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ORIGINAL ARTICLE

Phase II trial of induction irinotecan-cisplatin followed by concurrent irinotecan-cisplatin and radiotherapy for unresectable, locally advanced gastric and oesophageal-gastric junction adenocarcinoma

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Abstract
Purpose The prognosis of patients with unresectable M0 gastric cancer remains very poor. We performed a phase II trial to explore the efficacy and toxicity of induction irinotecan-cisplatin (IC) followed by concurrent irinotecan-cisplatin and radiotherapy (IC/RT) in this setting.
Methods and materials Patients with unresectable M0 gastric (GC) or oesophageal-gastric junction (EGJC) adenocarcinomas were treated with two courses of IC (irinotecan, 65 mg/m^2; cisplatin, 30 mg/m^2 on days 1 and 8 every 21 days) followed by IC/RT (daily radiotherapy—45 Gy—with concurrent IC: irinotecan, 65 mg/m^2, and cisplatin, 30 mg/m^2, on days 1, 8, 15, and 22). Resectability was reassessed after this treatment, and surgical resection was performed if feasible. The primary endpoint was the R0 resection rate after induction treatment.
Results Seventeen patients were included in the study (EGJC: 6; GC: 11). An R0 resection was achieved in only 5 patients (29%), and according to the design of the trial (Simon's optimal two-stage) accrual of patients was

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terminated after the first stage. No patient died during IC, whereas 3 patients (24%) died during IC/RT and one of 5 resected patients (20%) died during the first 30 days after resection. The median survival was 10.5 months, and the actuarial 2-year survival rate was 27%.

Conclusions Induction IC followed by IC/RT showed poor efficacy and significant toxicity in patients with unresectable GC/EGJC.

Keywords Unresectable gastric cancer · Unresectable oesophageal-gastric junction cancer · Induction chemoradiotherapy · Irinotecan · Cisplatin

Introduction

In spite of the large geographical differences observed in the incidence and mortality rates, gastric adenocarcinoma (GC) appears to be the second most common cause of cancer death worldwide. In the European Union [1], 96,000 new cases were diagnosed and 71,000 patients died as a consequence of the disease in 2006.

At the time of primary diagnosis, only 40% of patients in Western countries will have potentially resectable disease (30% will have unresectable locally advanced tumours and the other 30% will have metastatic disease) [2].

The prognosis of unresectable non-metastatic (M0) oesophageal-gastric junction cancer (EGJC) or GC is very poor, with a median overall survival (OS) of 10–12 months and a long-term OS of less than 5%. The treatment approach in patients with unresectable EGJC is substantially different to that considered for patients with unresectable GC. Patients with unresectable EGJC are commonly treated with definitive chemoradiotherapy, in a similar manner to patients with unresectable oesophageal cancer; the role of salvage surgery being not well defined in this setting [3]. On the other hand, patients with unresectable GC are usually treated with systemic chemotherapy, and the use of concomitant radiotherapy being much discussed in this setting. Importantly, some studies suggest that if a good response is achieved and salvage surgery becomes feasible, resection could be curative for a significant group of patients [4–7]. Induction chemoradiotherapy is an attractive approach in this setting as it could be more active as well as it could potentially render more patients resectable than induction chemotherapy alone. In a recently reported Phase III trial [8], preoperative chemoradiotherapy demonstrated a higher pathological complete response (pCR) rate and a trend towards a better loco-regional control. It also improved OS rather than preoperative chemotherapy in patients with resectable EGJC.

The efficacy of induction chemoradiotherapy in this setting may depend on the identification of more active chemotherapy regimens. One attractive option is the combination of irinotecan and cisplatin (IC), which has been shown to be quite active in advanced gastroesophageal cancer [9, 10]. In addition, both drugs have demonstrated notable radiosensitising effects. The therapeutic approach consisting in induction IC followed by IC with concomitant radiotherapy (IC/RT) and thereafter surgery was evaluated in a phase I trial in patients with resectable oesophageal cancer (84% of patients had distal adenocarcinomas), obtaining very promising results with a pCR rate of 21% [11]. Thus, aimed by the encouraging results of this phase I study, we performed a phase II trial to explore the activity and toxicity of this therapeutic sequential approach in patients with unresectable M0 GC or EGJC.

Patients and methods

Patient selection and evaluation

The present study was conducted between December 2003 and October 2004 at eight institutions participating in the Spanish Cooperative Group for Digestive Tumour Therapy (TTD). The protocol was approved by the Ethics Committees of all participating institutions and by the Spanish Health Authorities. The main inclusion criteria included initially unresectable M0 GC or EGJC with adenocarcinoma histology (disease that had invaded the head of the pancreas, hepatic hilium, upper mesenteric artery, aorta, transverse mesocolon, retro-peritoneum, or diaphragm was considered unresectable); age $\geq$ 18 years; ECOG performance status of $\leq$2; evaluable or measurable disease; no previous treatment with chemotherapy or radiotherapy; adequate bone marrow, renal, and hepatic function; no concomitant illnesses or medical conditions; and no psychological or sociological problems that could prevent a patient's understanding of the implications and requirements of the study.

Informed written consent was obtained from all patients prior to study entry. All patients underwent a multidisciplinary evaluation to assess the stage and resectability of the disease. Patients were staged with barium radiographs, an oesophagogastroduodenoscopy study, an endoscopic ultrasound (EUS) study, and a thoracic-abdominal-pelvic computed tomography (CT) scan. Laparoscopic staging was not required, although it was advised.

Study design

The primary endpoint of the study was the R0 resection rate after induction treatment. Secondary endpoints were the safety profile, clinical and pathological response and OS.

The overall study design was as follows. Induction treatment was concluded when either significant toxicity or disease progression occurred; further treatment was carried out at the investigator's discretion. The clinical response after induction chemotherapy (step 1) and after induction chemoradiotherapy (step 2) was assessed using CT and EUS. Resectability was reconsidered after the completion of induction treatment (resectability criteria at this point were the same as those considered at the inclusion). In patients with potentially resectable disease after induction treatment, surgical resection was attempted 5–8 weeks after concluding the chemoradiotherapy treatment.

R0 resection was defined as the removal of all gross tumours without any malignant cells more than 2 mm from the edge of the proximal, distal, and circumferential margins. No further therapy was provided if a patient underwent R0 resection. In patients for whom the resection was less than R0 (R1, positive margin; R2, residual gross carcinoma; no resection; or M1), palliative treatment was administered at the investigator's discretion. Pathological response was evaluated in all resected patients, according to Mandard criteria [12].

Toxicity was quantified using the common toxicity criteria (CTC) of the U.S. National Cancer Institute (NCI), version 2.0. Deaths due to toxicity were considered all those that occurred during the treatment period or during the 30 days after treatment completion. OS was calculated from the time of study entry until death.

A description of the outcomes and side effects according to tumour location was planned as part of the design of the trial. However, the study did not prove to be sufficiently statistically powered for detecting differences according to the tumour site. Therefore, the analysis according to the different tumour sites was performed on an exploratory basis only.

Treatment schedule

The complete treatment schedule is shown in Fig. 1 and summarised below.

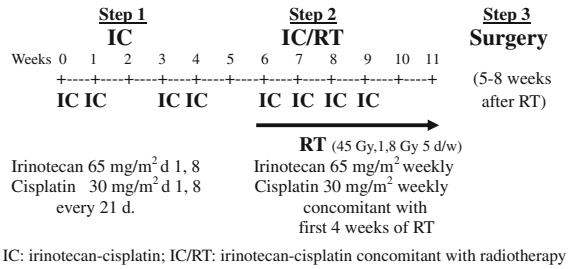

Fig. 1 Treatment schedule

Step 1: induction chemotherapy

Induction chemotherapy consisted of cisplatin (30 mg/m^2 i.v.) and irinotecan (65 mg/m^2 i.v.) (IC) administered on days 1 and 8 and every 21 days for two courses. Drug doses were decreased by 20% if grade $\geq$ 3 non-haematological or grade 4 haematological toxicity occurred.

Step 2: concurrent chemoradiotherapy

The radiotherapy-treated volume was determined using 3-dimensional planning systems; a multiple-field technique was used depending on the tolerance of the healthy tissues included in the fields. Radiation fields included the entire stomach, any perigastric extension, and the lymph nodes (gastric, coeliac, porta hepatis, gastroduodenal, splenic-suprapancreatic, and retropancreatic-duodenal). A 5-cm margin of the oesophagus was included for lesions involving the gastroesophageal junction, and a 5-cm margin of the duodenum was included for distal lesions near the gastroduodenal junction. Radiotherapy was delivered by linear accelerators, with a total dose of 45 Gy (25 fractions of 1.8 Gy each) delivered over 5 weeks using 6–18 MV photons. Concurrent chemotherapy consisted of cisplatin (30 mg/m^2 i.v.) and irinotecan (65 mg/m^2 i.v.) administered weekly during the first 4 weeks of radiotherapy (IC/RT). Drug doses were decreased by 20% if grade $\geq$ 3 non-haematological or grade 4 haematological toxicity occurred.

Step 3: surgery

The tumour was resected when feasible, along with more than a 5-cm luminal gastric margin; a 2-cm duodenal margin was used for distal cancers, and a 3-cm oesophageal margin was used for proximal cancers. A subtotal gastrectomy was considered adequate for distal GCs, and a total gastrectomy was carried out at the surgeon's discretion. Either total gastrectomy or oesophagogastrectomy was performed in patients with proximal cancers. In all cases, a $\geq$D1 lymphadenectomy was required. An en bloc resection was performed in those cases in which adjacent organs were involved. The spleen was preserved whenever possible.

Statistical design and methods

Calculation of the sample size was based on the R0 resection rate as a primary endpoint using Simon's optimal two-stage design [13]. An R0 rate of 40% was set as the lowest desirable rate, and 60% was set as the target rate. Type I and type II errors were established at 0.05 and 0.20, respectively. Using the specified parameters, a maximum of 46 assessable patients was required. In the first stage, 16

patients had to be evaluated, and in the event that less than 7 R0 were observed, the study had to be terminated. However, if ≥7 patients achieved an R0 resection, 30 additional patients (second stage) had to be entered. Finally, in case that more than 23 R0 resections were observed among 46 patients, this strategy would be considered for further phase III development.

All analyses were performed on an intention-to-treat basis. All reported *P* values were two-sided, and *P* values <0.05 were considered statistically significant. A chi-square analysis was used to detect statistical differences in proportions. OS curves were generated using the Kaplan–Meier method [14]. The log-rank test was used to compare the curves of the different subgroups. Analyses were performed using the SPSS software package, version 8 (SPSS Inc., Chicago, IL).

Results

Patient characteristics

Seventeen patients from eight different member institutions of the TTD cooperative group were included in the study. Patient characteristics are summarised in Table 1. The treatment administered and follow-up information are summarised in Fig. 2. According to the design of the trial (Simon's optimal two-stage), since the number of R0 resections performed was less than 7 (in fact, only 5) accrual of patients had to be terminated after the first stage, when 17 patients had been included.

Table 1 Patient characteristics

	All pts (17 pts) Pts (%)	EGJC (6 pts) Pts (%)	GC (11 pts) Pts (%)
Location			
EGJC			
Siewert I		2 (33)	
Siewert II		1 (17)	
Siewert III		3 (50)	
GC			
Proximal			4 (36)
Distal			7 (64)
Stage			
III-A (T4N0M0)	2 (12)	1 (17)	1 (9)
IV (T4N+M0)	15 (88)	5 (83)	10 (91)
PS (ECOG)			
0	5 (29)	2 (33)	3 (27)
1	11 (65)	4 (67)	7 (64)
2	1 (6)	0	1 (9)
Laparoscopic/Laparotomic staging	9 (53)	3 (50)	6 (55)
Unresectability cause			
Head of pancreas invasion	3 (18)	0	3 (27)
Hepatic hilum invasion	3 (18)	2 (33)	1 (9)
Transverse mesocolon invasion	2 (12)	1 (17)	1 (9)
Upper mesenteric artery invasion	1 (6)	1 (17)	0
Various	2 (12)	0	2 (18)
Not specified	6 (35)	2 (33)	4 (36)

EGJC oesophageal-gastric junction cancer, *GC* gastric cancer, *PS* performance status, *ECOG* Eastern Cooperative Oncology Group, *Pts* patients

Step 1: induction chemotherapy

All patients received at least one course of induction IC chemotherapy and therefore were evaluable for toxicity. Fourteen patients (82%) received 100% of the planned chemotherapy dose. The maximum toxicity per patient is shown in Table 2. No patient died during the induction chemotherapy.

The response after induction chemotherapy is summarised in Table 3. After step 1, thirteen patients proceeded to step 2 (IC/RT) and 4 patients proceeded to palliative treatment (3 patients progressed during IC and IC was discontinued in the other patient because of toxicity).

Step 2: concurrent chemoradiotherapy

Thirteen patients received at least one course of IC concomitant with radiotherapy and were evaluated for toxicity. Ten patients (76%) received 100% of the planned chemotherapy dose. The maximum toxicity per patient is shown in Table 2. Three patients (23%) died during chemoradiotherapy: one death was due to cerebral progression, the second to febrile neutropenia, and the third to cardiac failure. The response after step 2 is summarised in Table 3. After step 2, 8 patients proceeded to step 3 (surgery); the other 2 patients were considered non-resectable.

Step 3: surgery

Surgical resection was attempted in 8 patients after IC/RT, and R0 resections were achieved in 5 patients (29% of the 17 patients included). One patient (20%) died during the first 30 days after R0 resection due to peritonitis. No pCR was observed.

Follow-up

After a median follow-up of 25 months (range, 13–40 months), the status of the group of 17 patients who made up the study population was as follows: 3 patients were alive and disease-free, 2 were alive with disease, and 12

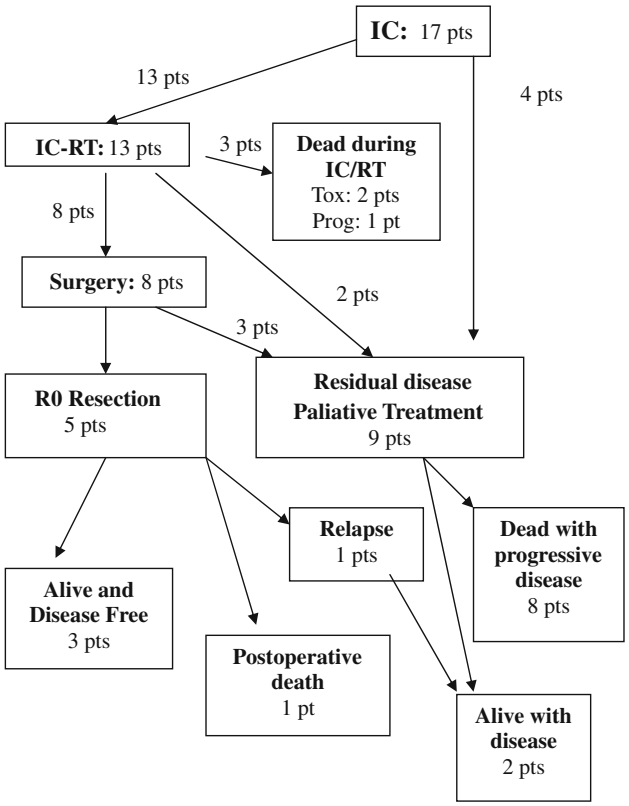

Fig. 2 Administered treatment and follow-up

patients had died (1 after an R0 resection, 2 as a result of chemoradiotherapy toxicity and 9 owing to disease progression). Therefore, 13 patients suffered either relapse or disease progression, which was only loco-regional in 10 patients (59%) and loco-regional plus systemic in 3 patients (18%). The median OS time was 10.5 months (95% CI: 6.9–14.1), and the 2-year OS rate was 27% (Fig. 3).

Oesophago-gastric junction cancer versus gastric cancer

A subgroup analysis of toxicity and efficacy according to tumour location was attempted. However, the results of this analysis should be considered with caution due to the small sample size. Nonetheless, we found that there were no statistically significant differences between the two groups in terms of patient characteristics (Table 1). Regarding efficacy, a trend towards a higher R0 resection rate was observed in EGJC. When toxicity was examined, no differences were observed in patients during step 1 (IC), but there was a trend towards a higher rate of haematological toxicity during step 2 (IC/RT) and a higher postoperative mortality rate in patients with GC. No significant differences in OS were observed between patients with EGJC and GC (median/2-year OS: 8.4 months/25% and 12.8 months/28%, respectively, log-rank $P = 0.81$).

Table 2 Toxicity (highest toxicity per patient)

Step 1 (IC)	All pts (17 pts) %	EGJC (6 pts) %	GC (11 pts) %
Neutropenia (G 3–4)	23	33	18
Febrile neutropenia	6	0	9
Anaemia (G 3–4)	6	17	0
Diarrhoea (G 3)	6	0	9
Emesis (G 3–4)	12	17	9
Asthenia (G 3–4)	12	0	18
Deaths during step 1	0	0	0
Step 2 (IC/RT)	(13 pts)	(4 pts)	(9 pts)
Neutropenia (G 3–4)	46	25	55
Febrile neutropenia	8	0	11
Thrombocytopenia (G 3–4)	15	25	11
Emesis (G 3–4)	8	25	0
Asthenia (G 3–4)	46	50	44
Cardiotoxicity (G 3–4)	8	0	11
Deaths during step 2	23 (3 pts)	25 (1 pt[a])	22 (2 pts[b])
Step 3 (surgery)	(5 pts)	(3 pts)	(2 pts)
Death <30 days after surgery	20 (1 pt)	0	50 (1 pt)

EGJC oesophageal-gastric junction cancer, *GC* gastric cancer, *IC* irinotecan-cisplatin, *IC/RT* irinotecan-cisplatin concomitant with radiotherapy, *Pts* patients

[a] CNS progression

[b] 1 pt: febrile neutropenia; 1 pt: cardiotoxicity

Table 3 Response, resection intent and R0 resection rate

Step 1 (IC)	All pts (17 pts) %	EGJC (6 pts) %	GC (11 pts) %
Partial response	6	0	9
Stable disease	53	17	73
Progression	0	0	0
Not evaluable	41	83	18
Step 2 (IC/RT)	(13 pts)	(4 pts)	(9 pts)
Partial response	8	0	11
Stable disease	48	50	55
Progression	10	0	11
Not evaluable	34	50	22
Step 3 (surgery)	(17 pts)	(6 pts)	(11 pts)
Resection intent	47 (8 pts)	67 (4 pts)	36 (4 pts)
R0 resection	29 (5 pts)	50 (3 pts)	18 (2 pts)
pCR	0	0	0

EGJC oesophageal-gastric junction cancer, *GC* gastric cancer, *IC* irinotecan-cisplatin, *IC/RT* irinotecan-cisplatin concomitant with radiotherapy, *pCR* pathologic complete response, *Pts* patients

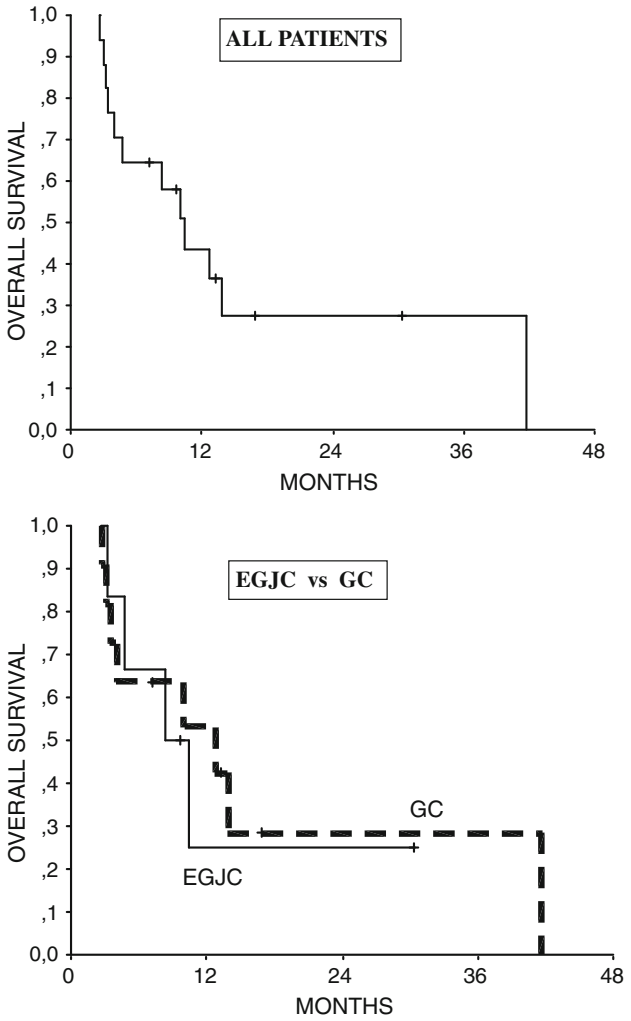

Fig. 3 Overall survival

Discussion

The results of this phase II study suggest that the preoperative chemoradiotherapy regimen explored in this trial (IC followed by IC/RT) has little efficacy as an induction treatment in unresectable M0 GC or EGJC and should not be considered for further development. The resection rate was only 29%, no patient achieved a pCR and the OS was somewhat disappointing (median OS 10.5 months, 2-year OS 27%). It should be pointed out that, although radiotherapy was added to the induction treatment with the intention of improving loco-regional control, loco-regional failure was present in all 13 patients who progressed or relapsed (10 of these patients displayed only loco-regional failure, and the other 3 patients also suffered from systemic progression). The efficacy of our approach seems to be clearly lower than that reported by other groups that have conducted phase II studies exploring the role of different induction chemotherapy regimens (without radiotherapy) in this setting (Table 4) [4–7]. In those studies, R0 resection rates ranged from 40 to 63% and the median OS ranged from 17 to 22 months.

There are several potential explanations for the low efficacy observed with our strategy. First of all, an staging laparoscopy was performed in only 53% of the patients included in the study and given to the fact that laparoscopy is a better staging technique for ruling out early peritoneal disease, it raises the question as to whether some patients with no-diagnosed peritoneal involvement could have been included in the study. Nevertheless, the lack of laparoscopy does not seem to have played an important role in the poor results of our trial because no patient was considered unresectable after induction treatment due solely to peritoneal disease, and no patient suffered an isolated peritoneal relapse.

Another possible matter that could contribute to the lack of efficacy of our strategy was the differences in the radiotherapy environment. Specifically, in the current study, radiotherapy involved neither centralised planning nor centralised quality review, although there were general guidelines regarding the field extension, total dose, and fractionation. It has recently been shown that radiotherapy quality assessment plays a critical role in studies involving radiotherapy of the upper abdominal area, as great variability in radiotherapy could have occurred in these types of studies [15]. Whether this may have had a detrimental effect in our study cannot be ruled out, but centralised planning and quality review of the radiotherapy treatment should be included in future studies to avoid this problem.

Table 4 Induction chemotherapy in unresectable, locally advanced gastric or oesophageal-gastric junction adenocarcinoma

Study (author)	Chemotherpy	No. of pts	R0 (%)	Medium OS	3 year OS
Wilke [4]	EAP	35	47	18 m	26%
Plukker [5]	FMTX	20	40	22 m	
Cascinu [6]	FLEP	82	45	17 m	31% (4y)
Shim [7]	DCX	49	63	19 m	31%

EAP etoposide-doxorubicin-cisplatin, *FMTX* 5FU-methotrexate, *FLEP* 5FU-leucovorin-epirubicin-cisplatin, *DCX* docetaxel-cisplatin-capecitabine, *Pts* patients, *R0* R0 resection rate, *OS* overall survival, *m* months, *y* year

Finally, another possible cause of the low efficacy observed in the present study could be related to the chemotherapy schedule employed. When this trial was planned out, only data from phase II studies performed in patients with advanced GC [9, 10], suggesting promising activity for the IC combination, were available. However, the results of a randomised phase II study comparing the IC combination with the irinotecan-5FU-leucovorin combination were subsequently published, demonstrating a lower response rate for the IC combination [16]. Moreover, the recently presented results from a phase III trial comparing irinotecan-5FU-leucovorin with cisplatin-5FU in patients with advanced GC failed to demonstrate an improvement in OS in patients treated with the irinotecan-based combination [17].

IC followed by concurrent IC/RT and then by surgery (a preoperative three-step approach that included IC) was also evaluated by our group in a phase II study in 23 patients with resectable GC or EGJC cancer [18]. In this phase II study, we observed preoperative chemoradiotherapy (IC followed by IC/RT) to be only moderately efficacious, in our study population, showing a pCR rate of 9%, an R0 resection rate of 65%, and a 2-year OS rate of 35%. These efficacy rates appear to be better than those observed in the present trial for unresectable patients, but seem to be lower than those reported by other groups that have conducted phase II studies of preoperative chemoradiotherapy with other chemotherapy regimens in patients with resectable GC [15, 19, 20], suggesting that the IC combination has limited efficacy in this setting.

Another important issue is the high mortality rate observed in our trial, mainly during concomitant IC/RT (3 deaths in 13 patients, 23%) or after surgery (1 death in 5 resected patients, 20%). In the trial performed by our group using the same regimen (IC followed by concurrent IC/RT and then by surgery) in resectable patients [18], no deaths occurred during IC/RT (21 evaluable patients) and only one out of 15 resected patients (7%) died during the first 30 days after resection. The higher toxicity rate observed in this unresectable population of patients could be related to several reasons including the more advanced stage and the poorer performance status of these patients as well as the wider radiotherapy fields that were used to include all the extension of the disease. On the basis of the toxicity figures observed in this population of patients with unresectable M0 disease, less aggressive approaches would be better explored in this setting.

In considering the efficacy and safety of this therapeutic approach according to the disease site (EGJC vs. GC), although no major differences were observed in terms of OS (log-rank $P = 0.81$), the results appear to be better in EGJC (less toxicity during IC/RT, lower mortality after surgery and higher R0 resection rate) than in GC. However, as noted earlier, this subgroup analysis did not possess sufficient power, as the number of patients in each subgroup was too low to draw any meaningful conclusion. Nevertheless, the results of our exploratory analysis suggest that definitive or induction chemoradiotherapy, which is already considered a standard option in the treatment of unresectable distal oesophageal cancer and EGJC, could be less effective and too toxic in patients with unresectable GC.

In conclusion, induction IC followed by IC/RT showed poor activity and significant toxicity in patients with unresectable GC/EGJC, and this regimen should not be further investigated. Therefore, new strategies are warranted to improve the current therapeutic results in this disease. In this regard, new biological therapies aimed to inhibit or modulate different targets of the signal transduction pathways that are thought to be functionally selective or overexpressed in certain tumour types, such as GC or EGJC, are currently being evaluated in the advanced setting. The results of the phase III trial TOGA have been recently reported and have shown a significant improvement in response rate and OS in patients with Her-2 + advanced EGJC/GC by the addition of the anti-Her-2 monoclonal antibody trastuzumab to standard cisplatin-fluoropyrimidin-based chemotherapy [21]. Several studies are evaluating the role of other targeted therapies, including EGFR inhibitors and anti-angiogenic agents, in combination with chemotherapy, in advanced GC and EGJC. Most of these studies have included both, unresectable locally advanced and metastatic disease; however, it would be better to perform specific trials for patients with locally advanced disease to evaluate the role of new systemic regimens and the utility (or lack thereof) of adding loco-regional treatments (radiotherapy and/or surgery) in this setting. These studies should include properly designed analyses of the possible predictive factors that could enable clinicians to choose the best treatment option for each patient.

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Conflict of interest Fernando Rivera served on the advisory board and received travel and research grants from Roche, Sanofi –Aventis and Merck-Serono. Maica Galán served on the advisory board for Roche. No conflicts of interest pertain to the remaining authors.

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