Review

A Systematic Review of the Randomised Phase III Clinical Trials Employing Palliative Chemotherapy in the Management of Advanced Esophagogastric Adenocarcinoma

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ABSTRACT

Background: Two-thirds of patients with esophagogastric cancer will be treated with palliative intent, with palliative chemotherapy being the most widely applied therapy. Just over half of those scheduled to receive this treatment will complete treatment as planned, with other patients failing to complete either because of disease progression or treatment side effects. The aim of this review was to report response rates, survival and toxicity of palliative chemotherapy for esophagogastric adenocarcinoma.

Methods: Forty-three randomised phase III clinical trials, reporting on 12,945 patients during the years indicate 1990-2016 were evaluated and information on response rate, survival and treatment related toxicity extracted. Thirty-three studies described patients receiving 1st line therapy and ten studies described patients receiving 2nd line therapy.

Results: Combination regimens were the most widely applied treatment worldwide as first line, with response rates in the order of 20-62%, and median overall survival in the order of 7.2-14.1 months. 30-85% of patients went on to receive second line therapy, generally single agent therapy, with reported response rates in the order of 7-22%, and median overall survival in the range 4.0-13.9 months. With the exception of trastuzumab, the effects of biological agents have been largely disappointing. The principal toxicities for chemotherapy were gastrointestinal (0-58%) and neutropenia (1-39% single agent, 12-82% combination therapy).

Conclusions: At the current time, combination therapy remains the standard of care for patients with advanced esophagogastric adenocarcinoma.

Keywords: adenocarcinoma esophagus; adenocarcinoma stomach; biological agents; chemotherapy; outcome measures; palliation

INTRODUCTION

The American Cancer Society estimate that each year over 40,000 patients are diagnosed with esophagogastric cancer, and that more than 25,000 patients will die from these cancers (1). Only around one third of these patients will be amenable to radical therapy, with the remaining two thirds receiving palliative oncology treatments, endoscopic therapies, principally stenting, or best supportive care only (2,3).

The UK National Esophagogastric Cancer Audit which evaluated in excess of 20,000 patients with cancer diagnosed during the time period 1st April 2011 and 31st March 2013 found that 36% of patients received curative intent treatment, 44% received palliative intent treatment, and 20% received best supportive care only. The most widely employed palliative intent treatment was chemotherapy (2,3). Of those scheduled to receive palliative chemotherapy, just over half of the patients completed the treatment as planned (53%) (2,3). For the remaining patients, 11% died during treatment, 18% developed progressive disease, 12% developed acute toxicity requiring discontinuation, and in 6% of patients, treatment was stopped at patient request. Older patients (aged over 80 years) and those with poorer performance status were the least likely to complete planned treatment (2,3).

The principal chemotherapy drugs employed over the last two decades have comprised fluoropyrimidine and platinum combinations, either as a two drug regimen (4-10) or as part of a three drug regimen (11-15), with taxanes, popular in the US and anthracyclines, popular in the UK. In recent years, these have been combined with biological agents (16-22).

The aim of the current article was to review in a systematic way, the accrued evidence from published phase III randomised clinical trials (RCTs) of patients with esophagogastric adenocarcinoma treated with palliative chemotherapy. Included studies were those which reported on the outcome measures of interest; response rate, survival and treatment related toxicity. The rationale for restricting the inclusion criteria to phase III RCTs was on the basis that they would constitute the best available evidence.

METHODS

Literature search and study identification

A Pubmed search of the English language literature was undertaken employing the following keywords: *chemotherapy*, *palliative*, *esophageal*, *stomach* and *cancer*. The inclusion criteria were phase three randomised controlled trials describing patients with advanced esophagogastric or gastric adenocarcinoma being treated with palliative intent using either single agent or combination chemotherapy. The review included articles published between January 1990 and January 2016. Exclusion criteria were combined chemotherapy and radiotherapy regimes, studies reporting exclusively on patients with squamous cell cancer or mixed study populations, where it was not possible to extract information relating to those with adenocarcinoma, and chemotherapy given in a perioperative setting. Outcome measures of interest included the chemotherapy related toxicity, radiological response to treatment, quality of life and survival analysis. The process and inclusion of eligible papers were independently reviewed by two of the authors (AME, DJB). Radiological response rates were assessed using the RECIST criteria and in some of the early studies, the WHO criteria. Chemotherapy toxicity was assessed using the Common Toxicity Criteria, according to the version in use at the time of the study.

Table 1: Summary of the reported phase III randomized clinical trials of 1st line palliative chemotherapy for advanced esophagogastric adenocarcinoma (highlighted studies are those where significant differences were identified)

Study	# patients	Regimen	RR (%)	PFS	OS	Toxicity related mortality (%)	% receiving subsequent 2nd line treatment
(6)	685	S-1, oxaliplatin	56%	5.5	14.1	1.2%	85%
		S-1, cisplatin	52%	5.4	13.1	2.4%	84%
(34)	416	Epirubicin, cisplatin, capecitabine	39%	5.2	9.4	4.3%	48%
		5-FU, leucovorin, irinotecan	38%	6.7	9.7	3.4%	39%
(9)	244	Capecitabine, cisplatin, placebo	29%	4.6	11.5	NR	NR
		Capecitabine, cisplatin, simvastatin	27%	5.2	11.6	NR	NR
(4)	635	S-1, docetaxel	39%	5.3	12.5	0.6%	70%
		S-1	27%	4.2	10.8	0%	76%
(37)	237	5-FU	NR	NR	9.4	1.7%	81%
		5-FU, leucovorin, methotrexate	NR	NR	10.6	0.9%	73%
(38)	315	S-1	27%	3.6	10.5	0%	47%
		S-1, irinotecan	41%	4.5	12.8	1.2%	53%
(7,39)	1053	S-1, cisplatin	29%	4.8	8.6	2.5%	30%
		5-FU, cisplatin	32%	5.5	7.9	4.9%	33%
(40)	120	S-1	29%	4.3	9.2	0%	NR
		S-1, cisplatin	62%	5.7	12.5	0%	NR
(41)	704	5-FU	9 %	2.9	10.8	0%	83%
		S-1	28 %	4.2	11.4	0.4%	74%
		Irinotecan, cisplatin	38 %	4.8	12.3	1.3%	78%
(10)	316	Capecitabine, cisplatin	46%	5.6	10.5	1%	NR
		5-FU, cisplatin	32%	5.0	9.3	1%	NR
(42)	174	5-FU, heptaplatin	35%	2.5	7.3	0%	NR
		5-FU, cisplatin	36%	2.3	7.9	0%	NR
(8)	220	5-FU, leucovorin, oxaliplatin	35%	5.8	10.7	NR	52%
		5-FU, leucovorin, cisplatin	25%	3.9	8.8	NR	59%
(33,36)	333	5-FU, folinic acid, irinotecan	32%	5.0	9.0	0.6%	NR
		5-FU, cisplatin	26%	4.2	8.7	3.0%	NR
(5)	298	S-1	31%	4.0	11.0	0%	75%
		S-1, cisplatin	54%	6.0	13.0	0%	74%
(31)	86	5-FU, epirubicin, cisplatin	40%	NR	12.0	NR	NR
		5-FU, docetaxel, cisplatin	41%	NR	12.0	NR	NR
(11,35, 43)	445	5-FU, docetaxel, cisplatin	37%	5.6	9.2	2.7%	32%
		5-FU, cisplatin	25%	3.7	8.6	4.5%	41%
(44)	280	5-FU	11%	1.9	7.1	1%	57%
		5-FU, cisplatin	34%	3.9	7.3	4%	52%
		Uracil, tegafur, mitomycin	9%	2.4	6.0	1%	49%
(45)	120	Cisplatin, etoposide & doxorubicin (bolus)	28%	6	7	4.0%	NR
		doxorubicin (infusion)	20%	4	5	3.4%	NR
(12)	245	5-FU, leucovorin, etoposide	9%	3.3	7.2	0%	NR
		5-FU, cisplatin	20%	4.1	7.2	2.4%	NR
		5-FU, doxorubicin, methotrexate	12%	3.3	6.7	5.9%	NR

(13)	131	Epirubicin, cisplatin, etoposide	20%	6	6	0%	NR
		5-FU, epirubicin, cisplatin	15%	7	5	0%	NR
(14)	256	5-FU, epirubicin, cisplatin	45%	7.4	8.9	0.9%	NR
		5-FU, doxorubicin, methotrexate	21%	3.4	5.7	1.8%	NR
(46)	50	5-FU, epirubicin, cisplatin, leucovorin& glutathione	76%	NR	14	NR	NR
		placebo	52%	NR	10	NR	NR
(47)	41	5-FU, epirubicin, methotrexate	29%	5.4	12.3	4.8%	NR
		Best supportive care	NA	1.7	3.1	NA	NR
(15)	295	5-FU	26%	2.2	7.6	NR	NR
		5-FU, cisplatin	51%	5.4	9.2	NR	NR
		5-FU, doxorubicin, mitomycin	25%	3.0	7.3	NR	NR
(48)	40	5-FU, doxorubicin, methotrexate	50%	NR	9	3.3%	NR
		Best supportive care	NA	NR	3	NA	NR

5-FU = 5-fluorouracil, NA = not applicable, NR = not reported, OS = overall survival in months, PFS = progression free survival in months, RR = response rate

RESULTS

The search strategy yielded 132 evaluable articles which were screened for inclusion. Forty three full articles met the inclusion criteria and form the basis of this review (Figure 1). Thirty three of the forty three studies reported on patients receiving first line palliative chemotherapy, and the remaining 10 studies reported on patients who received second line chemotherapy. Heterogeneity between the included studies made it impossible to perform a formal meta-analysis. The combined reports describe the outcome for a total of 12,945 patients.

Summary of studies reporting on 1st line palliative chemotherapy

Table 1 summarises the clinical trials of 1st line palliative chemotherapy. It is evident that a wide variety of drug combinations have been employed, with the majority of studies over the last decade employing two drug combinations. In those studies that compared treatment to best supportive care, overall survival for participants in the latter group was around three months. Response rates for single agent fluoropyrimidine therapy (seven studies) ranged from 9-31%, with higher values observed for S-1 compared to 5-fluorouracil. Overall survival ranged from 7.1-11.4 months.

Response rates for combined fluoropyrimidine / platinum combinations (13 studies) ranged from 20-62% and overall survival ranged from 7.2-14.1 months. A number of three drug combinations have been employed. Those reporting on fluoropyrimidine / platinum / anthracycline combinations (five studies) have noted response rates ranging from 15-76%, and overall survival ranging from 5-12 months. Heterogeneous drug combinations in other studies limit meaningful conclusions. Head-to-head comparisons of regimens (where significant) indicated superiority of two agents over single agent, of capecitabine over 5-fluourouracil in combination with cisplatin, and of three drug combinations over best supportive care. Earlier studies did not indicate subsequent therapies, but it is evident from Table 1 that many of the first line trial participants in more recently published articles went on to receive subsequent second (and third) line therapy (range 30-85%).

Summary of studies reporting on 2nd line palliative chemotherapy

Table 2: Summary of the reported phase III randomized clinical trials of 2nd line palliative chemotherapy for advanced esophagogastric adenocarcinoma (highlighted studies are those where significant differences were identified)

Study	# patients	Regimen	RR (%)	PFS	OS	Toxicity related mortality (%)
(49)	163	Irinotecan	15%	4.1	12.7	0%
		vs				
		Irinotecan, cisplatin	17%	4.6	13.9	0%
(30)	168	Docetaxel	7%	3.1	5.2	0%
		vs				
		Best supportive care	NA	NR	3.6	0%
(50)	130	Irinotecan	16%	2.8	10.1	0%
		vs				
		Irinotecan, cisplatin	22%	3.8	10.7	0%
(51)	219	Paclitaxel	21%	3.6	9.5	0%
		vs				
		Irinotecan	14%	2.3	8.4	1.8%
(52)	188	Docetaxel or Irinotecan	13%	NR	5.3	NR
		vs				
		Best supportive care	NA	NR	3.8	NR
(53)	40	Irinotecan	0%	2.5	4.0	0 %
		vs				
		Best supportive care	NA	NR	2.4	NA

NA = not applicable, NR = not reported, OS = overall survival in months, PFS = progression free survival in months, RR = response rate

Table 2 summarises those studies reporting on second line chemotherapy. Three of these compared single agent taxane or irinotecan to best supportive care. Observed response rates were generally lower than for first line therapy (range 7-22%), with overall survival ranging from 4.0-13.9 months. By comparison, overall survival with best supportive care ranged from 2.4-5.3 months. Those where significant findings were noted concluded that single agent therapy was superior to best supportive care.

Summary of studies reporting on palliative chemotherapy in combination with biological agents

Table 3 summarises those studies that employed biological agents as part of the treatment regimen, With the exception of the ToGA and TyTAN studies which enrolled only patients with proven immunohistochemical expression of the antibody target in tumour tissue, the other studies enrolled unselected participants.

The use of biological agents in the treatment of esophagogastric adenocarcinoma has been largely disappointing, with the exception of Trastuzumab (Herceptin®), a human epidermal growth factor receptor 2 antibody, in patients with tumours expressing the HER-2 gene or protein. The latter was associated with impressive response rates in phase II clinical trials (up to 94%) and notably, the ability to downstage unresectable gastric cancer to potentially resectable disease. The effects have been largely restricted to those patients whose primary cancer has demonstrated HER-2 expression (23-28). In a phase III clinical trial, the use of trastuzumab plus fluoropyrimidine / platinum in patients

Table 3: Comparison of the reported phase III randomized clinical trials in patients who received palliative chemotherapy with or without biological agents

Study	patients	Regimen	RR (%)	PFS	OS	Toxicity related mortality	receiving subsequent 2nd line therapy
(17)	202	Capecitabine, cisplatin, bevacizumab	41%	6.3	10.5	4%	NR
		vs					
		Capecitabine, cisplatin, placebo	34%	6.0	11.4	8%	
(18)	665	Paclitaxel, ramucirumab	27%	4.4	9.6	12%	NA
		vs					
		Paclitaxel, placebo	16%	2.9	7.4	16%	
(29)	355	Ramucirumab	3%	2.1	5.2	2%	NA
		vs					
		placebo	3%	1.3	3.8	2%	
(16)	261	Paclitaxel	9%	4.4	8.9	NR	NA
		vs					
		Paclitaxel, Lapatinib	27%	5.5	11.0	NR	
(19)	904	Capecitabine, paclitaxel	29%	5.6	10.7	8%	53%
		vs					
		Capecitabine, paclitaxel, cetuximab	30%	4.4	9.4	9%	53%
(20)	553	Epirubicin, oxaliplatin, capecitabine	42%	7.4	11.3	2%	NR
		vs					
		Epirubicin, oxaliplatin, capecitabine, panitumumab	46%	6.0	8.8	1%	
(21, 54)	774	Capecitabine, paclitaxel, bevacizumab	46%	6.7	12.1	2 %	41%
		vs					
		Capecitabine, paclitaxel, placebo	37%	5.3	10.1	3 %	45%
(22)	584	Capecitabine/5-FU, cisplatin, trastuzumab vs	47 %	6.7	13.8	3%	42%
		Capecitabine/5-FU, cisplatin	35 %	5.5	11.1	1%	45%

5-FU = 5-fluorouracil, NA = not applicable, NR = not reported; OS = overall survival in months, PFS = progression free survival in months, RR = response rate.

with HER-2 positive cancers has been demonstrated to improve response rate, quality of life and survival compared to those patients treated with chemotherapy alone (22).

Therapy with the other biological agents has yielded largely negative results, with no superiority over conventional chemotherapy being demonstrated for bevacizumab, cetuximab or panitumumab. Ramucirumab as a second line treatment has been shown to be superior to placebo, with a toxicity profile similar to conventional chemotherapy (29). When combined with paclitaxel as second line therapy, it has been demonstrated to effect a modest improvement in survival at the expense of a higher frequency of grade 3 or 4 toxicity (18). Lapatinib as second line therapy demonstrated a higher response rate when combined with paclitaxel compared to paclitaxel alone, but no significant improvement in survival was demonstrated (16). Two recent studies of rilotumumab have been terminated early for safety reasons.

Table 4: Comparison of the reported grade 3 or 4 toxicities of interest to biological drugs in those receiving and not receiving the drug

Study	Biological agent	VTE (%)	ATE (%)	HTN (%)	Bleeding (%)	GI perforation (%)	Skin reaction (%)	Heart failure (%)	Infusion related (%)
(17)	Bevacizumab	1%	3%	0%	4%	1%	NR	NR	NR
	Placebo	1%	4%	1%	12%	0%	NR	NR	NR
(18)	Ramucirumab	2%	1%	15%	4%	1%	NR	<1%	<1%
	Placebo	3%	1%	3%	2%	0%	NR	<1%	0%
(29)	Ramucirumab	1%	1%	8%	3%	<1%	NR	0%	0%
	Placebo	4%	0%	3%	3%	<1%	NR	0%	0%
(16)	Lapatinib	NR	NR	NR	NR	NR	3%	<1%	NR
	No drug	NR	NR	NR	NR	NR	0%	0%	NR
(19)	Cetuximab	6%	NR	NR	NR	NR	13%	<1%	3%
	No drug	3%	NR	NR	NR	NR	0%	<1%	<1%
(20)	Panitumumab	11%	NR	NR	<1%	NR	11%	NR	NR
	No drug	7%	NR	NR	0%	NR	1%	NR	NR
(21, 54)	Bevacizumab	*6%	*1%	6%	4%	2%	NR	<1%	0%
	Placebo	*9%	*2%	<1%	4%	<1%	NR	<1%	0%
(22)	Trastuzumab	NR	NR	NR	NR	NR	NR	<1%	6%
	No drug	NR	NR	NR	NR	NR	NR	<1%	0%

*ATE = arterial thromboembolism, GI = gastrointestinal, HTN = hypertension, VTE = venous thromboembolism, NR= not reported *grade 3-5 toxicities were reported as combined information. It was not possible to extract individual toxicity grades.*

Chemotherapy related toxicities

Tables 5 and 6 summarise the reported grade 3 or 4 toxicities, non-hematological (Table 5) and haematological (Table 6). The most commonly observed toxicities were gastrointestinal adverse effects, which occurred in 0-25% with single agent fluoropyrimidine therapy, 0-26% with single agent irinotecan and 0-58% with combination therapy. Neutropenia was noted in 1-11% with single agent fluoropyrimidine therapy, 18-39% with single agent irinotecan, 15-29% with single agent taxane, and 12-82% with combination therapy.

Targeted therapy additional side effects

With the exception of the REAL 3 study, the reported toxicities were similar between those treated with and without biological agents. In the REAL 3 study, the use of panitumumab was associated with an increased frequency of grade 3 and 4 toxicity, and as there was no improvement in survival, the study was terminated early. Compared to combination epirubicin, oxaliplatin and capecitabine alone, the addition of panitumumab was associated with higher frequencies of diarrhea (17% vs 11%), skin rash (11% vs 1%), mucositis (5% vs 0%) and hypomagnesaemia (5% vs 0%).

Table 4 summarises the reported toxicities of special interest to the biological drugs used and related mortalities.

Table 5: Summary of the reported non haematological grade 3 or 4 toxicities in published phase III randomized clinical trial of palliative chemotherapy in patients with advanced esophagogastric adenocarcinoma

	Study	Chemotherapy	Diarrhea (%)	Nausea (%)	Vomiting (%)	Fatigue (%)	Infection (%)	Neuropathy (%)
Single drug regimens	(52)	Best supportive care	5%	6%	NR	27%	NR	NR
	(49)	Irinotecan	3%	5%	4%	4%	NR	NR
	(50)	Irinotecan	6%	5%	0%	6%	NR	NR
	(51)	Irinotecan	5%	5%	1%	NR	NR	0%
	(52)	Irinotecan	8%	3%	NR	10%	NR	NR
	(53)	Irinotecan	26%	5%	5%	NR	16%	NR
	(40)	S-1	0%	0%	0%	NR	NR	NR
	(4)	S-1	5%	3%	2%	5%	NR	NR
	(38)	S-1	6%	6%	2%	7%	4%	NR
	(41)	S-1	8%	6%	-	5%	6%	1%
	(5)	S-1	3%	1%	2%	1%	1%	0%
	(37)	5-FU	1%	10%	NR	NR	6%	NR
	(41)	5-FU	<1%	7%	NR	2%	4%	0%
	(44)	5-FU	0%	5%		NR	NR	0%
	(15)	5-FU	5%	25%		NR	2%	0%
	(52)	Docetaxel	3%	5%	NR	26%	NR	NR
	(51)	Paclitaxel	1%	2%	3%	NR	NR	7%
Two Drug Combination	(49)	Irinotecan, cisplatin	0%	4%	1%	9%	NR	NR
	(50)	Irinotecan, cisplatin	2%	5%	0%	3%	NR	NR
	(41)	Irinotecan, cisplatin	9%	21%	NR	10%	12%	1%
	(38)	Irinotecan, S-1	16%	7%	3%	6%	2%	NR
	(36)	Irinotecan, 5-FU *	22%	5%	7%	7%	3%	0%
	(4)	S-1, docetaxel	3%	6%	3%	6%	NR	NR
	(6)	S-1, oxaliplatin	6%	4%	1%	6%	NR	5%
	(40)	S-1, cisplatin	0%	6%	3%	NR	NR	NR
	(5)	S-1, cisplatin	4%	11%	4%	4%	3%	0%
	(6)	S-1, cisplatin	7%	4%	1%	9%	NR	0%
	(7)	S-1, cisplatin	5%	7%	8%	12%	NR	<1%
	(7)	5-FU, cisplatin	4%	10%	10%	13%	NR	1%
	(36)	5-FU, cisplatin	7%	9%	8%	7%	5%	3%
	(11)	5-FU, cisplatin	8%	17%	17%	14%	7%	3%
	(44)	5-FU, cisplatin	3%	8%		NR	NR	1%
	(8)	5-FU, cisplatin *	5%	9%	6%	7%	NR	2%
Two Drug Combination	(12)	5-FU, cisplatin	6%	26%		NR	5%	1%
	(42)	5-FU, cisplatin	2%	29%	12%	0%	NR	NR
	(42)	5-FU, heptaplatin	0%	8%	2%	3%	NR	NR
	(10)	5-FU, cisplatin	4%	3%	8%	<1%	NR	NR
	(15)	5-FU, cisplatin	11%	58%		NR	4%	5%
	(8)	5-FU, oxaliplatin *	6%	4%	3%	4%	NR	14%
	(9)	Capecitabine, cisplatin ‡	3%	7%	3%	NR	NR	2%
	(9)	Capecitabine, cisplatin †	3%	2%	3%	NR	NR	1%
	(10)	Capecitabine, cisplatin	5%	2%	7%	2%	NR	NR
	(37)	5-FU, methotrexate *	10%	12%	NR	NR	8%	NR
	(12)	5-FU, etoposide *	5%	7%		NR	7%	0%

Three drug combinations	(11)	5-FU, docetaxel, cisplatin	19%	14%	14%	19%	13%	8%
	(12)	5-FU, doxorubicin, methotrexate	3%	8%		NR	7%	0%
	(13)	5-FU, epirubicin, cisplatin	1%	9%		NR	1%	0%
	(14)	5-FU, doxorubicin, methotrexate	7%	5%		NR	20%	0%
	(14)	5-FU, epirubicin, cisplatin	6%	17%		NR	8%	0%
	(47)	5-FU, doxorubicin, methotrexate	2%	8%		NR	NR	NR
	(15)	5-FU, doxorubicin, mitomycin	5%	38%		NR	0%	0%
	(48)	5-FU, doxorubicin, methotrexate	NR	3%		NR	3%	0%
	(45)	Etoposide, cisplatin, doxorubicin infusion	6%	5%		NR	NR	NR
	(45)	Etoposide, cisplatin, doxorubicin bolus	2%	8%		NR	NR	NR
	(44)	Tegafur, uracil, mitomycin	0%	11%		NR	NR	0%
	(13)	Epirubicin, cisplatin, etoposide	2%	6%		NR	2%	0%

*5-FU = 5-fluorouracil, NR= not reported, * leucovorin was given, † simvastatin was given*

Quality of life assessment

Quality of life (QoL) has been reported in seven phase III RCTs comparing two or more treatment regimens (biological agents employed in three) and two comparing single agent therapy with best supportive care (biological agents employed in one) (14,18,29-35). The most widely used questionnaire was the EORTC QLQ-C30 questionnaire and its modules, but the reporting approach was inconsistent in all trials.

In the ToGA study, Satoh *et al* reported a median time to 10% deterioration in global health score of 10.2 months for patients treated with trastuzumab and chemotherapy compared to 6.4 months for those patients treated with chemotherapy alone. The beneficial effect was more pronounced in those patients whose primary tumour demonstrated high levels of HER-2 protein expression (32). In the V325 study, the authors compared the quality of life in patients receiving either 5-fluorouracil, cisplatin or 5-FU, cisplatin and docetaxel. A 5% deterioration in quality of life from baseline was observed after 4.2 months with dual therapy, and after 6.5 months, with triple therapy. Similar findings were observed when quality of life was assessed using the EQ-5D instrument (11,35). Curran *et al,* and Dank *et al* reported a 5 % deterioration of quality of life after 5.9 and 4.9 months for 5-fluorouracil, cisplatin and 5-fluorouracil, irinotecan combinations respectively (33,36).

Sadighi *et al*, compared QoL in patients who received 5-fluorouracil, cisplatin, docetaxel to that observed in patients who received 5-fluoruuracil, cisplatin, epirubicin. Both groups showed improvement in their QoL measures compared to baseline scores with the exception of the domains of cognitive functioning, diarrhea and financial aspect of the disease. Those treated with the taxane containing regimen had evidence of a clinically and statistically significance improvement in global QoL (p=0.001), social functioning (p=0.03), emotional functioning (p=0.004), pain (p=0.03) and sleep difficulties (p=0.02) (31).

Ford *et al* showed statistically superior symptom control for patients who received single agent docetaxel compared to best

Table 6: Summary of the reported grade 3 or 4 hematological toxicities in published phase III randomized clinical trial investigating the effect of palliative chemotherapy on patients with advanced esophagogastric adenocarcinoma

	Study	Chemotherapy	Neutropenia (%)	Thrombocytopenia (%)	Anemia (%)
Single drug regimens	(30)	Best supportive care	NR	NR	5%
	(52)	Best supportive care	2%	0%	23%
	(53)	Best supportive care	NR	NR	NR
	(49)	Irinotecan	28%	0%	4%
	(50)	Irinotecan	36%	2%	18%
	(51)	Irinotecan	39%	2%	30%
	(52)	Irinotecan	18%	3%	32%
	(53)	Irinotecan	NR	NR	11%
	(30)	Docetaxel	NR	NR	6%
	(52)	Docetaxel	15%	2%	30%
	(51)	Paclitaxel	29%	1%	21%
	(4)	S-1	5%	1%	8%
	(38)	S-1	11%	4%	11%
	(40)	S-1	4%	1%	NR
	(41)	S-1	6%	NR	13%
	(5)	S-1	11%	0%	4%
	(37)	5-FU	1%	0%	10%
	(41)	5-FU	1%	NR	16%
	(44)	5-FU	5%	2%	10%
	(15)	5-FU	NR	0%	<1%
	(46)	Cisplatin ‡	NR	0%	21%
	(46)	Cisplatin ♦	NR	0%	17%
Two drug combination	(9)	Capecitabine, cisplatin †	41%	3%	13%
	(9)	Capecitabine, cisplatin ‡	41%	3%	10%
	(10)	Capecitabine, cisplatin	16%	NR	NR
	(36)	5-FU, irinotecan *	25%	2%	11%
	(7)	5-FU, cisplatin	40%	8%	19%
	(42)	5-FU, cisplatin	0%	0%	0%
	(42)	5-FU, heptaplatin	8%	0%	17%
	(10)	5-FU, cisplatin	19%	NR	NR
	(8)	5-FU, cisplatin *	15%	4%	7%
	(36)	5-FU, cisplatin	52%	12%	17%
	(11)	5-FU, cisplatin	57%	13%	26%
	(44)	5-FU, cisplatin	53%	18%	25%
	(12)	5-FU, cisplatin	35%	9%	NR
	(15)	5-FU, cisplatin	NR	0%	<1%
	(8)	5-FU, oxaliplatin *	12%	5%	3%
	(6)	S-1, oxaliplatin	19%	10%	15%
	(6)	S-1, cisplatin	42%	10%	32%
	(7)	S-1, cisplatin	19%	5%	16%
	(40)	S-1, cisplatin	21%	6%	NR
	(5)	S-1, cisplatin	40%	5%	26%
	(4)	S-1, docetaxel	29%	1%	12%
	(38)	S-1, irinotecan	27%	1%	15%
	(49)	Irinotecan, cisplatin	35%	1%	16%
	(50)	Irinotecan, cisplatin	39%	0%	16%
	(41)	Irinotecan, cisplatin	65%	NR	39%
	(12)	5-FU, etoposide*	39%	2%	NR
	(37)	5-FU, methotrexate*	32%	2%	16%

Three drug combination	(14)	5-FU, epirubicin, cisplatin	36%	4%	8%
	(11)	5-FU, docetaxel, cisplatin	82%	8%	18%
	(44)	Uracil, tegafur, mitomycin c	38%	30%	15%
	(45)	Etoposide, cisplatin, doxorubicin infusion	NR	6%	13%
	(45)	Etoposide, cisplatin, doxorubicin bolus	NR	16%	19%
	(12)	5-FU, doxorubicin, methotrexate	43%	5%	NR
	(14)	5-FU, doxorubicin, methotrexate	58%	8%	10%
	(47)	5-FU, doxorubicin, methotrexate	NR	2%	1%
	(48)	5-FU, doxorubicin, methotrexate	NR	0%	NR
	(15)	5-FU, doxorubicin, mitomycin c	NR	0%	1%

*5-FU = 5-fluorouracil, NR= not reported, * leucovorin was given, † simvastatin was given, ‡ placebo, ♦ glutathione was given*

supportive care (dysphagia, general pain, abdominal pain, nausea and vomiting and constipation) (30). Webb *et al*, demonstrated superiority of the 5-fluorouracil, cisplatin, epirubicin regimen over 5-fluorouracil, doxorubicin, methotrexate at 24 weeks (p=0.04) (14).

In the REGARD study, no difference in global QoL was identified between patients treated with ramucirumab monotherapy and those treated with placebo (29). In the RAINBOW study, no difference was identified in global quality of life scores between those treated with paclitaxel plus ramucirumab, and those treated with paclitaxel plus placebo (18). Guimbaud *et al* showed no statistical significant difference in QoL between those treated with capecitabine, cisplatin, epirubicin and those treated with 5-fluorouracil, folinic acid and irinotecan (34).

In summary

Two-thirds of patients with esophagogastric cancer will be treated with palliative intent, with palliative chemotherapy being the most applied therapy. Combination regimens are the most widely applied treatment worldwide, with response rates in the order of 20-62% and median overall survival in the order of 7.2-14.1 months. 30-85% of patients will go to have second or third line therapy, with reported response rates in the order of 7-22%, and median overall survival in the range 4.0-13.9 months. With the exception of trastuzumab, the effects of biological agents have been largely disappointing.

Abbreviations

5-FU, 5-fluorouracil;
ATE, arterial thromboembolism;
GI, gastrointestinal;
HER2, Human Epidermal Growth Factor Receptor 2;
HTN, hypertension;
NA, not applicable;
NR, not reported;
OS, overall survival;
PFS, progression free survival;
QOL, quality of life;
RCT, randomized controlled trial;
RECIST, Response Evaluation in Solid Tumors;
RR, response rate;
UK, United Kingdom;
US, United States;
VTE, venous thromboembolism;
WHO, World Health Organization

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