Cancer Management and Research

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REVIEW

New and emerging combination therapies for esophageal cancer

This article was published in the following Dove Press journal:
Cancer Management and Research
26 June 2013
Number of times this article has been viewed

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Abstract: Esophageal cancer comprises two different histological forms – squamous cell carcinoma (SCC) and adenocarcinoma (AC). While the incidence of AC has increased steeply in Western countries during the last few years, the incidence of SCC is fairly stable. Both forms differ in pathogenesis and response to chemotherapy and radiation therapy. Plenty of studies have evaluated new chemotherapy combination regimens in the neoadjuvant, adjuvant, and palliative setting. In addition, new radiation and chemoradiation protocols have been investigated. Finally, molecular-targeted therapy has been included in several new randomized prospective trials. Therefore, this review presents new data on this topic and critically discusses promising approaches towards a more effective treatment in a disease with a grim prognosis.

Keywords: chemotherapy, chemoradiation, molecular targeted therapy

Introduction

The crude incidence of esophageal cancer in the European Union is about four to five cases per 100,000 population. In Germany, the tumor holds ninth place of all cancer casualties for men and 15th place for women. It comprises two different histological forms, squamous cell carcinoma (SCC) and adenocarcinoma (AC). In contrast to Asian countries, the incidence of AC has increased steeply in Western countries, based on an increased incidence of Barrett's esophagus as the precursor. In contrast, the incidence of SCC has been fairly stable during the last decade. The tumor TNM staging system, as outlined by the Union for International Cancer Control, groups esophageal cancer in different stages (Table 1).[1] Local endoscopic resection ± thermal ablation (photodynamic therapy, and endoscopic radio-frequency ablation of Barrett's esophagus with dysplasia) is indicated for tumors restricted to the mucosa with a size < 2 cm. T2 tumors without metastases are suitable for primary surgery; in most cases, subtotal en bloc esophagectomy with two-field lymphadenectomy is preferred. T3 tumors and T4 tumors should be primarily treated with neoadjuvant chemotherapy (mainly AC) or chemoradiation (SCC and AC) to increase the chance of curative (R0) resection. Definitive chemoradiation (or chemotherapy in the case of distant metastases) should be provided to functional nonoperable patients. In the case of nonresectable obstructive tumor growth, endoscopic metal stent placement as the best supportive care may give relief in these patients. The prognosis of esophageal cancer is very poor. About 50% of patients have advanced disease at the diagnosis, and the natural course encompasses only 8 to 10 months overall survival (OS) time, with a 5-year survival rate of 5%–17%. In addition, though some patients receive curative surgical treatment, the disease recurs

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Table 1 TNM- and UICC-classification of esophageal cancer 2010

TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	High-grade dysplasia		
T1a	Tumor invades lamina propria or muscularis mucosae		
T1b	Tumor invades submucosa		
T2	Tumor invades muscularis propria		
T3	Tumor invades adventitia		
T4a	Tumor invades pleura, pericardium, or diaphragm		
T4b	Tumor invades neighboring structures, such as aorta, vertebral body, or trachea		
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	1–2 regional lymph node metastases		
N2	3–6 regional lymph node metastases		
N3	≥7 regional lymph node metastases		
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2	N1	M0
Stage IIIA	T4a	N0	M0
	T3	N1	M0
	T1, T2	N2	M0
Stage IIIB	T3	N2	M0
Stage IIIC	T4a	N1, N2	M0
	T4b	any N	M0
	any T	N3	M0
Stage IV	any T	any N	M1

Abbreviations: TNM, TNM Classification of Malignant Tumors; UICC, Union for International Cancer Control.

and metastasizes in up to 65% of patients after 5 years. (For further review, see Mawhinney et al.[2]) Therefore, there is a need for new treatment strategies, which will be discussed in the review article.

Perioperative treatment of esophageal cancer

Neoadjuvant chemotherapy

A recent meta-analysis including ten studies and 2062 randomized patients with AC and SCC showed a significant improvement in OS after neoadjuvant chemotherapy, with a relative risk reduction of 13% (hazard ratio [HR] 0.87; 95% CI [confidence interval], 0.79–0.96; $P = 0.005$), resulting in a 2-year survival increase of 5.1%. While this difference was not significant for patients with SCC (HR 0.92; 95% CI, 0.81–1.04; $P = 0.18$), it was highly significant for patients with AC (HR 0.83; 95% CI, 0.71–0.95; $P = 0.01$).[3] However, in Japan, neoadjuvant chemotherapy for SCC with cisplatin/5-fluorouracil (FU) is still regarded as standard treatment and cannot be replaced by adjuvant chemotherapy with the same regimen.[4]

Perioperative (neoadjuvant and adjuvant) chemotherapy

Perioperative chemotherapy of distal esophageal and esophagogastric junction cancer was first established with the Phase III UK Medical Research Council Adjuvant Gastric Infusional Chemotherapy-study, published in 2006 in the *New England Journal of Medicine* and primarily designed for stomach cancer patients.[5] In this trial, a perioperative epirubicin/cisplatin/5-FU (ECF) regimen (n = 250) decreased tumor size and stage and significantly improved progression-free survival (PFS) (HR 0.66; 95% CI, 0.53–0.81; $P < 0.001$) and OS (HR 0.75; 95% CI, 0.6–0.93; $P = 0.009$) in comparison to surgery alone (n = 253). Cisplatin/5-FU regimen as an alternative in this setting (distal esophageal, esophagogastric junction, and stomach cancer) was published 5 years later, derived from the results of the French Fédération Francophone de Cancérologie Digestive (FFCD) multicenter Phase III trial (n = 113 for perioperative chemotherapy and n = 111 for surgery alone).[6] This trial showed a significantly increased curative resection rate, disease-free survival (HR 0.65; 95% CI, 0.48–0.89; $P = 0.003$) and OS (HR 0.69; 95% CI, 0.5–0.95; $P = 0.02$). Recently, two Phase II studies (both on distal esophageal, esophagogastric junction, and stomach cancer) evaluated docetaxel/cisplatin/capecitabine (DCX)[7] (n = 51) and docetaxel/cisplatin/5-FU (DCF)[8] (n = 43) combinations as alternative tolerable and highly effective regimens because disadvantages of ECF include anthracycline-induced cardiotoxicity and a lengthy 21-day continuous infusion of 5-FU at each cycle.

Neoadjuvant-targeted therapy

In contrast, addition of angiogenesis inhibitor bevacizumab to neoadjuvant chemotherapy with cisplatin/5-FU showed no extra benefit in patients with SCC (n = 6) or AC (n = 22) in comparison to a historical control group (n = 37) that was treated with cisplatin/5-FU alone.[9] In this study, the response rate (RR) was 39%; the R0 resection rate was 43%; and the median OS was 17 months for the experimental group. The triple regimen was well-tolerated, with the most common severe toxicities being venous thromboembolism (10%), nausea (7%), and gastrointestinal bleeding (7%).

Adjuvant chemoradiation

In the pivotal Intergroup-0116 Phase III trial by Macdonald et al,[10] adjuvant chemoradiation (without

preoperative chemotherapy) improved both disease-free survival (HR 1.52; 95% CI, 1.23–1.86; $P < 0.001$) and OS (HR 1.35; 95% CI, 1.09–1.66; $P = 0.005$) in curatively resected patients with mainly gastric and esophagogastric junction adenocarcinoma.[10] Updated results from last year confirmed that adjuvant chemoradiation (45 gray [Gy] radiation dose) remains a rational standard therapy for curatively resected gastric and esophagogastric junction cancer with primaries T3 or greater and/or positive nodes (n = 559 in the study), at least in the United States, where D2 resection is less common than in Europe or Japan.[11] For this reason, the Intergroup-0116 study was criticized in Asia and Europe, because a majority of patients received less than a D1 lymph node dissection at surgery, while fewer than 10% underwent the more extensive D2 resection. This led to speculation that postoperative chemoradiation simply compensated for inadequate surgery. Although significantly fewer local and regional recurrences were found in the chemoradiation group, the absolute number of local recurrences was too small to draw definitive conclusions. However, a Danish Phase II study examining only patients with esophagogastric junction adenocarcinoma recently confirmed the Intergroup-0166 results (116 patients were treated with adjuvant chemoradiation).[12] Median time of survival was prolonged by 10 months in favor of those who received chemoradiation.

Perioperative chemoradiation

More recently, the Southwest Oncology Group designed a trimodal, Phase II, single-arm trial with the objective of achieving a pathological complete remission (pCR) rate of 40% after neoadjuvant treatment with oxaliplatin/5-FU/radiation and adjuvant chemotherapy in esophageal adenocarcinoma.[13] Ninety-three patients were evaluable. Seventy-nine patients (84.9%) underwent surgery, and 67.7% of patients had R0 resections. Twenty-six patients (28.0%) had confirmed pCR (95% CI, 19.1%–38.2%). At a median follow-up of 39.2 months, estimates of median and 3-year OS were 28.3 months and 45.1%, respectively.

Neoadjuvant chemoradiation

After a neoadjuvant combination of irinotecan/cisplatin/radiation 69% of AC and SCC patients (n = 55) of another Phase II study underwent R0 resection. The incidence of pCR was 16% (95% CI 8%–29%). Median OS was 31.7 months.[14] Neoadjuvant treatment with docetaxel, cisplatin, 5-FU, and radiation in untreated stage II–III AC and SCC of mid-distal thoracic esophagus was also investigated in another recent Phase II study.[15] pCR was found in 47% (35 of 74) and near pCR (microfoci of tumor cells on the primary tumor without lymph nodal metastases [pnCR]) in 15% of the patients (11 of 74). Median survival of all 74 patients was 55 months, while in the pCR subset the median survival could not be calculated, as >50% of the patients were still alive. The large Phase III Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) study from the Netherlands additionally established a neoadjuvant carboplatin/paclitaxel/radiation regimen.[16] Two hundred seventy-five patients (75%) had adenocarcinoma, 84 (23%) had squamous cell carcinoma, and 7 (2%) had large-cell undifferentiated carcinoma. Complete resection (R0) was achieved in 92% of patients in the chemoradiation-surgery group versus 69% in the surgery group ($P < 0.001$). Postoperative complication rate was similar in the two treatment groups, and in-hospital mortality was 4% in both. Median OS was 49.4 months in the chemoradiation-surgery group versus 24.0 months in the surgery group (HR 0.657; 95% CI, 0.495–0.871; $P = 0.003$). Finally, two meta-analyses of older randomized-controlled trials for neoadjuvant chemoradiation showed a clear benefit in terms of OS in comparison to surgery alone, especially for patients with adenocarcinoma.[3,17] In detail, the meta-analysis by Jin et al[17] comprised eleven randomized-controlled trials from 1992 to 2008, including 1308 patients.[18–28] The meta-analysis by Sjoquist et al[3] included 17 randomized-controlled trials from their previous meta-analysis and seven further studies. Twelve were randomized comparisons of neoadjuvant chemoradiotherapy versus surgery alone (n = 1854);[16,18–26,29,30] nine were randomized comparisons of neoadjuvant chemotherapy versus surgery alone (n = 1981); and two compared neoadjuvant chemoradiotherapy with neoadjuvant chemotherapy (n = 194) in patients with resectable esophageal carcinoma. One factorial trial included two comparisons and was included in analyses of both neoadjuvant chemoradiation (n = 78) and neoadjuvant chemotherapy (n = 81).

Neoadjuvant chemoradiation plus targeted therapy

In contrast, the addition of molecular-targeted therapy with bevacizumab and erlotinib to neoadjuvant chemoradiation (paclitaxel/carboplatin/5-FU/radiation) in AC/SCC-patients (including tumors of the gastroesophageal junction) did not demonstrate a survival benefit or improved pathologic complete response rate over similar regimens (n = 62). While the overall rates of toxicity were not increased, targeted agent-specific toxicity (grade 3/4 leukopenia in 64%; grade

3/4 neutropenia in 44%; grade 3/4 mucositis/stomatitis in 42%; grade 3/4 diarrhea in 27%; and grade 3/4 esophagitis in 27%) was evident.[31]

Definitive chemoradiation

A randomized-controlled Phase III study from the US (Radiation Therapy Oncology Group trial 85–01) clearly demonstrated superiority of chemoradiation in comparison to radiation alone in patients with SCC and AC.[32] However, chemotherapy could be administered as planned in only 89 (68%) of 130 patients (10% had life-threatening toxic effects with combined therapy versus 2% in the radiation-only group). Stahl et al[33] compared chemoradiation (etoposide and cisplatin, 40 Gy) followed by surgery (arm A; n = 86) with definitive chemoradiation (60 Gy) (arm B; n = 86). The OS was equivalent in both SCC groups; local PFS was better in arm A (HR 2.1; 95% CI, 1.3–3.5; $P = 0.003$), but treatment-related mortality less in arm B (3.5% versus 12.8%; $P = 0.03$).[33] These results were confirmed by a similar randomized French trial (259 patients were randomly assigned) using 5-FU and cisplatin as combination partners for radiation (only SCC patients).[34] Median survival time was 17.7 months in the surgery group versus 19.3 months in the definitive chemoradiation group. A third prospectively randomized study from Hong Kong (81 patients were randomly assigned) demonstrated a remarkable 5-year survival rate of 48.6% for the definitive chemoradiation (5-FU/cisplatin/50–60 Gy) group and a trend to improved 5-year survival in node-positive disease (only SCC patients).[35] In a recent study presented at ASC0 2012 (PRODIGE 5/ACCORD 17 trial; Conroy et al; LBA 4003)[36] patients with nonoperable localized esophageal carcinoma (85% SCC; 15% AC) were randomized to two different chemoradiation protocols. Radiation dose was 50 Gy in both arms. Patients in arm A received six cycles of FOLFOX (5-FU/oxaliplatin) every 2 weeks; patients in arm B had four cycles of 5-FU/cisplatin every 3 weeks. PFS (9.7 months versus 9.4 months), the primary study end point, and OS survival (20.2 months versus 17.5 months) were similar in both arms. Addition of epithelial derived growth factor receptor (EGFR) 1 inhibitor cetuximab to a capecitabine/cisplatin/radiation backbone did result in greater toxicity, a lower rate of completion of standard therapy, and significantly worse survival (22 months versus 25 months; $P = 0.043$) in patients with locally advanced SCC (73%) or AC (27%) as demonstrated by a recent large UK study (SCOPE-1, National Clinical Trial [NCT]00509561, Crosby et al; 2013 Gastrointestinal Cancers Symposium, LBA3).[37] Docetaxel/cisplatin/radiation combination is feasible too, as demonstrated in a Korean Phase II study (36 SCC patients).[38] In a recent meta-analysis of three randomized studies, definitive chemoradiation in patients with SCC did not demonstrate any survival benefit over other curative strategies, but treatment-related mortality rates were lower (HR 7.60; $P = 0.007$).[39] A study from Korea suggested vascular endothelial growth factor (VEGF) as a positive predictive factor and cyclooxygenase-2 (COX-2) as a negative prognostic factor for OS in patients with SCC after definitive chemoradiation.[40]

Palliative first-line treatment of esophageal cancer

Chemotherapy

In past decades, there was not much improvement in the outcome and survival of advanced esophageal cancer due to the lack of effective chemotherapy agents. The traditional chemotherapy drugs to treat esophageal cancer include 5-FU and cisplatin, and the combination of them results in a 25%–35% RR in both first-line and second-line treatment (Table 2).[41] Unfortunately, the main side effect of cisplatin is renal toxicity. The peak age of esophageal cancer patients is 65 to 70 years, and many of them have other diseases at the same time, such as hypertension, diabetes, and chronic kidney disease, which cause varying damage to renal function, and limit the use of cisplatin in these patients. Therefore, it is both urgent and crucial to seek an alternative to cisplatin in the combination chemotherapy treatment. Due to high-response rates in Asian patients, a combination of cisplatin/oral fluoropyrimidine (S-1) was compared with cisplatin/infusional 5-FU in patients with advanced gastric or gastroesophageal adenocarcinoma (FLAGS trial).[42] One thousand fifty-three patients were stratified, and the primary end point was superiority in OS from cisplatin/S-1 (Table 2). Although this goal was not met in the cisplatin/S-1 arm (HR 0.92; 95% CI, 0.80–1.05; $P = 0.20$), significant safety advantages were observed in the cisplatin/S-1 arm, compared with the cisplatin/infusional fluorouracil arm, for the rates of grade 3/4 neutropenia (32.3% versus 63.6%), complicated neutropenia (5.0% versus 14.4%), stomatitis (1.3% versus 13.6%), hypokalemia (3.6% versus 10.8%), and treatment-related deaths (2.5% versus 4.9%; $P < 0.05$). 5-FU can also be replaced by oral capecitabine[43] (Xeloda [Roche, Basel, Switzerland] platinum regimen) and cisplatin by oxaliplatin,[44] based on Phase II studies. Dual replacement was also successful.[45,46] Regarding toxicity, 5-FU/leucovorin/oxaliplatin (FLO) seems to be less toxic

Table 2 Prospective clinical trials of first-line chemotherapy of esophageal cancer

Design	Treatment	n	Histology	RR	Median OS	Reference
Phase II	Cisplatin/5-FU	44	SCC	35%	8.25 months	41
Phase II	Paclitaxel/5-FU/cisplatin	60	SCC/AC	48%	10.8 months	49
Phase II	Cisplatin/irinotecan	35	SCC/AC	57%	14.6 months	50
Phase II	Cisplatin/vinorelbine	71	SCC	34%	6.8 months	51
Phase II	Oxaliplatin/5-FU	35	SCC/AC	40%	7.1 months	44
Phase II	Docetaxel/ capecitabine	16	SCC/AC + GEJ	56%	15.8 months	54
Phase II	Docetaxel/cisplatin	76	GEJ +	26%	10.5 months	56
	Docetaxel/cisplatin/5-FU	79	GASTRIC	43%	9.6 months	
Phase II	Docetaxel/capecitabine	44	GEJ + GASTRIC	39%	9.4 months	53
Phase II	Oxaliplatin/ capecitabine	43	AC + GEJ + GASTRIC	35%	6.4 months	46
Phase II (first, second l)	Oxaliplatin/ capecitabine	51	SCC/AC + GEJ	39%	8 months	45
Phase II	Docetaxel/ capecitabine/ carboplatin	25	AC + GEJ + GASTRIC	48%	8 months	58
Phase II	Docetaxel/cisplatin/5-FU	60	GEJ + GASTRIC	47%	17.9 months	57
Phase III	ECF	249	SCC +	41%	9.9 months	55
	ECX	241	AC +	46%	9.9 months	
	EOF	235	GEJ +	42%	9.3 months	
	EOX	239	GASTRIC	48%	11.2 months	
Phase II	Cisplatin/paclitaxel	35	SCC	49%	13 months	48
Phase II	Capecitabine/cisplatin	45	SCC	58%	11.2 months	43
Phase III	Cisplatin/S-1	82	GEJ +	29%	8.6 months	42
	Cisplatin/5-FU	88	GASTRIC	32%	7.9 months	
Phase II	Docetaxel/cisplatin/ 5-FU	50	SCC/AC + GEJ + GASTRIC	47%	11.2 months	59
Phase II (first, second l)	Paclitaxel/ capecitabine	32	SCC	75% 45%	14.3 months 8.4 months	52
Phase II	Cisplatin/paclitaxel	46	SCC	57%	17 months	60

Notes: *$P < 0.05$; **$P < 0.01$.

Abbreviations: 5-FU, 5-fluorouracil; AC, adenocarcinoma; ECF, epirubicin/cisplatin/5-FU; ECX, epirubicin/capecitabine/5-FU; EOF, epirubicin/oxaliplatin/5-FU; EOX, epirubicin/oxaliplatin/capecitabine; GASTRIC, gastric cancer; GEJ, gastroesophageal junction carcinoma; S-1, oral fluoropyrimidine; SCC, squamous cell carcinoma; OS, overall survival; RR, response rate.

than 5-FU/leucovorin/cisplatin (FLP), according to a Phase III study that included mostly gastric cancer patients but also patients with gastroesophageal tumors.[47] A paclitaxel-plus-cisplatin regimen is another promising treatment of esophageal cancer and has been proven effective at Phase II level (Table 2).[48] This combination has become a standard treatment of esophageal cancer, especially of SCC. In addition, paclitaxel or docetaxel can be combined with capecitabine (Table 2).[52–54]

In AC patients with a good general condition triplet regimen, such as ECF, epirubicin/cisplatin/capecitabine (ECX), epirubicin/oxaliplatin/5-FU (EOF), and epirubicin/oxaliplatin/capecitabine (EOX), or DCF/DCX, and DCC (docetaxel/carboplatin/capecitabine) are even more effective regarding response rate; however, toxicity is markedly increased (Table 2).[55–59]

Targeted therapy

EGFR, a member of the ErbB tyrosine kinase family, is a target that was examined in several studies. Binding of the ligand leads to receptor dimerization and consecutively to activation of downstream signals regulating cell cycle, apoptosis, cell proliferation, and angiogenesis. Overexpression of EGFR was detected in 30%–90% of esophagogastric tumors, correlating with increased invasion, dedifferentiation, and worse prognosis.[61–64] In contrast to colorectal and lung cancer, *KRAS* mutation status and EGFR mutations do not seem to play a role. Anti-EGFR therapies include monoclonal antibodies (eg, cetuximab and panitumumab) and receptor tyrosine kinase inhibitors (eg, erlotinib and gefitinib).

The results of a multicenter, open-label, randomized Phase III trial (EXPAND) testing the efficacy of cetuximab (Erbitux™, Merck KGaA, Darmstadt, Germany) in

combination with cisplatin and capecitabine first line for patients with 69% advanced gastric adenocarcinoma and 31% adenocarcinoma of the gastroesophageal junction (GEJ) failed to show a significant improvement of PFS, when compared to cisplatin and capecitabine alone (Lordick et al,[68] ESMO 2012). The EXPAND trial followed promising results from four Phase II trials. This first trial combined cetuximab with cisplatin and docetaxel (DOCETUX) in patients with locally advanced or metastatic gastric cancer (82%) or GEJ tumors (18%). It showed a disease control rate of 77% among 68 patients (Table 4).[65] The second trial combined cetuximab with irinotecan and 5-FU in patients with locally advanced or metastatic gastric cancer (71%) or GEJ tumors (29%). It showed a disease control rate of 79% among 48 patients (Table 4).[66] The third trial again combined cetuximab with irinotecan and 5-FU (FOLCETUX) in patients with locally advanced or metastatic gastric cancer (89%) or GEJ tumors (11%). It showed a disease control rate of 91% among 38 patients (Table 4).[67] The fourth trial combined cetuximab with oxaliplatin and 5-FU in patients with locally advanced or ± metastatic gastric cancer (52%) or GEJ tumors (48%). It showed a disease control rate of 83% among 52 patients (Table 4).[68] Regarding patients with SCC, a combination of cetuximab and cisplatin/5-FU (CF) was compared with CF in a prospective randomized study.[69] It was concluded that cetuximab can be safely combined with CF chemotherapy and may increase the efficacy of standard CF chemotherapy (Table 4). In contrast, the combination of another EGFR-antibody panitumumab with EOX in patients with AC, led to a decreased OS in comparison to EOX alone (Table 4). In this prospective Phase II/III UK study (NCT00824785, Randomized Trial of EOX ± Panitumumab for Advanced and Locally Advanced Esophagogastric Cancer [REAL-3]),[70] 553 patients with locally advanced AC of the esophagus and stomach cancer were recruited (Waddell et al, ASCO 2012, LBA4000).[71] A combination with panitumumab, in comparison to EOX alone, was associated with increased G3/4 diarrhea (17% versus 11%), skin rash (14% versus 1%), and thrombotic events (12% versus 7%), but less hematological toxicity (>G3 neutropenia 14% versus 31%). Interestingly, in the combination arm, OS was significantly improved in patients with G1-3 rash (median OS 10.2 versus 4.3 months [$P < 0.001$]), with similar significant improvements seen in RR and PFS. Regarding study results for receptor tyrosine kinase inhibitors (eg, erlotinib and gefitinib), 5-FU/oxaliplatin (FOLFOX6) was tested in combination with erlotinib in 33 patients with metastatic or advanced AC of the esophagus and gastroesophageal junction, resulting in a sufficient RR and decent OS (Table 4).[72]

HER2R/NeuR (Human Epidermal Growth Factor Receptor 2, ERBB2R) is another member of the HER tyrosine kinase receptor family; overexpression in AC of the GEJ has been detected between 0%–43%.[73,74] Anti-HER2 therapies that have been evaluated in metastatic GEJ cancer are the monoclonal antibody trastuzumab and the oral small tyrosine kinase inhibitor lapatinib. Based on positive Phase II data in gastric cancer patients, trastuzumab was evaluated in a large Phase III trial, including gastric cancer patients and patients with AC of the GEJ if their tumors showed overexpression of HER2 protein by immunohistochemistry or gene amplification by fluorescence in situ hybridization.[75] Participants were randomly assigned in a 1:1 ratio to receive capecitabine (or 5-FU)/cisplatin chemotherapy or chemotherapy in combination with intravenous trastuzumab. Since OS was significantly prolonged in the experimental group, trastuzumab in combination with chemotherapy can be considered as a new standard option for patients with HER2-positive advanced gastric or GEJ cancer (Table 4). Use of lapatinib, a dual EGFR and HER2R inhibitor, was associated with a lack of response in patients with GEJ cancer (Table 4).[76] Currently, a combination with capecitabine/oxaliplatin (CapeOx) is being investigated (see Current investigations section).

Another principle of molecular-targeted therapy that has been studied in small patient groups is inhibition of vascular endothelial growth factor (VEGF), which is overexpressed in 30%–60% of patients with esophageal cancer.[77–80] Since VEGF inhibition by bevacizumab (a humanized immunoglobulin [Ig] G1 antibody), in combination with cisplatin/irinotecan and docetaxel/oxaliplatin seemed promising, with a RR of 65% and 59%, a Phase III study was initiated investigating a capecitabine/cisplatin combination ± bevacizumab.[81,82] Although 774 patients with inoperable, locally advanced, or metastatic stomach/GEJ AC with no prior therapy were randomized, no survival benefit could be detected for the targeted therapy (Avastin in Gastric Cancer [AVAGAST]-study, ASCO 2010, LBA 4007).[83]

Finally, oral multitarget tyrosine kinase inhibitors – sunitinib,[84] sorafenib,[85] and protein kinase C inhibitor bryostatin-1[86,87] – have shown minor activity in GEJ AC.

Palliative second-line treatment of esophageal cancer

In case of treatment failure or relapse, second-line treatment may be indicated in patients who are still fit enough to tolerate

Table 3 Prospective clinical trials of second-line chemotherapy of esophageal cancer

Design	Treatment	n	RR	Median OS	Reference
Phase II	Vinorelbine	16[+]	6%	6 months	88
Phase II	Docetaxel	11[++]	0%	4 months	89
Phase II	Docetaxel/irinotecan	24[+++]	12.5%	6.5 months	94
Phase II	Paclitaxel	13[+++]	0%	NA	91
Phase II	Docetaxel	38[+++]	16%	8.1 months	90
Phase II	Docetaxel/capecitabine	8[+++]	25%	6.2 months	54
Phase II	Docetaxel/nedaplatin	28[+++]	39.3%	8.5 months	100
Phase II	Docetaxel/nedaplatin	12[+]	25%	NA	97
Phase II	Irinotecan	13[++]	15.4%	5 months	92
Phase II	Docetaxel/cisplatin/5-FU	20[+++]	35%	8 months	101
Phase II	Docetaxel/cisplatin/5-FU	32[+++]	50%	NA	102
Phase II	Mitomycin/ifosfamide/cisplatin	19[+]	12.5%	5.2 months	103
Phase II	Docetaxel/nedaplatin	20[+]	25%	6.5 months	98
Phase II	Docetaxel/irinotecan	15[++]	20%	11.4 months	95
Phase II	Docetaxel/nedaplatin	46[+]	27.1%	5.9 months	99
Phase II	Docetaxel/cisplatin	35[+]	34.2%	7.4 months	96
Phase III	Docetaxel	84[#]	7%[#]	5.2 months[#,*]	93
	BSC	84[#]	0%[#]	3.6 months[#]	

Notes: *$P < 0.05$; [+]squamous cell carcinoma; [++]adenocarcinoma; [+++]squamous cell carcinoma/adenocarcinoma; [#]including stomach cancer.
Abbreviations: 5-FU, 5-fluorouracil; RR, response rate; OS, overall survival; NA, nonapplicable; BSC, best supportive care.

Table 4 Molecular-targeted therapy of esophageal cancer

Design	Treatment	n	RR	Median OS	Reference
Phase II (2nd line)	Erlotinib	44[++]	9%	6.7 months	108
Phase II (2nd line)	Gefitinib	36[+++]	3%	5.5 months	109
Phase II (1st/2nd)	Gefitinib	27[++]	11%	4.5 months	110
Phase II	Irinotecan/5-FU/cetuximab	38[++,#]	44%[#]	16 months[#]	67
Phase II	Cisplatin/5-FU/ cetuximab versus	32[+]	19%	9.5 months	69
	cisplatin/5-FU	30[+]	13%	5.5 months	
Phase II	Cisplatin/docetaxel/cetuximab	13[++]	41%[#]	9 months	65
Phase II	Oxaliplatin/5-FU/ cetuximab	25[++]	77%	9.5 months[#]	68
Phase II (2nd line)	Cetuximab	55[++]	6%	4.0 months	105
Phase III	5-FU (capecitabine)/	58[++]	47%[#]	13.8[#,**]	75
	cisplatin ± trastuzumab	48[++]	35%[#]	11.1[#]	
Phase II (2nd line)	Cetuximab/ irinotecan	50[++]	14%	5.5 months	106
Phase II (2nd line)	Erlotinib	13[+]	15%	8.2 months	107
		17[++]	0%	11.2 months	
Phase II (2nd line)	Cetuximab	35[++]	3%	3.1 months	104
Phase II	Irinotecan/5-FU/cetuximab	13[++]	46%[#]	16.5 months[#]	66
Phase II	5-FU/oxaliplatin/erlotinib	33[++]	52%	11.0 months	72
Phase II/III	Epirubicin/oxaliplatin/	278[#]	46%	8.8 months[#]	71
	capecitabine ± panitumumab	275[#]	42%[#]	11.3 months[#]	
Phase II	Lapatinib	16[++]	6%	NA	76
Phase III (2nd line)	Ramucirumab	238[++,#]	3.4%[#]	5.2 months[#,**]	111
	BSC	117[++,#]	2.6%[#]	3.8 months[#]	

Notes: **$P < 0.01$; [+]squamous cell carcinoma; [++]adenocarcinoma; [+++]squamous cell carcinoma/adenocarcinoma; [#]including gastric cancer patients.
Abbreviations: 5-FU, 5-fluorouracil; BSC, best supportive care; NA, non-applicable; RR, response rate; OS, overall survival.

chemotherapy. These are approximately 40% of the patients who received first-line treatment. Unfortunately, currently there is only scarce data from prospective Phase II studies dealing with this group of patients.

Single-agent chemotherapy

Vinorelbine,[88] docetaxel,[89,90] paclitaxel,[91] and irinotecan[92] were investigated as monotherapy (Table 3). Due to the low number of study participants and low RR in these studies, none of the substances could be recommended for second-line therapy. However, a recently presented randomized study (Cougar-02, Ford et al;[93] 2013 Gastrointestinal Cancers Symposium, LBA4) which compared docetaxel monotherapy with best supportive care in patients with stomach (46%), GEJ (34%), and esophageal cancer (20%) demonstrated that docetaxel significantly improves OS (Table 3).

Combination chemotherapy

Taxane-based combinations were tested in several prospective Phase II trials, including a combination of docetaxel plus capecitabine,[54] docetaxel plus irinotecan,[94,95] docetaxel plus cisplatin,[96] and docetaxel plus nedaplatin (Table 3).[97–100] In the first three combination regimens, RR was still low, and the rate of hematologic toxicity high; eg, severe neutropenia occurred in almost 50% of the patients receiving docetaxel plus capecitabine. Although hematologic toxicity and non-hematologic toxicity were relatively low in the docetaxel-plus-nedaplatin combination, these studies included only Asian patients, making it difficult to interpret these results for Caucasians. In addition, RR was still low. In view of the high activity of DCF-type regimens in first-line treatment, the combination of docetaxel, cisplatin, and 5-FU was investigated in the second-line setting as well.[102] While dose reduction of all drugs in the first study resulted in lower RR, increased dose in the second study resulted in a remarkable hematologic toxicity. Finally, only a single non-taxane combination regimen consisting of mitomycin, ifosfamide, and cisplatin was tested.[103] Although the toxicity rate was acceptable, the RR was low as well.

Targeted therapy

Cetuximab as second line treatment was studied either as monotherapy[104,105] or in combination with irinotecan (Cetiri) in patients with AC (Table 4).[106] In these studies, both RR and OS time were low. In contrast, there are contradictory results regarding erlotinib activity in AC as second-line monotherapy.[107,108] Gefitinib as monotherapy in adenocarcinoma has shown only a minor activity.[109,110] However, a recent prospectively randomized Phase III study was able to show that ramucirumab (RAM; IMC-1121B),[111] a fully human immunoglobulin (Ig)G1 monoclonal antibody targeting VEGF-receptor (R) 2, significantly improves OS in patients with gastric and GEJ AC (REGARD, Fuchs et al;[111] 2013 Gastrointestinal Cancers Symposium, LBA5) (Table 4).

Current investigations

Regarding locally advanced esophageal cancer, several Phase III studies are now recruiting patients to investigate new chemotherapy combinations, such as S-1/cisplatin, S-1/paclitaxel, cisplatin/paclitaxel, and 5-FU/leucovorin/oxaliplatin/docetaxel (FLOT), as first-line treatment (Table 5). In addition, molecular-targeting compounds as combination partners, such as trastuzumab (monoclonal antibody against ErbB-2), lapatinib (dual EGFR and ErbB-2 tyrosine kinase inhibitor), and cetuximab (monoclonal antibody against EGFR), are studied, too (Table 5). Unfortunately, there is a paucity of Phase III trials investigating second- and third-line treatment. A UK study is currently testing gefitinib (EGFR tyrosine kinase inhibitor); a German study, paclitaxel/RAD 001 (everolimus, mTOR-inhibitor) combination (Table 5). At least four Phase III trials are investigating new combination partners for radiation in the neoadjuvant setting. Paclitaxel/carboplatin/radiation, paclitaxel/carboplatin/trastuzumab/radiation, navelbine/cisplatin/radiation, and docetaxel/cisplatin/cetuximab/radiation are these regimens (Table 5). Inhibition of angiogenesis through the VEGF-inhibitor bevacizumab is another approach tested in the neoadjuvant setting. The UK-Study ST03 selects ECX as backbone chemotherapy combination partner (Table 5). Finally, improvement of definite chemoradiation for locally advanced disease is another focus of current research. Proton-beam therapy and intensity-modulated radiation therapy are both forms of radiation therapy designed to treat a specific area of the body while affecting as little of the surrounding normal tissue as possible. Proton-beam therapy is a newer technology designed to further reduce the amount of radiation that affects the surrounding normal tissue (Table 5). A particle accelerator is used during treatment to hit the tumor with a beam of protons. As a result, DNA damage of cells is induced by these charged particles, ultimately resulting in cell death or decrease of cell proliferation. Since tumors show a high rate of cell division and a reduced rate of cell repair, they are particularly vulnerable to attacks on DNA. Protons have little lateral side scatter in the tissue, due to their relatively

Table 5 Ongoing/recruiting major Phase III clinical trials in esophageal cancer (according to ClinicalTrials.gov)

Name	Drug	Indication
BO27798 (NCT01450696) Worldwide	Capecitabine/cisplatin (XP) ± trastuzumab	Locally advanced AC and stomach cancer
LOGiC (NCT00680901) Worldwide	Capecitabine/oxaliplatin (CapeOx) ± lapatinib	Locally advanced AC and stomach cancer
POWER (NCT01627379) Germany	Cisplatin/5-FU ± panitumumab	Locally advanced SCC
NCT00678535 Worldwide	Capecitabine/cisplatin (XP) ± cetuximab	Locally advanced AC and stomach cancer
DIGEST (NCT01285557) Worldwide	S-1/cisplatin versus 5-FU/cisplatin	Locally advanced AC and stomach cancer
NCT01704690 China	S-1/paclitaxel versus cisplatin/paclitaxel versus 5-FU/cisplatin	Locally advanced SCC or AC
FLOT-4 (AIO-STO-0210) Germany	5-FU/leucovorin/oxaliplatin/ docetaxel (FLOT) versus epirubicin/ cisplatin/5-FU (ECF)	Locally advanced AC and stomach cancer
OXFORD-COG (NCT01243398) UK	Gefitinib	2nd-line therapy for SCC or AC
AIO STO-0111 (NCT01248403) Germany	Paclitaxel + RAD001 (everolimus)	2nd- and 3rd-line therapy for AC and stomach cancer
ICORG 10–14 (NCT01726452) Ireland	Paclitaxel/carboplatin/radiation (CROSS protocol) (neoadjuvant) versus epirubicin/cisplatin/5-FU (ECF, MAGIC protocol) (neo- and adjuvant)	Resectable, locally advanced AC
NCT01216527 China	Navelbine/cisplatin/radiation (neoadjuvant) versus surgery alone	Resectable, locally advanced SCC
SAKK 75/08 (NCT01107639) Europe	Docetaxel/cisplatin/cetuximab/radiation (neoadjuvant) ± cetuximab (adjuvant)	Resectable, locally advanced SCC or AC
RTOG-1010 (NCT01196390) USA	Paclitaxel/carboplatin/radiation ± trastuzumab (neoadjuvant) + trastuzumab (adjuvant)	Resectable, locally advanced AC
ST03 (NCT00450203) UK	Epirubicin/cisplatin/capecitabine (ECX) ± bevacizumab (neoadjuvant and adjuvant)	Resectable, locally advanced AC
NCT01512589 USA	Radiation (PBT) ± CT versus radiation (IMRT) ± CT	Potentially resectable or unresectable SCC or AC
FRE-FNCLCC-ACCORD-17-0707 (NCT00861094) France	FOLFOX/radiation versus cisplatin/5-FU/radiation	Locally advanced SCC or AC
ESO2012-01 (NCT01591135) China	Paclitaxel/5-FU/radiation versus cisplatin/ 5-FU/radiation	Locally advanced SCC
CONCORDE (NCT01348217) France	FOLFOX-4/radiation (50 Gy) versus FOLFOX-4/ radiation (66 Gy)	Locally advanced SCC or AC
RTOG-0436 (NCT00655876) USA	Paclitaxel/cisplatin/radiation ± cetuximab	Locally advanced SCC or AC
ESCC-307PLAH-XJM (NCT01752205) China	Paclitaxel/radiation ± erlotinib	Locally advanced SCC
Shixiu – 1 (NCT00686114) China	Paclitaxel/cisplatin/radiation ± erlotinib	Locally advanced SCC or AC

Abbreviations: SCC, squamous cell carcinoma; AC, adenocarcinoma; XP, Xeloda (Roche, Basel, Switzerland) platinum; Gy, gray; PBT, proton beam therapy; CROSS, Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study; MAGIC, Medical Research Council Adjuvant Gastric Infusional Chemotherapy; SAKK, Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung; RTOG, Radiation Therapy Oncology Group; IMRT, intensity-modulated radiation therapy; FOLFOX, 5-FU/oxaliplatin; S-1, oral fluoropyramidine; CT, chemotherapy; 5-FU, 5-fluorouracil.

large mass. The beam stays focused on the tumor shape, does not broaden much, and causes only low-dose side effects to surrounding tissue. Intensity-modulated radiation therapy, which is less expensive, comprises an advanced mode of high-precision radiotherapy that uses computer-controlled linear accelerators (3-D computed tomography or magnetic resonance images are used for planning) to deliver precise radiation doses to a malignant tumor or specific areas within the tumor. The radiation dose can be more precisely adjusted to the 3-D shape of the tumor by modulating – or controlling – the intensity of the radiation beam in multiple small volumes. Using intensity-modulated radiation therapy, higher radiation doses, and combinations of multiple intensity-modulated fields coming from different beam directions can be focused to regions within the tumor, while the dose to surrounding normal critical structures can be minimized.

FOLFOX, paclitaxel/5-FU, and paclitaxel/cisplatin are potential combination partners for small molecular-targeting compounds cetuximab or erlotinib (Table 5).

Summary

Diagnosis and therapy of esophageal cancer is an interdisciplinary challenge. Exact staging is a prerequisite for optimized and individualized therapy planning. Neoadjuvant chemotherapy, now available in different combinations, should be provided to patients with locally advanced adenocarcinoma. Alternatively, there is now sufficient evidence that these patients might undergo neoadjuvant chemoradiation, too. In contrast, patients with locally advanced squamous cell carcinoma are more likely to benefit from neoadjuvant chemoradiation than from chemotherapy alone; however, there is a lack of randomized studies comparing both modalities. In general, postoperative complication and mortality rate are higher after chemoradiation than chemotherapy alone. Definitive chemoradiation has been shown to be effective in selected patients with squamous cell carcinoma (data for adenocarcinoma are scarce). In the palliative situation, combination chemotherapy with two drugs has been shown to be effective, both in patients with adeno- and squamous cell carcinoma. Effectiveness can be further increased with a triple combination in patients with adenocarcinoma, at the cost of increased side effects. Addition of monoclonal antibody trastuzumab in HER2 positive metastatic gastroesophageal junction cancer increases OS even further. Second-line therapy after failure of first-line therapy or tumor recurrence is still experimental, but docetaxel monotherapy, and targeting VEGF-R2 with ramucirumab have improved OS, according to two separate Phase III studies. In the past, many different predictors for response of AC/SCC to chemotherapy/chemoradiation have been investigated, ranging from simple histology to various molecular markers, such as p53, proliferative cell nuclear antigen, EGFR, Ki-67, cyclin D1, expression of thymidylate synthase, and microvessel density, in both tissue and serum. None are reliable, and results cannot help clinical decision making. Metabolic imaging with positron-emission tomography scanning is promising, with its ability to predict response early in the course of treatment.[112] Therefore, definition of predictive and prognostic factors, optimization of chemo- and chemoradiation regimens and evaluation of the role of molecular-targeted therapy are the goal of current studies. One major limitation to cancer therapies results from the heterogeneity of the cancer cells even within a single tumor. As tumors increase in size, many cancer cells grow distant from the blood supply, which may cause them to divide less frequently than others in the population. In addition, with increasing numbers of cancer cells, there is an increase in genetic mutations with each generation that will help cancer cells to escape the toxicity of treatment. It is, therefore, a big challenge to target these treatment-resistant cancer cells that are responsible for disease recurrence. The combination of therapeutic regimens that target different mechanisms of cancer cell development to provide the maximal cell killing without increasing toxic side effects to the patient is, therefore, mandatory.

Disclosure

The authors report no conflicts of interest in this work.

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