Table 2. Multivariate analysis for overall survival

Variables	Category	HR	95% CI	P[a]
Regimen	SOX (versus CS)	0.955	0.802–1.138	0.61
Gender	Male (versus female)	1.108	0.904–1.357	0.32
Age (years)	≥70 (versus <70)	0.924	0.762–1.119	0.42
ECOG performance status	1, 2 (versus 0)	1.603	1.328–1.935	<0.0001
Disease status	Recurrent (versus unresectable)	0.588	0.451–0.767	0.0001
Tumor histology	Diffuse (versus intestinal)	1.378	1.151–1.649	0.0005
Peritoneal metastasis	Yes (versus no)	1.099	0.878–1.377	0.41
Sum of tumor diameter[b]	≥Median[c] (versus <median)	1.437	1.195–1.728	0.0001
ALP	≥Median[d] (versus <median)	1.097	0.916–1.315	0.31

Multivariate analyses showed that ECOG performance status (1, 2), unresectable, diffuse-type, and sum of tumor diameter (≥median) correlated with poor prognosis in overall survival.

[a]Wald test.

[b]Sum of tumor diameter, according to the Response Evaluation Criteria In Solid Tumors version 1.0.

[c]Median of sum of tumor diameter : 76.5 mm.

[d]Median of ALP: 258 IU/l.

HR, hazard ratio; CI, confidence interval; SOX, S-1 plus oxaliplatin; CS, cisplatin plus S-1; ECOG, Eastern Cooperative Oncology Group; ALP, alkaline phosphatase.

Table 3. Treatment-related adverse events

	SOX ($N = 338$)				CS ($N = 335$)				P^a	
	Any		≥Grade 3		Any		≥Grade 3		Any	≥Grade 3
Hematological										
Leukopenia	205	60.7	14	4.1	248	74.0	65	19.4	0.0002	<0.0001
Neutropenia	233	68.9	66	19.5	266	79.4	140	41.8	0.0019	<0.0001
Anemia	187	55.3	51	15.1	247	73.7	109	32.5	<0.0001	<0.0001
Thrombocytopenia	265	78.4	34	10.1	232	69.3	35	10.4	0.0069	0.87
Nonhematological										
Febrile neutropenia	3	0.9	3	0.9	23	6.9	23	6.9	<0.0001	<0.0001
Total bilirubin	131	38.8	9	2.7	80	23.9	4	1.2	<0.0001	0.17
AST	205	60.7	10	3.0	77	23.0	4	1.2	<0.0001	0.11
ALT	136	40.2	10	3.0	80	23.9	3	0.9	<0.0001	0.052
Creatinine	30	8.9	1	0.3	132	39.4	6	1.8	<0.0001	0.056
Hyponatremia	74	21.9	15	4.4	154	46.0	45	13.4	<0.0001	<0.0001
Diarrhea	163	48.2	19	5.6	196	58.5	25	7.5	0.0075	0.33
Nausea	208	61.5	13	3.8	231	69.0	13	3.9	0.043	0.98
Vomiting	118	34.9	2	0.6	119	35.5	5	1.5	0.87	0.25
Stomatitis	109	32.2	5	1.5	138	41.2	4	1.2	0.016	0.75
Anorexia	252	74.6	52	15.4	271	80.9	62	18.5	0.048	0.28
Fatigue	195	57.7	22	6.5	203	60.6	29	8.7	0.44	0.29
Sensory neuropathy	289	85.5	16	4.7	79	23.6	0	0	<0.0001	<0.0001

Data are presented as *n* (%).

[a]χ^2 test; comparing frequency of adverse events of any grades, and grade 3 or higher.

SOX, S-1 plus oxaliplatin; CS, cisplatin plus S-1; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Therefore, trastuzumab treatment would not seem to impact on comparing OS between both groups.

In conclusion, SOX was as effective as CS for AGC. Generally, SOX was less toxic and more convenient clinically, in which forced hydration is not needed unlike cisplatin, than CS. SOX can thus replace CS in the first-line treatment of AGC.

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REVIEW ARTICLE

Optimal chemotherapy for advanced gastric cancer: is there a global consensus?

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Abstract The optimal medical treatment for advanced gastric cancer is currently the source of debate. Cytotoxic treatment has been shown to prolong survival and provide improved symptom control compared with best supportive care alone, but a global standard has not yet been defined. A literature research was undertaken. Results were evaluated by an international author team. The conclusions of this are presented in this paper. Combination chemotherapy with cisplatin and 5-fluorouracil was the preferred first-line chemotherapy, but oxaliplatin has shown equivalent efficacy to cisplatin. Oral fluoropyrimidines, especially S-1 and capecitabine, can substitute for 5-fluorouracil. Modern doublet regimens are preferred in the majority of patients on the basis of a balanced benefit-to-risk ratio. In selected fit and compliant patients, especially those with a high tumor burden or potential secondary resectability, a third drug may be added because triplet chemotherapy led to higher responses rates and enhanced efficacy. However, docetaxel also adds a significant increase in side effects. Monotherapy and early dose modifications should be considered in elderly and infirm patients. Beyond that, our understanding of gastric cancer tumor biology is increasing. In HER2-positive gastric cancer, the addition of the monoclononal anti-HER2 antibody trastuzumab to cisplatin and fluoropyrimidines has prolonged survival duration. Second-line chemotherapy with single agents has now become a proven treatment option. Alternatively, anti-angiogenic treatment with ramucirumab is on the horizon. In conclusion, combination chemotherapy is regarded as the global standard of care for the first-line treatment of advanced gastric cancer. Molecularly targeted treatments are being explored, preferably in combination with a backbone of chemotherapy doublets.

Keywords Gastric cancer · Chemotherapy · Metastases · Consensus · Recommendation

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Introduction

Gastric cancer (GC), including adenocarcinoma of the distal esophagus and the esophagogastric junction (EGJ), is a major global health problem. Around 1 million new cases and 750,000 deaths occur per year worldwide, accounting for 10 % of all deaths due to cancer [1, 2]. The highest incidence rates are found in East Asia, East Europe, and parts of South America, while the lowest rates occur in North America [2–4] (Fig. 1).

In Europe and North America, the overall 5-year survival for GC is approximately 25 % [3], while superior outcomes with 5-year-survival rates of approximately 60 % are reported in East Asia [5]. Early diagnosis due to well-

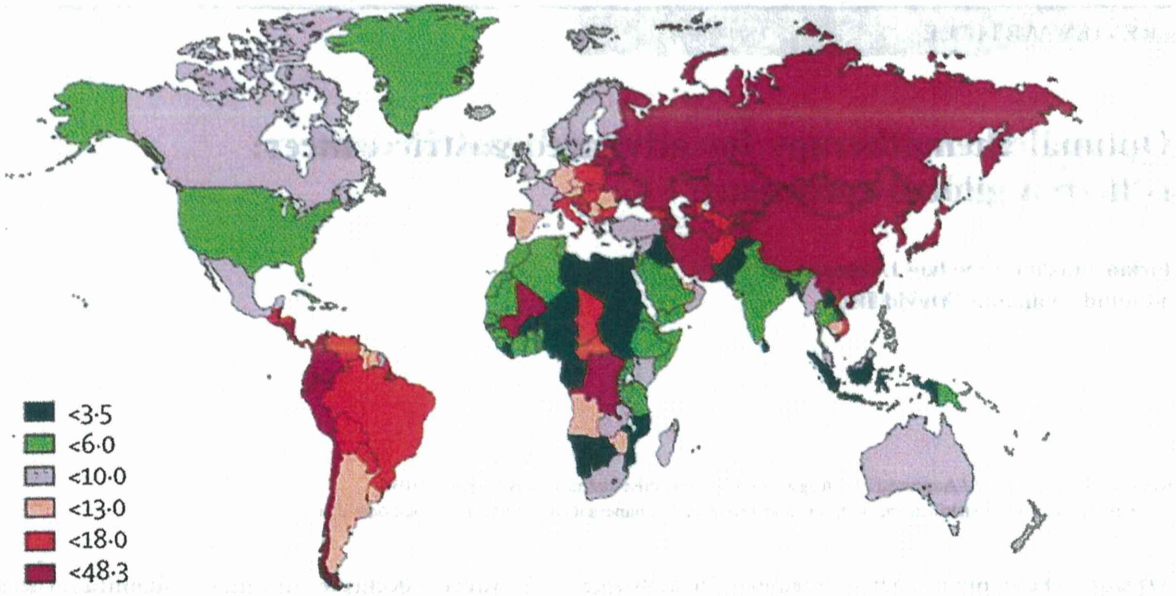

Fig. 1 Age-adjusted gastric cancer incidence per 100,000 inhabitants (according to Lozano et al. [2])

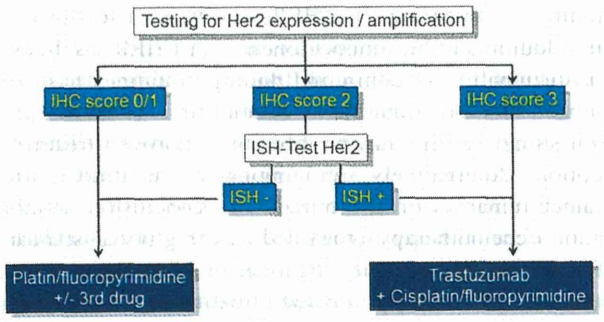

Fig. 2 HER2 testing and treatment algorithm in advanced gastric cancer. *IHC* immunohistochemistry, *ISH* in situ hybridization

established screening programs, careful surgical lymph node dissection in localized disease, and consistent use of postoperative adjuvant chemotherapy may explain some of the differences in patient outcomes [3, 6, 7]. Epidemiological studies indicate a progressive decrease in the intestinal type of gastric cancer and an increase in the diffuse type [8], while intestinal-type tumors still predominate in East Asia and East Europe. As our understanding of gastric cancer biology has improved, differential treatment approaches for specific subtypes of gastric cancer have emerged [9]. HER2-positive advanced GC is now treated by the addition of the monoclonal antibody trastuzumab to standard chemotherapy [10] (Fig. 2). More molecular characteristics are being identified and more specific and targeted treatments are being studied [11].

Methods

References for this review were identified through searches of PubMed with the search terms "chemotherapy," "gastric cancer," "esophagogastric junction cancer," "advanced," "metastatic," and "quality of life" from 1990 until April 2013. Articles were also identified through searches of the major oncology congress abstract search machines (American Society of Clinical Oncology Annual Meetings 2010–2013, European Society of Medical Oncology and European Cancer Organization Annual Meetings 2010–2012).

The benefit of chemotherapy in advanced gastric cancer

In this review, the term "advanced" indicates a disease extent that is no longer amenable to curative surgical treatment. It has been shown that chemotherapy can prolong survival in this setting [12]. This is true for first-line treatment as well as for second- and further-line chemotherapy (Table 1) [13–17]. Symptom control and quality of life have also been looked at in some studies, and have been demonstrated to be improved by chemotherapy.

For the first-line treatment of GC, it has been shown that combination chemotherapy is, in principle, more efficacious than monotherapy [12, 18, 19]. It should be noted that the benefit observed in the Cochrane review was rather marginal [hazard ratio (HR) for survival of 0.82; 95 % CI 0.74–0.90]. In addition, toxicity increases with combination schedules. Therefore, careful evaluation of the patient's performance status and the different toxicity

Table 1 Phase III trials of chemotherapy versus best supportive care (BSC) for advanced gastric cancer

Study	Setting	Number of patients	Treatment	Response rate (%)	Median overall survival (months)	Quality of life
Pyrhönen et al. [13]	1st line	21 20	FEMTX vs. BSC	29	12.3 vs. 3.1 ($P = 0.0006$)	–
Murad et al. [14]	1st line	30 10	FAMTX vs. BSC	50	9 vs. 3 ($P = 0.001$)	–
Glimelius et al. [15]	1st line	31 30	ELF vs. BSC	NR	8 vs. 5 (NS)	In favor of ELF
Thuss-Patience et al. [16]	2nd line	40	Irinotecan vs. BSC	0 (58 stable disease)	4 vs. 2.4 ($P = 0.0023$)	–
Kang et al. [17]	2nd line	202	Irinotecan or docetaxel vs. BSC	6	5.3 vs. 3.8 ($P = 0.007$)	–

FEMTX fluorouracil/epidoxorubicin/methotrexate, *FAMTX* fluorouracil/doxorubicin/methotrexate, *ELF* etoposide/leucovorin/fluorouracil, *NR* not reported, *NS* not significant

profiles of the treatment regimens should be performed before choosing the therapy. Although the majority of patients are ≥65 years old, elderly patients are generally underrepresented in clinical trials, mainly due to concerns regarding toxicity. Moreover, elderly patients who are enrolled in clinical studies may not represent the typical characteristics of an elderly GC population. Analyzing data from three randomized controlled trials, there were no significant differences in the incidence of grade 3/4 toxicity between younger and elderly adults. In terms of response rates, failure-free and overall survival elderly patients did benefit from chemotherapy to a similar degree as younger patients. In a multivariate analysis, independent prognostic factors for survival were performance status and locally advanced disease, but not age [20]. Nevertheless, careful assessment of functional status and comorbidities before the start of therapy is highly recommended, and the selection of sequential one-, two-, or three-drug regimens should be evaluated individually.

Systemic chemotherapy can prolong survival, improve symptom control and stability, and potentially improve quality of life. Combinations are more effective than single-agent chemotherapy and can also be recommended for elderly patients after proper evaluation of performance status and comorbidities. A combination comprising a platinum compound and a fluoropyrimidine can be regarded as an accepted first-line practice.

Which platinum compound should be used?

Cisplatin has been an integral part of GC reference regimens globally [12]. Due to its specific side effects, including nephrotoxicity, ototoxicity, and emetogenicity, other platinum salts have been studied. Carboplatin did not exhibit sufficient activity in phase II studies and was therefore not studied any further in randomized controlled trials [21]. In contrast, oxaliplatin, which had improved the efficacy of 5-fluorouracil (5-FU) treatment in colorectal cancer, was extensively studied in GC. Following promising phase II study results [22–24], oxaliplatin was compared with cisplatin in two randomized controlled trials. Both studies were designed to prove the non-inferiority of oxaliplatin compared with cisplatin. The Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer-2 (REAL-2) study had a two-by-two design. One thousand two patients were included, who received epirubicin/cisplatin plus either 5-FU (ECF) or capecitabine (ECX) or epirubicin/oxaliplatin plus either 5-FU (EOF) or capecitabine (EOX). For the oxaliplatin–cisplatin comparison, the hazard ratio for the oxaliplatin group [0.92 (95 % confidence interval CI, 0.80–1.10)] proved that oxaliplatin is non-inferior to cisplatin. As compared with cisplatin, oxaliplatin was associated with lower incidences of neutropenia, alopecia, renal toxicity, and thromboembolism, but with slightly higher incidences of diarrhea and neuropathy [25]. At the same time, the German Arbeitsgemeinschaft Internistische Onkologie (AIO) compared 5-FU/leucovorin and cisplatin (FLP) with 5-FU/leucovorin and oxaliplatin (FLO) [26]. The AIO study found a trend towards improved progression-free survival (PFS) with FLO versus FLP in 220 randomized patients, but no significant difference in overall survival (OS). Remarkably, FLO was associated with significantly less toxicity, including anemia, nausea, vomiting, alopecia, fatigue, renal toxicity, thromboembolic events, and other serious treatment-related adverse events. Sensory neuropathy was more common in the oxaliplatin group. In patients aged >65 years ($n = 92$), treatment with oxaliplatin resulted in significantly superior PFS (6.0 vs. 3.1 month; $P = 0.029$) and improved OS (13.9 vs. 7.2 months) as compared with cisplatin.

Cisplatin plus S-1 (CS) is the standard first-line treatment regimen for advanced gastric cancer in Japan [19].

Oxaliplatin plus S-1 (SOX) showed non-inferiority to CS in PFS [27]. The median PFS was 5.5 months for SOX vs. 5.4 months for CS (hazard ratio 1.00; 95 % CI, 0.84–1.20). The response rate was 56 % for SOX and 52 % for CS (χ^2 test, $P = 0.37$). The most common grade 3/4 toxicities in SOX vs. CS were neutropenia 19.5 vs. 41.5 %, thrombocytopenia 9.5 vs. 10.4 %, febrile neutropenia 0.9 vs. 6.9 %, and anorexia 14.8 vs. 18.5 %, respectively. Accordingly, SOX is considered a new standard option for first-line treatment in Japan.

In conclusion, oxaliplatin is generally less toxic than cisplatin. In view of its non-inferior efficacy, oxaliplatin can substitute for cisplatin in the treatment of advanced GC. Elderly patients may derive a particular benefit from treatment with oxaliplatin instead of cisplatin. However, oxaliplatin has not been approved in Europe, North America, or Japan by the medicine agencies and is therefore not reimbursed for the treatment of GC in some countries. In Korea, capecitabine–oxaliplatin or 5-FU, leucovorin, plus oxaliplatin is reimbursed and frequently used as first-line treatment for advanced GC.

Can oral fluoropyrimidines substitute for 5-FU?

Intravenous 5-FU has been the standard combination partner for platinum salts and other cytotoxic compounds in the treatment of GC.

The REAL-2 study compared capecitabine, an orally available 5-FU prodrug, with intravenous 5-FU [25]. The fluoropyrimidine comparison in REAL-2 showed non-inferiority of capecitabine with a hazard ratio for death of 0.86 (95 % CI, 0.80–0.99). The ML17032 study was performed in parallel in Korea and included 316 patients who were randomly assigned to receive either cisplatin/5-FU or cisplatin/capecitabine. The response rate was significantly higher in the capecitabine group (42 vs. 32 %, $p = 0.02$). The survival analysis proved the non-inferiority of capecitabine [28]. In a combined analysis of REAL-2 and ML17032, OS was even superior in patients treated with capecitabine combinations compared with patients treated with 5-FU; HR 0.87 (95 % CI 0.77–0.98, $P = 0.02$) [29]. However, the reported substantial toxicity of hand foot syndrome (HFS), which 22 % experienced with capecitabine compared to only 4 % with 5FU in the ML17032 study [28], and 46 % compared to 29 % all-grade HFS with capecitabine compared to 5FU in the REAL-2 study [25], may undercut the potential advantage of oral over continuous infusion administration.

Another oral fluoropyrimidine, S-1, is now approved in East Asia and Europe for the treatment of advanced GC. S-1 contains tegafur/gimeracil/oteracil potassium in a molar ratio of 1.0:0.4:1.0. Gimeracil reduces the degradation of 5-FU and oteracil improves its gastrointestinal tolerability. S-1 in combination with cisplatin has been established as the standard first-line chemotherapy in advanced GC in Japan (SPIRITS trial) [19]. S-1 was also shown to be non-inferior to infusional 5-FU when both were given as single agents [30]. With a dose established in a Western patient population [31] and with the hypothesis that cisplatin/S-1 could improve overall survival, safety, and convenience compared to cisplatin/5-FU, a randomized comparison was attempted in a non-Asian phase III trial into which 1053 patients were enrolled. The median OS was 8.6 months in the cisplatin/S-1 arm and 7.9 months in the cisplatin/5-FU arm, showing no significant difference. However, significant safety advantages were observed with S-1/cisplatin for the rates of complicated neutropenia, stomatitis, hypokalemia, and treatment-related deaths [32]. Note that cisplatin was administered at a reduced dosage in the S-1 arm (75 mg/m^2) compared to the standard arm (100 mg/m^2), possibly explaining the more favorable toxicity profile with S1/cisplatin. The results of a randomized trial proving the efficacy of S-1 and oxaliplatin in Japanese patients treated for advanced gastric cancer has already been reported [33]. Nevertheless, due to considerable pharmacokinetic differences when used in non-Asians, clinical experience with S-1 in Western countries suggests a different toxicity than that reported in Asian populations. Several polymorphisms have been identified in genes encoding drug-metabolizing enzymes, which may explain this differential toxicity of fluoropyrimidines between Asian and Western populations [34].

Oral fluoropyrimidines can substitute for intravenous 5-FU and are now subsidized for advanced GC in most countries. Although no superior survival was shown with the combination cisplatin/S-1, significant safety advantages were observed compared to cisplatin/5-FU. Cisplatin and capecitabine has become the standard backbone chemotherapy in trials investigating monoclonal antibodies in GC [10, 35, 36]. In the treatment of elderly or frail patients, or in cases where platinum agents are contraindicated, single-agent fluoropyrimidine, although not as effective as doublet regimens, should also be considered an option [37, 38].

Doublets or triplets—the rationale for adding a third cytotoxic drug

Triplet combination chemotherapy comprising an anthracycline or a taxane in addition to a platinum compound and a fluoropyrimidine has resulted in higher response rates and a modest improvement in overall survival compared with doublet combinations, but it also exposes patients to more serious side effects [12, 19]. A variety of treatment regimens have been established in randomized phase III studies which are the standard of care in different parts of the world, but not globally (Table 2).

Table 2 First-line treatment regimens developed in randomized controlled trials in advanced gastric cancer

Chemotherapy agents	Dosage (mg/m^2)	Application	Setting	Response rate (%)	Median PFS (months)	Median OS (months)
Triplet combinations						
ECF [25]			1st line	40.7	6.2	9.9
Epirubicin	50	i.v. day 1				
Cisplatin	60	i.v. day 1				
5-Fluorouracil	200	i.v. continuous infusion day 1–21				
Q3w						
ECX [25]			1st line	46.4	6.7	9.9
Epirubicin	50	i.v. day 1				
Cisplatin	60	i.v. day 1				
Capecitabine	1250	p.o. day 1–21				
Q3w						
EOF [25]			1st line	42.4	6.5	9.3
Epirubicin	50	i.v. day 1				
Oxaliplatin	130	i.v. day 1				
5-Fluorouracil	200	i.v. continuous infusion day 1–21				
Q3w						
EOX [25]			1st line	47.9	7.0	11.2
Epirubicin	50	i.v. day 1				
Oxaliplatin	130	i.v. day 1				
Capecitabine	1250	p.o. day 1–21				
Q3w						
DCF [41]			1st line	37.0	5.6	9.2
Docetaxel	75	i.v. day 1				
Cisplatin	75	i.v. day 1				
5-Fluorouracil	750	i.v. day 1–5				
Q3w						
Doublet combinations						
FLO [26]			1st line	34.8	5.8	10.7
Oxaliplatin	85	i.v. day 1				
Folinic acid	200	i.v. day 1				
5-Fluorouracil	2600	i.v. 24 h				
Q2w						
FLP [26]			1st line	24.5	3.9	8.8
Cisplatin	50	i.v. day 1				
Folinic acid	200	i.v. day 1				
5-Fluorouracil	2000	i.v. 24 h				
Q2w						
Cisplatin/capecitabine [28]			1st line	46.0	5.6	10.5
Cisplatin	80	i.v. day 1				
Capecitabine	2000	p.o. day 1–14				
Q3w						
Western cisplatin + S1 [32]			1stline	29.1	4.8	8.6
Cisplatin	75	i.v. day 1				
S1	50	p.o. day 1–21				
Q4w						
Asian cisplatin + S1 [19]			1st line	54	6.0	13.0
Cisplatin	60	i.v. day 8				
S1	40–60 mg	p.o. day 1–21				

Table 2 continued

Chemotherapy agents	Dosage (mg/m^2)	Application	Setting	Response rate (%)	Median PFS (months)	Median OS (months)
Q5w						
Asian oxaliplatin + S1 [27]			1st line	56	5.5	Not available
Oxaliplatin	100 mg/m^2	i.v. day 1				
S1	40–60 mg	p.o. day 1–14				
Q3w						

i.v. intravenous, *OS* overall survival, *PFS* progression-free survival, *p.o.* per os

Anthracycline-containing triplet combinations

The literature is inconsistent regarding the potential value of anthracyclines. In the UK and in some other countries, the incorporation of anthracyclines into the palliative medical treatment of gastric cancer has become common practice. According to the Cochrane analysis, randomized studies have proven the value of anthracyclines given in addition to platinum and 5-FU [12]. However, the evidence to support the activity of an anthracycline-based triplet [i.e., epirubicin, cisplatin, and 5-fluorouracil (ECF)] is provided by only three randomized studies, with a total sample size of 501 patients [12]. Note that the largest study included in this meta-analysis is a comparison between ECF and another triplet (mitomycin C plus CF, MCF) [39], which may lead us to question the conclusion that the addition of an anthracycline improves outcome, presuming that mitomycin C had a negative effect on CF efficacy. More recently, a relatively small randomized trial from Korea could not demonstrate improved efficacy upon the addition of epirubicine to cisplatin and capecitabine (ECX) compared to only cisplatin and capecitabine (CX) [40]. Despite the uncertainty regarding the value of adding an anthracycline to cisplatin and 5-FU, this anthracycline triplet remains the standard treatment in the UK. The combination of epirubicine, oxaliplatin, and capecitabine (EOX regimen) has shown superior survival compared with ECF in the randomized REAL-2 study (ECF) [25] (9.9 vs. 11.2 months; HR: 0.8; $p = 0.02$); however, a comparison to common two-drug regimens such as CF is lacking.

Docetaxel-containing triplet combinations

The randomized controlled TAX 325 trial showed a significantly improved overall survival (median 9.2 vs. 8.6 months; HR 1.29; $P = 0.0021$) for the addition of docetaxel (DCF) compared with cisplatin/5-FU (CF). Secondary endpoints were response rate (37 vs. 25 %) and time to progression (5.6 vs. 3.7 months; HR1.47; $P = 0.0004$), which were also in favor of DCF [41]. The median age of the patients included was 55 years, with only 24 % of patients aged ≥65. The majority of the patients had a good Karnofsky performance status (≥90:64 %). However, DCF was associated with substantial toxicity, particularly myelosuppression, with a 29 % incidence of febrile neutropenia, and gastrointestinal side effects were markedly increased (49 % grade 3/4). As a consequence, half of the patients discontinued treatment with DCF for either adverse events or patient refusal. Given that patients in clinical trials are usually carefully selected to be of a younger age and to have near-optimal organ and functional status, and thus do not necessarily reflect the geriatic and frail patients more commonly treated in clinical practice, the routine use of this toxic DCF regimen is rather questionable [41]. Due to the high rates of hematologic and other toxicities observed with the original DCF regimen, alternative docetaxel-containing regimens have been investigated in several phase II studies (Table 3). The principle of splitting docetaxel from 3-weekly into weekly or bi-weekly administration has led to a considerable decrease in hematological toxicity. Although evidence from phase III studies is lacking, the modification of DCF by alternative scheduling has decreased the toxicity, apparently without compromising the efficacy. Therefore, if docetaxel-based first-line treatment is considered, one should refrain from using classic DCF and choose an alternative treatment protocol such as Gastro-Tax [42], FLOT [43], or ATTAX [44]. Regarding the use of an intensive docetaxel-based triplet combination in elderly patients (≥65 years), the FLOT combination appears to be feasible and effective but no better than FOLFOX, although toxicity was markedly increased and quality of life was negatively impacted in a significant proportion of patients during the first 8 weeks of treatment [45]. Therefore, despite all of the associated improvements, docetaxel-containing treatment regimens should be only considered in fit and compliant patients, and proper patient selection—including critical evaluation of performance status and comorbidities, as well as access to frequent assessment of toxicity—should be performed before the onset of therapy. An alternative highly active and tolerable doublet chemotherapy regimen is the combination of docetaxel and S-1, which showed a promising median overall survival of 14.3 months and a median TTP of

Table 3 Docetaxel-containing combination regimens: phase II/III

Study	Phase	Number of patients	Regimen	Overall response rate (%)	Median PFS (months)	Median OS (months)
van Cutsem et al. [41]	III	224	DCF	37	5.6	9.2
Q3w		221	CF	25	3.7	8.6
Roth et al. [54]	II	61	TCF	41	4.6	10.4
Q3w		59	TC	38	3.6	11.0
		58	ECF	40	4.9	8.3
Tebbutt et al. [44]	II	50	wDCF	47	5.9	11.2
Q3w		56	wDX	26	4.6	10.1
Shah et al. [69]	II	30	mDCF	52	NR	15.1
Q3w		31	DCF + G-CSF	34	NR	12.6
Van Cutsem et al. [70]	II	79	TE Q3w	23.1	4.5	9.0
Q2w/Q3w		89	TEF Q2w	46.6	7.7	14.6
		86	TEX Q3w	25.6	5.6	11.3
Al-Batran et al. [43]	II	54	FLOT	58	5.2	11.1
Q2w						
Lorenzen et al. [42]	II	60	T-PLF	47	8.1	15.1
Q2w						
Yoshida et al. [46]	II	48	DS	56.3	7.3	14.3
Q3w						
Koizumi et al. [48]	II	59	DCS	81	8.7	18.5
Q4w						
Yoshida et al. [47]	III	314	DS	38.8	5.3	12.5
Q3w		314	S	26.8	4.2	10.8

PFS progression-free survival, *OS* overall survival, *ECF* epirubicin/cisplatin/FU, *ECX* epirubicin/cisplatin/capecitabine, *EOF* epirubicin/oxaliplatin/FU, *EOX* epirubicin/oxaliplatin/capecitabine, *TE* docetaxel/oxaliplatin, *TEF* docetaxel/oxaliplatin/FU, *TEX* docetaxel/oxaliplatin/capecitabine, *FLOT* docetaxel/oxaliplatin/FU/leucovorin, *T-PLF* docetaxel/cisplatin/FU/leucovorin, *DCF* docetaxel/cisplatin/FU, *DX* docetaxel/capecitabine, *DF* docetaxel/FU, *m* modified, *DCS* docetaxel/cisplatin/S-1, *DS* docetaxel/S-1, *G-CSF* granulocyte colony-stimulating factor, *w* weekly

8.3 months in a single center in Asia [46]. This trial was the basis for the randomized phase III START trial comparing docetaxel/S-1 with S-1 in patients with advanced gastric cancer. An updated analysis presented at ESMO 2012 showed an improved median survival time of 12.5 months in the combination therapy group compared to 10.8 months in patients who received S-1 alone ($p = 0.0319$) [47]. Another Japanese approach involving a triplet regimen was evaluated in a phase I/II trial in which patients received S-1, docetaxel (40 mg/m^2 on day 1), and cisplatin (60 mg/m^2 on day 1) (DCS), or S-1 (80–120 mg/day), 2 weeks on, 2 weeks off, every 4 weeks [48]. The most commonly observed grade 3/4 toxicity was neutropenia in 70 % of patients. The gastrointestinal toxicities were very low. The median PFS was 8.7 months and the median survival was 18.5 months. DCS is also being compared with CS in an ongoing phase III trial in Japan (JCOG 1013), from which known HER2-positive patients are excluded. The study aims to recruit a total of 740 patients and the primary endpoint is overall survival. The patients will be stratified according to institution, number of metastatic sites, measurable or nonmeasurable, and diffuse or intestinal type. The key secondary endpoint is survival by histology.

Irinotecan-containing regimens

Irinotecan-based combination regimens have been studied as a first-line alternative to platinum-based chemotherapy. The first phase II study results suggested that irinotecan and 5-fluorouracil combinations had promising antitumoral activity and efficacy [49, 50]. A randomized controlled phase III trial failed to show the superiority of irinotecan and high-dose 5-fluorouracil over only cisplatin and 5-fluorouracil [51]. However, quality of life tended to be better during treatment with irinotecan and 5-fluorouracil. Due to the lack of superior efficacy, irinotecan was not approved for the first-line treatment of gastric cancer in many health systems, but can be used as a "reserve regimen" with proven efficacy. Capecitabine could substitute for 5-fluorouracil as a combination partner of irinotecan [52].

Recommended regimens

Both doublet and triplet drug-regimens based on a platinum compound and a fluoropyrimidine can be used for the medical treatment of advanced GC. However, careful consideration of the potential toxic complications, impairment of the patient's quality of life, and the relative benefit should be undertaken. An indication for using three drugs in the first-line treatment is the presence of severe tumor symptoms, life-threatening tumor manifestations leading to the need for an instant tumor response, and the patient's preference for receiving the most active drug combination (and acceptance of enhanced side effects). Preferred regimens are the anthracycline-containing EOX regimen and the different modifications of DCF.

If doublet chemotherapy is chosen, one should be aware of the considerable toxicity associated with older high-dose cisplatin-based regimens. The CF regimen used in the control arm of the TAX 325 trial and other trials, cisplatin 100 mg/m^2 and a 5-day infusion of 1000 mg/m^2 5-FU every 4 weeks, was associated with substantial grade 3/4 toxicity, mainly neutropenia (57 %), stomatitis (27 %), diarrhea (8 %), nausea (17 %), and vomiting (17 %). Newer modified regimens using a weekly or biweekly infusion schedule of 5-FU combined with either biweekly cisplatin (50 mg/m^2) or oxaliplatin (85 mg/m^2) demonstrated markedly reduced toxicity [26] (Table 2), indicating that these regimens should be preferred in the treatment of advanced GC. Cisplatin/capecitabine (XP), cisplatin/S-1 or oxaliplatin plus a fluoropyrimidine (FLO, CapOx, or SOX) also represent more tolerable alternatives (Table 2), with dose reductions and various supportive measures considered in the case of severe toxicity.

Alternatively, although not as effective as combination therapy, single-agent fluoropyrimidines show activity in GC, and thus first-line fluoropyrimidine monotherapy (oral or infusional) should be considered as a reasonable option in the treatment of elderly patients or patients in whom platinum agents are contraindicated.

Quality of life

There are few reliable data on the quality of life associated with cytotoxic treatment of advanced GC. An analysis from the TAX-325 study shows that—despite being associated with considerable toxicity—DCF led to a prolongation of the time until definitive deterioration of the "global health status" as assessed by the European Organization of Research and Treatment of cancer (EORTC) quality of life C30 questionnaire [53]. This indicates that, in advanced GC, the global health status is very much influenced by the burden of disease. Comparing docetaxel-based triplet chemotherapy with anthracycline-based therapy indicated a higher treatment burden and a worse health status/QOL for docetaxel compared to anthracycline-based therapy [54]. Several studies with ECF confirmed that improved global QOL scores were obtained compared to DCF or MCF therapy in the first 6 months of treatment [39, 54]. Nevertheless, high treatment intensity over longer periods of time in patients with GC may again worsen health status and quality of life. Therefore, the clinical concept of starting with intensive induction regimens that reduce the disease burden followed by less intensive and better tolerated maintenance regimens that prolong the time to symptomatic tumor progression should be explored.

Biologically targeted therapy

Only modest progress has been made with novel chemotherapy agents such as oxaliplatin, docetaxel, capecitabine, and S1. Therefore, in order to further improve outcome, the identification of certain pathways that are key to cancer development is of the utmost importance. A number of biological therapies aim to inhibit components of signal transduction pathways that are amplified or functionally activated by specific genetic or epigenetic alterations. Pathways with targeted therapies where data are available or which are currently under clinical evaluation comprise HER2, VEGF, EGFR, mTOR, and c-Met.

The human epidermal growth factor receptor 2 (HER2) is overexpressed in approximately 20 % of GC patients. In HER2-positive advanced GC, the international phase III Trastuzumab for Gastric Cancer (ToGA) study showed a significant improvement in the median OS of patients upon the addition of trastuzumab to cisplatin and fluoropyrimidine backbone therapy [10]. Trastuzumab in combination with chemotherapy is now a new reference treatment for the first-line treatment of HER2-positive GC. Note that the appropriate selection of patients for anti-HER2 treatment is highly dependent on the quality of HER2 assessment by immunohistochemistry (IHC) and on the evaluation of HER2 gene amplification by in situ hybridization (ISH) techniques. Testing for HER2 in GC has its pitfalls and challenges. Optimal tumor samples should be used, and testing should be done in well-trained and quality-assured pathology laboratories [55, 56]. The greatest benefitof using trastuzumab may be gained by patients with the highest degree of HER2 overexpression: those that are IHC 3+ or IHC 2+ and FISH+.

Lapatinib, an oral tyrosine kinase inhibitor against both EGFR and HER2, has modest single activity in the first-line setting [57]. Results of the randomized phase III TRIO-013/Logic trial were recently presented [58]. The Logic trial could not demonstrate a statistically significant