatin AUC=2, weekly for 6 weeks with concurrent radiation of 50.4 Gy. Sixty patients were enrolled, 57 with esophageal cancer (48 had adenocarcinoma) and 3 with gastric cancer. No grade 4 toxicities were reported and the most common grade 3 toxicity was dermatologic (23%), secondary to cetuximab. There was no increase in chemoradiation-induced mucositis/esophagitis secondary to cetuximab and no enteral feeding tubes were required. Forty of 57 patients (70%) had an endoscopic complete clinical response after chemoradiation and rates were equal among adeno- and squamous-carcinomas. Of 49 patients who went to surgery, 27% had a

pCR [Safran *et al.* 2008]. This is similar to pCR rates reported in many of the chemoradiation trials discussed earlier. The RTOG 0436 study is currently evaluating the addition of cetuximab to paclitaxel/cisplatin, and radiation in nonoperative esophageal cancer patients. The primary endpoint is overall survival and patients with either adenocarcinoma or squamous cancers are being enrolled.

A limited phase II study of cisplatin/irinotecan and radiation was combined with cetuximab followed by surgery for locally advanced esophageal cancer was recently reported in abstract form. Only 17 patients had been enrolled at the time of reporting, but the pCR rate was disappointing at 13% and grade 3 toxicities were seen in 100% of patients [Enzinger *et al.* 2006]. These results are inferior to those reported previously with this regimen without cetuximab [Ilson *et al.* 2003]. A preliminary report of neo-adjuvant cetuximab in combination with cisplatin/irinotecan in gastric/GEJ cancer has also been reported. Patients ($n=20$) received induction cisplatin/irinotecan and cetuximab, proceeded to surgery and then received adjuvant chemoradiation as per the Intergroup 0116 study with the addition of cetuximab. Eight patients were downstaged at surgery and 16 patients underwent an R0 resection. The authors concluded that the addition of cetuximab to neo-adjuvant cisplatin/irinotecan and then adjuvant chemoradiation was well tolerated [Ma *et al.* 2009]. The Hoosier Oncology Group and the University of Texas-Southwestern reported a single-arm, open-label pilot study combining cetuximab with radiation for patients with resectable esophageal and GEJ carcinomas. Of 15 patients who underwent esophagectomy, five achieved a pCR and grade 3 toxicities were infrequent. Accrual is continuing to full study enrollment of 41 patients [SgROI *et al.* 2008]. Several phase I/II trials incorporating cetuximab into neo-adjuvant/pre-operative chemoradiotherapy are currently accruing and results are pending (see Table 3). To date, the integration of this biologic agent has been tolerable. Efficacy will be established by the ongoing RTOG 0436 trial discussed above.

Gefitinib and erlotinib are oral inhibitors of the EGFR TK domain. TKIs inhibit adenosine triphosphate binding within the TK domain and completely inhibit EGFR autophosphorylation and signal transduction. Both agents have demonstrated activity in EGFR-expressing

Table 3. Ongoing trials and planned trials of anti-epidermal growth factor receptor (EGFR) monoclonal antibodies or EGFR tyrosine kinase inhibitors in resectable gastro-esophageal cancer.

Phase	Trial# NCT00	Start date	End date	Enroll	Primary outcome	Intervention
I/II (G)	857246	Jul. 2005	Mar. 2014	38	RR to induction CPT/Cisp/Cetux	CPT/Cisp/Cetux S Adj CRT
II (E)	57821	Nov. 2007	Nov. 2009	80	RR to FOLFOX Cetux + RT	FOLFOX/RT/Cetux + S
III (E)	655876	Jun. 2008	Dec. 2015	420	OS	Cisp/Paclitax+ Cetux + RT + S
I/II (E)	544362	Jul. 2007		45	pCR rate Toxicity	Cisp/5FU+ Cetux/RT + S
II/III (E)	509561	Feb. 2008	Jan. 2010	420	OS Failure at 24 wks	Cisp/Capecit+ Cetux/RT
I/II (E)	425425	Jul. 2006		43	MTD RR	Oxali/5FU+ Cetux/RT + S
II (E)	733889	Dec. 2006	Sep. 2010	45	Clinical RR	DCF + Cisp/Cetux/RT + S
II (E)	82761	Mar. 2009	Sep. 2011	30	pCR + R0 rate	Cetux/RT + S
II(E)	815308	Jan. 2009	Apr. 2013	44	RR	Cisp/Paclitax+ Cetux/RT + S
II(E)/GEJ	493025	Apr. 2005	Jun. 2008	36	pCR	Cisp/Paclitax/Gefit/RT + S Gefit
II(E) older	524121	Mar. 2006	Oct. 2011	35	OS	Erlot/RT (no S)
III (E)	686114	May 2008	Mar. 2013	300	OS Local control	Cisp/Paclitax Erlot/RT (no S)
II (E)	393068	Feb. 2007	Feb. 2010	61	Preliminary efficacy	Cisp/Paclitax/5FU/Erlot/ Bev/RT + S

Adj, adjuvant; Bev, bevacizumab; Capecit, capecitabine; Cetux, cetuximab; Cisp, cisplatin; CPT, irinotecan; DCF, docetaxel/cisplatin/5-fluorouracil; E, esophagus; Enroll, targeted patient number to be enrolled; Erlot, erlotinib; FOLFOX, oxaliplatin plus 5-fluorouracil/leucovorin; G, gastric; GEJ, gastro-esophageal junction; Gefit, gefitinib; MTD, maximum tolerated dose; Oxali, oxaliplatin; Paclitax, paclitaxel; pCR, pathologic complete response; RR, response rate; RT, radiotherapy; S, surgery.

esophageal cell-lines, and both appear to have a synergistic action when concurrently administered with radiation [Raisch *et al.* 2003]. In the metastatic setting, it appears that the EGFR TKIs have no activity in gastric cancer, and limited activity in esophageal/GEJ cancers [Dragovich *et al.* 2006]. Phase I/II studies have looked at the TKIs given as single agents. Almost all patients progressed immediately on these agents and response rates ranged from 0–9% [Dragovich *et al.* 2006]. The main toxicities were grade 1 or grade 2 acne-like rash and diarrhea. A phase I study by Dobelbower and colleagues of the University of Alabama has reported experience with pre-operative (neo-adjuvant) erlotinib and cisplatin/5FU/radiation in localized esophageal cancer [Dobelbower *et al.* 2006]. This regimen was well tolerated and the main toxicities were rash, diarrhea, nausea and dehydration. No dose-limiting toxicities were reported. A phase II trial is planned.

Activity of EGFR monoclonal antibodies and EGFR-TKIs are predicted by KRAS and EGFR mutations [Lievre *et al.* 2008; Riely *et al.* 2006]. Mutations in these genes are rare in esophageal cancer [Karamouzis *et al.* 2007; Kwak *et al.* 2006]. There is currently no correlation with potential biomarkers of response to EGFR therapy and potential response to these agents is an issue compounded by the very low level of activity observed for both TKIs and monoclonal antibodies. Lack of synergy between cetuximab, chemotherapy and radiation has also

been noted in rectal cancer and recent work has shown that gene expression changes after cetuximab-based radiation may predict response and outcome [Debucquoy *et al.* 2009; Rodel *et al.* 2008; Machiels *et al.* 2007]. These findings may have implications for the role and timing of cetuximab in neo-adjuvant chemoradiation strategies for localized gastroesophageal cancer.

Anti-HER2 therapy

Trastuzumab is a humanized monoclonal antibody that targets the HER2/neu antigen, inhibits heterodimerization of the receptor with other activated receptors of the ERBB family, and therefore prevents downstream activation of the MAPK and PI3K molecular pathways. The net effect is decreased cell growth and promotion of apoptosis. Trastuzumab may also have antitumor activity by stimulating antibody-dependent cellular cytotoxicity [Mimura *et al.* 2005]. In esophageal cancer, HER2 overexpression by IHC ranges between 19 and 43% [Duhaylongsod *et al.* 1995]. In gastric cancer, approximately 22% of all cases are HER2 gene amplified by fluorescence *in situ* hybridization (FISH, intestinal subtype is HER2 positive in 30% of cases) and in GEJ cancers it is 34% as evidenced by the recent large HER2 expression screening effort for the ToGA trial [Bang *et al.* 2009; Kang *et al.* 2008]. This study was recently reported in abstract form and a significant OS benefit was seen with the addition of trastuzumab to cisplatin/5FU chemotherapy compared with chemotherapy alone for the treatment of

advanced/metastatic gastric and gastro-esophageal cancer (13.5 *versus* 11.1 months for the trastuzumab and chemotherapy alone arms respectively, $p=0.0048$) [Van Cutsem *et al.* 2009]. Prior studies have reported that trastuzumab is synergistic with cisplatin, paclitaxel and radiation [Pegram *et al.* 2000]. Studies have also shown that trastuzumab enhances radiosensitivity of esophageal cancer cell lines *in vitro* [Sato *et al.* 2005]. The Brown University Oncology Group investigated the addition of trastuzumab to standard chemoradiation with cisplatin/paclitaxel in patients with localized esophageal adenocarcinoma. Eleven of 19 patients enrolled for this study were HER2 positive (3+) by immunohistochemistry (IHC). Adequate tissue was available in 10 patients to perform FISH analysis. Eight of 10 had HER2 amplification by FISH. FISH was also performed on eight patients who were 2+ by IHC for HER2 overexpression, and two of eight (25%) had amplification of the HER2 gene. Toxicity was modest in this trial with only 10% of patients having grade III–IV esophagitis. No cardiac toxicity was reported. The authors concluded that the addition of trastuzumab does not increase toxicities when added to chemoradiation with cisplatin/paclitaxel in localized esophageal cancer. Eight of 14 patients with either IHC 3+ or FISH amplification of HER2 had a complete clinical response (57%). One of five patients with IHC 2+ and FISH negative had a complete clinical response. Seven patients went to surgery and three patients had a pCR. Median OS of all patients was 24 months and 3-year survival was 50% [Safran *et al.* 2007]. Further phase II trials with trastuzumab in localized esophageal cancer are underway.

Cross talk between molecular pathways in cancer is common. Studies have shown that HER2 gene amplification may have implications in predicting response to EGFR inhibition [Cappuzzo *et al.* 2005]. Lapatinib is an inhibitor of the TK domain of both the EGFR and HER2 genes and is being studied in gastro-esophageal cancers [Iqbal *et al.* 2007]. In metastatic gastric cancer, the SWOG reported a phase II study in abstract form of lapatinib as first-line treatment. No data on EGFR or HER2 expression was reported and the response rate was 7% [Iqbal *et al.* 2007]. Hecht and colleagues reported, in abstract form, on a series of 21 patients with advanced esophageal/GEJ cancer treated with lapatinib monotherapy. FISH amplification of the HER2

gene was seen in nine patients and the overall response rate was 0% [Hecht *et al.* 2008]. The phase III LOGIC (CIRG-TRIO13) trial of locally advanced or metastatic HER2-positive esophageal, GEJ and gastric cancer combines lapatinib with oxaliplatin and capecitabine and is currently accruing. Integration of dual kinase inhibitors like lapatinib into neo-adjuvant strategies for gastro-esophageal cancers may be a strategy for future study. Activity in the metastatic setting, however, is not encouraging.

Anti-VEGF therapy

VEGF is a crucial regulator of both normal and pathologic angiogenesis. VEGF is a potent mitogen for endothelial cells leading to their proliferation, migration and inhibition of apoptosis, resulting in increased permeability of blood vessels and neovascularisation of micrometastases. VEGF is overexpressed in 30–60% of patients with esophageal cancers and is associated with advanced stage and poor OS [Kleespies *et al.* 2004]. VEGF expression levels are similar in gastric cancer and are a negative prognostic factor for survival [Maeda *et al.* 1996]. Both monoclonal antibodies against VEGF, for example, bevacizumab, and TKIs against the VEGF receptor, for example, sunitinib, have reached clinical trial settings in gastro-esophageal settings. Bevacizumab is the most active agent and its use in gastro-esophageal cancers is largely confined to the metastatic setting [Jhawer *et al.* 2009; Enzinger *et al.* 2008, 2006; Shah *et al.* 2006]. A phase II trial combining cisplatin/irinotecan with bevacizumab in 47 patients with unresectable or metastatic gastric/GEJ cancers had a response rate of 65%, a median time-to-progression of 8.3 months and a median OS of 12.3 months [Shah *et al.* 2006]. The median OS reported for cisplatin/irinotecan alone in this setting is 8–9 months and the median time-to-progression is approximately 4 months [Ajani *et al.* 2002; Ilson *et al.* 1999]. There was no increase in chemotherapy-related toxicity and bevacizumab-specific toxicity was hypertension (grade 3, 28%) and thromboembolism (grades 3–4, 22.5%). The authors concluded that the addition of bevacizumab to cisplatin/irinotecan was safe and effective in gastric and GEJ cancers. Another phase II trial has been reported, in abstract form, by the same group combining modified docetaxel/cisplatin/fluorouracil (DCF) with bevacizumab. In 36 patients with measurable disease, the response rate was 64%, 6-month PFS was 84%, and median OS has not yet been reached (12- and 18-month OS was 63 and

46%, respectively) [Jhaver *et al.* 2009; Kelsen *et al.* 2009]. In this study, the grade 3–4 rate of thromboembolism was 29%, of which 93% were asymptomatic and identified on protocol-specified CT scans. Large multi-center phase III trials studying bevacizumab and chemotherapy in this setting are ongoing [AVAGST – Bevacizumab (Avastin®) in Combination With Capecitabine and Cisplatin as First-Line Therapy in Patients With Advanced Gastric Cancer].

In the neo-adjuvant setting, the Medical Research Council are studying the effect of adding bevacizumab to epirubicin/cisplatin/capecitabine (ECX) chemotherapy prior to, and after, surgery for resectable gastric and GEJ cancers [MAGIB-B, NCT00450203 www.clinicaltrials.gov]. The Memorial Sloan Kettering group are also studying the combination of neo-adjuvant ECX and bevacizumab in locally advanced but resectable gastric/GEJ adenocarcinoma [NCT00737438 www.clinicaltrials.gov].

As most patients with locally advanced esophageal cancer are treated with concurrent chemoradiation (see above) and studies have shown that VEGF levels increase in tumor and adventitial tissue during the course of radiation, even in patients who achieve a pCR, there is rationale for adding bevacizumab to pre-operative/definitive chemoradiation [Kulke *et al.* 2004; McDonnell *et al.* 2003]. Thus, based on data with pre-operative cisplatin/irinotecan/radiation, the nonoverlapping toxicities between this regimen and bevacizumab, and the potential for synergy between radiation and bevacizumab, the addition of bevacizumab to cisplatin/irinotecan and radiation is currently being explored by

Memorial Sloan Kettering in a phase II trial [NCT00578071 www.clinicaltrials.gov]. Early results of this trial have been reported, in abstract form, and indicate no increased toxicity and no increased surgical morbidity [Ilson *et al.* 2009a, 2009b]. Other groups are studying the addition of pre-operative bevacizumab to chemoradiation for localized esophageal cancer (see Table 4).

Small molecule VEGF TKIs are nonselective kinase inhibitors and act on both VEGF TK and the EGFR TK (vandetanib), or the PDGFR (sunitinib and sorafenib). Abstract reports in the metastatic and adjuvant settings are available. The University Health Network of Toronto has reported early feasibility data from a phase II trial (abstract form) on adjuvant sunitinib in surgically resected stage II or III esophageal cancer patients after neo-adjuvant cisplatin/irinotecan [Horgan *et al.* 2009]. A phase II trial has been reported (abstract form) on the combination of sorafenib and docetaxel/cisplatin in metastatic or advanced gastric/GEJ cancer. In 44 patients, objective rate was 38.6% and median OS was 14.9 months [Sun *et al.* 2008]. Based on this data, the integration of these small molecules into neo-adjuvant/pre-operative strategies for gastro-esophageal cancers has a potential rationale.

COX-2 inhibition

The COX enzyme affects several pathways in carcinogenesis, for example, apoptosis, angiogenesis, inflammation, and immune surveillance [Dannenberg *et al.* 2005]. Upregulation of COX-2 appears to play an important role in the transition of Barrett's metaplasia to esophageal carcinoma. There is a significant body of work

Table 4. Ongoing and planned trials of anti-vascular endothelial growth factor (VEGF) monoclonal antibodies or VEGF tyrosine kinase inhibitors in resectable gastro-esophageal cancer [www.clinicaltrials.gov].

Phase	Trial# NCT00	Start date	End date	Enroll	Primary outcome	Intervention
II (E)	570531	Jun. 2007	Jun. 2010	63	PFS	Cisp/Paclitax/5FU/RT/Bev Surgery Postop Bev
II (E)	354679	Apr. 2006	Apr. 2009	33	Toxicity Safety	Cisp/CPT/Bev/RT Surgery
II (E)	393068	Feb. 2007	Feb. 2010	61	Preliminary efficacy	Cisp/Paclitax/5FU/Erlotinib/ Bev/RT Surgery
II (G/GEJ)	737438	Aug. 2008	Aug. 2011	60	Efficacy of PET-directed switch	ECX/Bev(PET) Or D/CPT/Bev Surgery
II/III (G/GEJ)	450203	Oct. 2007		1100	Safety Efficacy OS	ECX/Bev Surgery ECX/Bev Bev

5FU, 5-fluorouracil; Bev, bevacizumab; Cisp, cisplatin; CPT, irinotecan; D, docetaxel; E, esophageal; ECX, epirubicin/cisplatin/capecitabine; Enroll, targeted patient number to be enrolled; Erlot, erlotinib; G, gastric; GEJ, gastro-esophageal junction; OS, overall survival; Paclitax, paclitaxel; PET, positron emission tomography; PFS, progression-free survival; Postop, postoperative; RT, radiotherapy.

on the role of nonsteroidal anti-inflammatory drugs (NSAIDs) and gastrointestinal cancer chemoprevention. Meta-analyses have shown that patients who take NSAIDs can have up to a 40% lower rate of esophageal cancer [Corley *et al.* 2003]. COX-2 overexpression also correlates with invasion, metastatic potential and resistance to radiotherapy of esophageal cancer as well as cancer proliferation through EGFR stimulation [Xi *et al.* 2005; Pai *et al.* 2002]. Thus, COX-2 inhibition strategies have been explored in metastatic and localized esophageal cancer. Several studies have been reported combining celecoxib, a COX-2 inhibitor, with chemoradiation for localized disease. A phase II study by the Hoosier Oncology Group reported a series of 31 patients who received combination cisplatin/5FU and celecoxib prior to surgery. Of the 22 patients who went to surgery, five had a pCR (22%) [Govindan *et al.* 2004]. An Australian group reported a series of 13 patients who received standard cisplatin/5FU and radiation in combination with celecoxib. The clinical complete response rate was 54% (all complete responses), and in six patients who had surgery there was one pCR. The trial was closed early due to safety concerns with celecoxib [Dawson *et al.* 2007]. In another trial, celecoxib was given with cisplatin/irinotecan and radiation as pre-operative treatment for locally advanced esophageal cancer. Of 36 patients, 33 patients had grade 3–4 toxicity and 25 completed treatment and went to surgery. The overall pCR rate was 35% [Enzinger *et al.* 2004]. A Dutch group has recently reported a study in which neo-adjuvant COX-2 inhibition selectively down-regulates hepatocyte growth factor receptor (MET) expression as well as COX-2 expression [Tuynman *et al.* 2005]. MET has been shown to be independently associated with a poor prognosis in esophageal cancer [Anderson *et al.* 2006]. This could potentially provide a role for selective MET and COX-2 inhibitors in the neo-adjuvant setting [Tuynman *et al.* 2008]. Recent data has shown an increased cardiovascular risk with the use of COX-2 inhibitors and as a result no trials involving these agents are currently accruing [Bertagnolli *et al.* 2009].

Other targets

Some activity has been seen in the metastatic setting with a variety of other targeted agents. Examples of these include histone deacetylase inhibitors, e.g. depsipeptide, mTOR inhibitors, and c-MET inhibitors [Jhawer *et al.* 2008;

Muro *et al.* 2008; Ocean *et al.* 2007]. Few of these agents have been studied in the neo-adjuvant/pre-operative setting. One agent that has been studied in this setting is prinomastat, a MMP inhibitor. MMP is a regulator of cell proliferation and growth and several MMPs are expressed in esophageal cancer [Yamashita *et al.* 2001]. Prinomastat was combined with cisplatin/paclitaxel/5FU and radiation in stage II–III esophageal cancer [Heath *et al.* 2006]. Five of 14 patients achieved a pCR, however, five patients had life-threatening thromboembolic events and the study closed early.

Prediction of response

Despite the progress in the multidisciplinary management of gastro-esophageal cancers, and the increasing integration of targeted therapies into treatment paradigms for metastatic and localized disease, pCR rates after chemoradiation remain at approximately 10–25% and 5-year OS after R0 resection is less than 30–35%. Work is being done on the role of predictive markers that can determine which patients may preferentially respond to neo-adjuvant therapies. Neo-adjuvant protocols are now incorporating response assessment strategies. Our knowledge of the molecular traits that characterize gastro-esophageal cancers is poorly understood however. In colorectal cancer, the progression from adenoma to carcinoma has been well characterized and the discovery of genetic changes such as germline mutations in the adenomatosis polyposis coli (APC) gene and mismatch repair genes has had a clear impact on clinical practice. Barrett's esophagus is a precursor lesion of esophageal adenocarcinoma and much work has been done in attempting to identify the molecular changes that lead to cancer. Sequential changes in loss of one chromosome (loss of heterozygosity), methylation of p16 and other genes, mutations in p53 and aneuploidy have all been tested but none have proven to be clinically useful to date [Jankowski and Odze, 2009]. The key to improving outcomes in gastro-esophageal cancers will lie in better understanding the underlying molecular pathogenesis.

Recent evidence suggests that functional imaging by (PET) with radiolabelled fluorodeoxyglucose (FDG) has a promising role in gastro-esophageal cancer. Predicting tumor response during the early phase of chemotherapy has been shown to be feasible, valuable and easily applicable to clinical practice. In the German Metabolic Response

Evaluation for Individualization of Neo-adjuvant Chemotherapy in Oesophageal and Oesophago-gastric Adenocarcinoma (MUNICON) study of locally advanced esophageal/GEJ cancer, early PET responders (decrease of $>35\%$ in the tumor glucose standardized uptake value [SUV]) after 2 weeks of induction cisplatin/5FU continued to receive the full 12-week course of pre-operative treatment and the nonresponders went straight to surgery. Outcome in the nonresponders who went to immediate surgery was similar to the results in the investigators previous trial in which nonresponders completed a total of 3 months of pre-operative chemotherapy. Stopping ineffective therapy early did not compromise outcome and avoided patient exposure to potentially toxic useless treatment. It was found that patients with a metabolic response, a surrogate for tumor response, survived significantly longer than the nonresponders (median not reached for the PET responders *versus* 25.8 months for the nonresponders). R0 resection rates (96 *versus* 74%) and major pathologic response (58 *versus* 0%) was also significantly higher in the PET responder group [Lordick *et al.* 2007]. Based on these results, the EUROCON study is currently randomizing metabolic nonresponders after 2 weeks of chemotherapy to immediate resection or chemoradiation followed by surgery. Switching chemotherapy in patients with progressive disease on early PET scan during induction chemotherapy has been reported in a phase II trial of locally advanced esophageal cancer from Memorial Sloan Kettering [Ku *et al.* 2007]. Durable disease control was obtained in three of four patients who progressed on induction cisplatin/irinotecan and were switched to paclitaxel/5FU during the radiation phase (one pCR, one pathological partial response and one clinical complete response). This strategy is being incorporated into a recently opened Memorial Sloan Kettering trial of neo-adjuvant ECX with bevacizumab in locally advanced but resectable gastric/GEJ adenocarcinoma [NCT00737438 www.clinicaltrials.gov]. In this trial, patients who do not respond to an early PET scan on week three of ECX will be switched to docetaxel/irinotecan. The utility of early metabolic response assessment during chemoradiation is currently being investigated by The M.D. Anderson group [NCT00833625 www.clinicaltrials.gov].

The challenge of identifying biomarkers in gastro-esophageal cancers that predict response

to chemo-targeted therapy has been more difficult. The identification of HER2/neu amplification and the estrogen/progesterone receptors in breast cancer, BCR-ABL translocation in gastro-intestinal stromal tumor and chronic myelogenous leukemia, EGFR TK-domain deletions/mutations in non-small cell lung cancer and KRAS/BRAF mutations in colorectal cancer have all identified subsets of patients who will respond to different targeted therapies. In gastro-esophageal cancer, the evolving story of HER2/neu aside, there is no consensus on genetic alterations that predict response to targeted agents. KRAS and BRAF mutations are rare ($<3\%$) and therefore mutation analysis on these genes to predict response to EGFR monoclonal antibody therapy is unhelpful [Lee *et al.* 2003]. The absence of validated markers for sensitivity to EGFR monoclonal antibodies or EGFR TKIs is compounded by the virtual lack of activity for these agents in gastro-esophageal cancers. Also, mutations in the EGFR gene have not been shown to predict response to EGFR TKIs [Guo *et al.* 2006; Personeni, 2006; Tew *et al.* 2005]. Debuquoy and colleagues have reported array and proteomic data on cetuximab-based chemoradiation in rectal cancer suggesting that the timing of cetuximab in relation to chemoradiation may be important in outcome. The downregulation of genes involved in proliferation and the upregulation of genes involved in inflammation after a loading dose of cetuximab was directly correlated with disease-free survival [Debuquoy *et al.* 2009]. The applicability of this work to the clinic and the relevance in gastro-esophageal cancers is currently unknown.

Much work has been done on the expression of chemotherapy-related genes and response to neo-adjuvant therapy. The main chemotherapy agents used to treat gastro-esophageal cancers are 5FU and platinum. Expression level of 5FU metabolism genes (thymidine phosphorylase, dihydropyrimidine dehydrogenase, thymidylate synthase, methylenetetrahydrofolate reductase) and platinum metabolism genes (excision repair cross-complementing group [ERCC]) has been extensively studied [Fareed *et al.* 2009]. Lenz and colleagues have reported on the association between thymidylate synthase genotypes and likelihood of recurrence in stage II/III colorectal cancer in patients treated with adjuvant 5FU-based therapy [Lurje *et al.* 2008]. In non-small cell lung cancer, low levels of the ERCC1 are associated with a benefit from platinum-based

chemotherapy compared with those tumors that are ERCC1 positive [Olaussen *et al.* 2006]. In gastric cancer, high levels of ERCC1/dihydropyrimidine dehydrogenase (DPD) and low levels of EGFR have been correlated with poor survival after first-line chemotherapy [Matsubara *et al.* 2008]. Level of expression and the presence of genetic polymorphisms have also been found to correlate with response to neo-adjuvant chemoradiation. Factors involved in apoptosis, e.g. survivin and Bax; transcription factors, e.g. TP53 and NF κ B; and hypoxia/angiogenesis, e.g. HIF-1 α and VEGF, have been correlated with response to neo-adjuvant therapy [Fareed *et al.* 2009; Boonstra *et al.* 2007]. Recent retrospective data in 210 patients with esophageal cancer who underwent neo-adjuvant chemoradiotherapy and then surgery has reported a modulation of clinical outcomes secondary to single nucleotide polymorphisms in the PI3K/PTEN/AKT/mTOR pathway [Hildebrandt *et al.* 2009]. The validation of this data in future studies may have implications for neo-adjuvant strategies in localized gastro-esophageal cancer and ultimately lead to individualized therapy. Inhibition of activated mTOR is a validated strategy in kidney cancer and this has led to targeting this protein in other cancers. In esophageal squamous cell carcinoma, studies have shown that activated mTOR was detected in up to 25% of cases [Boone *et al.* 2008]. mTOR-inhibiting strategies are therefore being considered. Technology is now evolving that can examine expression of multiple genes in tumors using DNR array. This will be of immense value in predicting response to neo-adjuvant therapy. Two recent studies in patients with esophageal cancer treated with neo-adjuvant chemoradiation reported molecular signatures correlating with pCR and survival [Luthra *et al.* 2007, 2006]. These studies found that decreased expression of the epidermal differentiation complex genes S100A2 and SPRR3 were associated with resistance to chemoradiation. Further studies using bigger sample sets are underway. Gene therapy is also an evolving technology in cancer treatment. To date there is one trial using this technology in patients with chemoradiotherapy resistant advanced esophageal cancer [Shimada *et al.* 2006]. Transfer of p53 in the tumor using an adenovirus was feasible and stable disease was seen in six of ten patients [Shimada *et al.* 2006].

Routine use of predictive biomarkers in the neo-adjuvant treatment of gastro-esophageal cancers is not yet standard practice. However, as the

choice of neo-adjuvant chemotherapy and targeted agents increases, it is imperative that future clinical trials study and validate the utility of potential predictive biomarkers. Gastro-esophageal cancers are especially suited in this regard as the procurement of tissue with pre- and post-treatment biopsies is relatively straightforward. Routine use of validated predictive biomarkers will not only identify those patients that will respond to treatment but will result in a significant cost saving with a more judicious use of expensive and toxic drug treatments.

Conclusion

Pre- and peri-operative strategies are rapidly becoming an accepted standard for the management of localized gastro-esophageal cancer. For localized gastric/GEJ cancer there are conflicting data that a peri-operative approach with cisplatin-based chemotherapy improves survival, with the benefits seen in esophageal cancer likely less than a 5–10% incremental improvement. Further trends toward improvement in both local tumor control and survival, when combined chemotherapy and radiation therapy are given pre-operatively, are suggested by more recent phase III trials. In medically fit patients, a significant survival benefit with pre-operative chemoradiation is achieved in those patients who achieve a pCR. In esophageal and GEJ cancer, definitive chemoradiation is now considered in medically inoperable patients. In patients with squamous cell carcinoma of the esophagus, surgery after primary chemoradiation is not clearly associated with an improved OS, however, local control may be better.

In localized gastric/GEJ cancer, the integration of bevacizumab with pre-operative chemotherapy is being explored in large randomized studies, and with chemoradiotherapy in pilot trials. In esophageal/GEJ cancers, the addition of anti-EGFR and anti-HER2 antibody treatment to pre-operative chemoradiation has been and continues to be explored. Early results show the integration of targeted therapy is feasible. Metabolic imaging can predict early response to pre-operative chemotherapy and further validation is underway in the randomized EUROCON trial. It is hoped biomarkers will further predict response to both pre-operative chemotherapy and targeted therapy.

A multi-modality approach to localized gastro-esophageal cancer has resulted in better outcomes. For T3 or node-positive disease, surgery

alone is no longer considered appropriate and neo-adjuvant therapy is recommended. The future of neo-adjuvant strategies in this disease will involve individualization of therapy with the integration of molecular signatures, targeted therapy, metabolic imaging and predictive biomarkers.

Conflict of interest statement

None declared.

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