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How I treat gastric adenocarcinoma

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ABSTRACT

Gastric and gastro-oesophageal junction cancer (GC) represents a worldwide problem, this being the fifth most common malignancy. The fragility of patients with GC together with the aggressiveness of this tumour makes it as one of the most difficult neoplasias to manage. This article summarises the main strategies for treating patients with GC. Correct assessment of patients with GC requires a multidisciplinary evaluation and close follow-up. For patients with resectable tumours, perioperative chemotherapy should be always considered, especially in the neoadjuvant setting given its capacity for tumour downstaging and eradication of micro-metastases. In the metastatic setting, first-line and second-line treatment improve survival and quality of life in patients with GC. In this setting, only trastuzumab as first-line therapy in patients with human epidermal growth factor receptor 2 positive tumours and ramucirumab as second-line therapy have demonstrated a clear survival improvement. The lack of adequate biomarker selection and the intrinsic heterogeneity of these tumours have jeopardised the possible usefulness of many other targeted agents. Finally, when considering GC carcinogenesis as a multiple stepwise process from initial inflammation starting in the gastric epithelia, immune checkpoint inhibitors may improve the survival of these patients, although the optimal setting for their activity has yet to be fully elucidated.

INTRODUCTION

Gastric and gastro-oesophageal junction cancers (GC) are the third cause of cancer-related deaths,[1] representing an international problem which needs precise individualised treatment. While the incidence of gastric cancer is globally decreasing, the contrary is occurring for proximal and junctional tumours.[2] These epidemiological distinctions are sustained by various associated risk factors which ultimately potentiate the occurrence of different molecularly driven tumours within the stomach. According to the Cancer Genome Atlas,[3] four molecular subtypes of GC have been identified, with inherent genetic features. Also important is the particular need for recognition of GC heterogeneity, not only to understand the failure of multiple phase III studies with targeted agents carried out over the last few years but also to provide physicians with adequate guided strategies.

DIAGNOSIS, STAGING AND TREATMENT PLANNING

Patients with GC represent a particularly fragile population. Symptomatology normally only appears once the tumour has increased in size to the point where it interferes with the nutritional process, resulting in these patients presenting with significant asthenia, difficulty for tolerating normal food (nausea, vomiting and early satiety), anaemia and non-depreciable weight loss. Correct evaluation of patients with GC requires particular consideration of supportive care and nutritional assessment.

Diagnosis of GC should be made from a gastroscopy with a biopsy, including histology reported according to the WHO criteria,[4] together with human epidermal growth factor receptor 2 (HER-2) receptor status (at least in metastatic cases). Staging is normally assessed by a thoracoabdominal CT scan. However, a positron emission tomography-CT scan might be necessary in cases with suspicious metastatic spread, while an exploratory laparoscopy may rule out peritoneal spread in cases considered upfront to be potentially resectable, and an endoscopic ultrasound may improve the accuracy of staging in locally advanced cases. The TNM stage should be reported according to the latest edition of the American Joint Committee on Cancer/Union for International Cancer Control guidelines and staging manual.[5] The evaluation of each patient with GC should always include a precise anamnesis and physical examination including weight, a differential blood count, as well as liver and renal function tests. Testing for tumour markers (CEA, CA19.9 and CA72.4), although not mandatory, may be helpful especially for detecting recurrences during follow-up, and anticipating progression in the metastatic setting. A thorough approach would ideally include a multidisciplinary tumour board, especially in locally advanced and resectable cases.

MANAGEMENT OF LOCAL/LOCOREGIONAL DISEASE

Surgery represents the cornerstone of curative treatment, although recurrences occur in

more than 50% of cases.[6] Indeed, GC should be considered a systemic disease from the start of care, such that treatment with systemic perioperative chemotherapy potentiates the downstaging and eradication of microscopic metastases. Endoscopic resection (if cT1a, clearly confined to the mucosa, well differentiated, ≤2 cm and non-ulcerated) or surgery alone can only be recommended for stage I disease. For stages Ib–III, perioperative treatment is mandatory.

The type of the surgery depends on the location of the tumour. Subtotal gastrectomies may only be carried out if a macroscopic proximal margin of at least 5 cm between the tumour and the gastro-oesophageal junction can be achieved (otherwise a total gastrectomy is mandatory). A D2 lymph node dissection is recommended, with the removal of perigastric lymph nodes plus those along the left gastric, common hepatic and splenic arteries and the coeliac axis, with a minimum of 15 lymph nodes removed. Only specialised, high-volume institutions with appropriate surgical expertise and postoperative care should be considered for performing these complex resections.

Perioperative (preoperative and postoperative) chemotherapy with a platinum and a fluoropyrimidine combination is recommended for patients with stage >Ib. The phase III UK Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial[6] demonstrated an improvement in 5year overall survival (OS) from 23% to 36% with six cycles of perioperative epirubicin, cisplatin and 5-fluorouracil (5-FU) (ECF) chemotherapy, compared with surgery alone in patients with stages II and III GC. A French study[7] demonstrated similar results with perioperative cisplatin plus 5-FU in a 28-day regimen, although it included a greater proportion of patients with proximal tumours, compared with the MAGIC trial. Finally, an European Organisation for Research and Treatment of Cancer study with a weekly schema of cisplatin and 5-FU demonstrated an increase in R0 resection rates in patients receiving chemotherapy plus surgery compared with those with surgery alone.[8] This study was closed early due to poor accrual and consequently was not powered to show differences in OS. These three phase III trials established perioperative treatment as the gold standard in European patients, with the schema from the MAGIC trial being the most widely accepted. Nevertheless, this paradigm radically changed in 2017 when the OS results from the German AIO study group demonstrated greater benefit with the addition of taxanes to the platinum-5-FU doublet.[9] This study compared the fluorouracil, leucovorin, oxaliplatin, docetaxel (FLOT) regimen versus ECF/X. Patients treated with FLOT presented a higher pathological response rate and a large improvement in survival (HR 0.77, p=0.012). Global toxicity rates were similar in both groups, although patients treated with FLOT presented more leucopenia/neutropenia and peripheral neuropathy.

Unfortunately, some patients with GC with stage >Ib are not eligible for perioperative treatment, mainly due to age and/or comorbidities or because of an urgent surgery requirement (when debuting with initial refractory bleeding or highly occlusive tumours). In this setting, adjuvant treatment after surgery either with chemoradiotherapy or with chemotherapy alone can be considered. The North American Intergroup-0116 trial demonstrated an OS benefit in patients who received postoperative 5-FU-based chemoradiotherapy,[10] although most of the patients had been treated with inadequate lymphadenectomy (less than D1). The results of the study suggested that postoperative treatment might compensate suboptimal surgery. Similar findings in the Dutch D1D2 trial corroborated this, demonstrating a greater survival benefit in patients who had undergone D1 (not D2) lymphadenectomies or R1 resections.[11 12] Moreover, the phase III ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach (CRITICS) trial,[13] which evaluated adjuvant chemoradiotherapy versus chemotherapy alone in patients who had received preoperative chemotherapy and surgery, confirmed the limited benefit of adjuvant radiotherapy. Finally, an Asian study reinforced the benefit of the adjuvancy with chemotherapy alone, demonstrating a benefit of performing 6 months of capecitabine–oxaliplatin after radical surgery in patients who had undergone R0 resection with an adequate lymphadenectomy but without having received preoperative chemotherapy.[14]

MANAGEMENT OF ADVANCED/METASTATIC DISEASE (CHEMOTHERAPY, TARGETED AGENTS, IMMUNOTHERAPY)

First-line treatment

Patients with locally advanced unresectable and/or metastatic disease should be considered for systemic treatment (chemotherapy), which has consistently demonstrated a benefit in both OS and quality of life.[15] The standard of care is based on a platinum (cisplatin or oxaliplatin) and a fluoropyrimidine doublet (5-FU, capecitabine, tegafur/gimeracil/oteracil (S-1)). Patients with HER-2 overexpression (immunohistochemistry (IHC) 3+ or IHC 2+ and in situ hybridisation positive) should also receive trastuzumab (table 1a).

The addition of epirubicin to a chemotherapy doublet has not definitively demonstrated an OS advantage and slightly increases toxicity. In contrast, the addition of docetaxel offers a small benefit in OS but with considerable toxicity with the original docetaxel, cisplatin and 5-FU (DCF) regimen assessed in the V325 phase III study.[16] This latter fact together with the fact that taxanes can be given in the second line makes the use of this drug in the first-line setting rare. The original DCF regimen, or better the analogous and less toxic FLOT regimen,[9] should only be considered in young/fit patients and if a very quick response is needed.

To date, no other targeted agents have demonstrated an OS benefit in this setting. The lack of biomarkei stratification and the intrinsic GC heterogeneity have likely contributed to the failure to demonstrate a benefit when using multiple targeted therapies against

Table 1 Main phase III clinical trials with chemotherapy (A and B) and targeted therapies (C).

Clinical trial	N	Treatment	OS		PFS		ORR	P value
(A) First-line chemotherapy treatment								
The V325 Trial *Van Cutsem* *J Clin Oncol 2006*	445	DPF PF	9.2 m 8.6 m	HR 1.29 p=0.02	5.6 m* 3.7 m	HR 1.47 p<0.01	37% 25%	0.01
The Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 2 (REAL-2) Trial *Cunningham* *NEJM 2008*	1002	EPF EPC EOF EOC	9.9 m 9.9 m 9.3 m 11.2 m	Non-inferiority meet	6.2 m 6.7 m 6.5 m 7 m		40.7% 46.4% 42.4% 47.9%	
The ML17302 Trial *Kang* *Ann Oncol 2009*	316	CP FP	10.5 m 9.3 m	HR 0.85 p=0.008	5.6 m 5.0 m	HR 0.81 p<0.01	46% 32%	0.020
The FLAGS Trial *Ajani* *J Clin Oncol 2010*	1053	P-S1 P-F	8.6 m 7.9 m	HR 0.92 p=0.2	4.8 m 5.5 m	HR 0.99 p=0.92	29.1% 31.9%	0.40
The French Intergroup Trial *Guimbaud* *J Clin Oncol 2014*	416	EPC FOLFIRI	9.49 m 9.72 m	HR 1.01 p=0.95	5.29 m 5.75 m	HR 0.99 p=0.96	39.2% 37.8%	
(B) Second-line treatment and beyond								
The Arbeitsgemeinschaft Internistische Onkologie (AIO) Trial *Thuss-Patience* *Eur J Can 2011*	40	CPT-11 BSC	4.0 m 2.4 m	HR 0.48 p=0.012	2.6 m –		0% –	
The Salvage Chemo Trial *Kang* *J Clin Oncol 2012*	188	D/CPT-11 BSC	5.3 m 3.8 m	HR 0.65 p=0.007	–		13% –	
The COUGAR-02 Trial *Ford* *Lancet Oncol 2014*	168	D BSC	5.2 m 3.6 m	HR 0.67 p=0.01			7% –	
The West Japan Oncology Group (WJOG) Trial 4007 (WJOG 4007) *Hironaka* *J Clin Oncol 2013*	223	Pac CPT-11	9.5 m 8.4 m	HR 1.13 p=0.38	3.6 m 2.3 m	HR 1.14 p=0.33	20.9% 13.6%	0.24
The KEYNOTE 061 Trial *Shitara* *Lancet 2018*	592	Pem Pac	9.1 m 8.3 m	HR 0.82 p=0.042	1.5 m 4.1 m	HR 1.27 –	16% 14%	–
The TAGS Trial *Shitara* *Lancet Oncol 2018*	507	TAS-102 PB	5.7 m 3.6 m	HR 0.69 p<0.01	2.0 m 1.8 m	HR 0.57 p<0.01	4% 2%	0.28
The JAVELIN 300 Trial *Bang* *Ann Oncol 2018*	371	Ave CPT-11/ Pac	4.6 m 5.0 m	HR: 1.1 p=0.81	1.4 m 2.7 m	HR: 1.73 p>0.99	2.2% 4.3%	–
(C) Targeted agents								
The TOGA Trial *Bang* *Lancet 2010*	594	CP/FP-T CP/FP	13.8 m 11.1 m	HR 0.74 p<0.01	6.7 m 5.5 m	HR 0.71 p<0.01	47% 35%	<0.01
The TRIO-013/LOGIC Trial *Hecht* *J Clin Oncol 2016*	545	OC+L OC	12.2 m 10.5 m	HR 0.91 p=0.34	6.0 m 5.4 m	HR 0.82 p=0.038	53% 39%	<0.01
The JACOB Trial *Tabernero* *Lancet Oncol 2018*	780	CP/FP-T- Per CP/FP-T	17.5 m 14.2 m	HR 0.84 p=0.057	8.5 m 7.0 m	HR 0.73 p<0.01	56.7% 48.3%	0.026

Continued

Table 1 Continued

Clinical trial	N	Treatment	OS		PFS		ORR	P value
The TyTAN (Tykerb With Taxol in Asian HER2-Positive Gastric Cancer) Trial *Satoh* *J Clin Oncol 2014*	261	Pac +L Pac	11.0 m 8.9 m	HR 0.84 p=0.104	5.4 m 4.4 m	HR 0.85 p=0.244	27% 9%	<0.01
The GATSBY Trial *Tuss-Patience* *Lancet Oncol 2017*	345	T-DM1 D/Pac	7.9 m 8.6 m	HR 1.15 p=0.86	2.7 m 2.9 m	HR 1.13 p=0.31	20.6% 19.6%	0.840
The Erbitux (cetuximab) in combination with Xeloda (capecitabine) and cisplatin in advanced esophago-gastric cancer (EXPAND) Trial *Lordick* *Lancet Oncol 2013*	904	CP-Cet CP	9.4 m 10.7 m	HR 1.00 p=0.95	4.4 m 5.6 m	HR 1.09 p=0.32	30% 29%	0.77
The REAL3 Trial *Waddell* *Lancet Oncol 2013*	553	EOC-Pan EOC	8.8 m 11.3 m	HR 1.37 p=0.013	6.0 m 7.4 m	HR 1.22 p=0.068	46% 42%	0.42
The Avastin in Gastric cancer (AVAGAST) Trial *Ohtsu* *J Clin Oncol 2011*	774	CP-Bev CP	12.1 m 10.1 m	HR 0.87 p=0.100	6.7 m 5.3 m	HR 0.80 p=0.003	46% 37.4%	0.031
The RAINFALL Trial *Fuchs* *Lancet Oncol 2019*	645	CP-Ram CP	11.2 m 10.7 m	HR 0.96 p=0.68	5.7 m† 5.4 m	HR 0.75 p=0.011	41.1% 36.4%	0.17
The REGARD Trial *Fuchs* *Lancet 2014*	355	Ram PB	5.2 m 3.8 m	HR 0.77 p=0.047	2.1 m 1.3 m	HR 0.48 p<0.01	3% 3%	0.76
The RAINBOW Trial *Wilke* *Lancet Oncol 2014*	665	Pac-Ram Pac	9.6 m 7.4 m	HR 0.80 p=0.017	4.4 m 2.9 m	HR 0.63 p<0.01	28% 16%	<0.01
The Apatinib Trial *Li* *J Clin Oncol 2016*	267	Apa PB	6.5 m 4.7 m	HR 0.70 p=0.015	2.6 m 1.8 m	HR 0.44 p<0.01	2.84% 0%	0.169
The RILOMET-1 Trial *Catenacci* *Lancet Oncol 2017*	609	EPC-Rilo EPC	8.8 m 10.7 m	HR 1.34 p=0.003	5.6 m 6.0 m	HR 1.26 p=0.016	29.8% 44.6%	<0.01
The METGASTRIC Trial *Shah* *Jama Oncol 2016*	562	FOLFOX-Ona FOLFOX	11.0 m 11.3 m	HR 0.82 p=0.24	6.7 m 6.8 m	HR 0.90 p=0.43	46.1% 40.6%	0.25
The GOLD Trial *Bang* *Lancet Oncol 2017*	643	Pac-O Pac	8.8 m 6.9 m	HR 0.79 p=0.026	3.7 m 3.2 m	HR: 0.84 p=0.065	17% 11%	0.055
The GRANITE-1 Trial *Othsu* *J Clin Oncol 2013*	656	Eve PB	5.4 m 4.3 m	HR 0.90 p=0.124	1.7 m 1.4 m	HR 0.66 p<0.001	4.5% 2.1%	–

List of phase III clinical trials in (A) first-line treatment, (B) second-line treatment and beyond and (C) targeted agents. In green, those trials with statistically positive results.
*Time to progression (not PFS).
†Not confirmed by central independent review.
–, not reported; Apa, apatinib; Ave, avelumab; BSC, best supportive care; Bev, bevacizumab; C, capecitabin; CPT-11, irinotecan; Cet, cetuximab; D, docetaxel; E, epirrubicin; Eve, everolimus; FOLFIRI, irinotecan, leucovorin, 5-fluorouracil; FOLFOX, oxaliplatin, leucovorin, 5-fluorouracil; 5-FU, 5-fluorouracil; L, lapatinib; O, olaparib;OS, overall survival; OX, oxaliplatin; Ona, onartuzumab; P, cisplatin; PB, placebo; PFS, progression-free survival; Pac, paclitaxel; Pan, panitumumab; Pem, pembrolizumab; Per, pertuzumab; Ram, ramucirumab; Rilo, rilotumumab;T, trastuzumab; TAS-102, trifluridine/tipiracil; m, months.

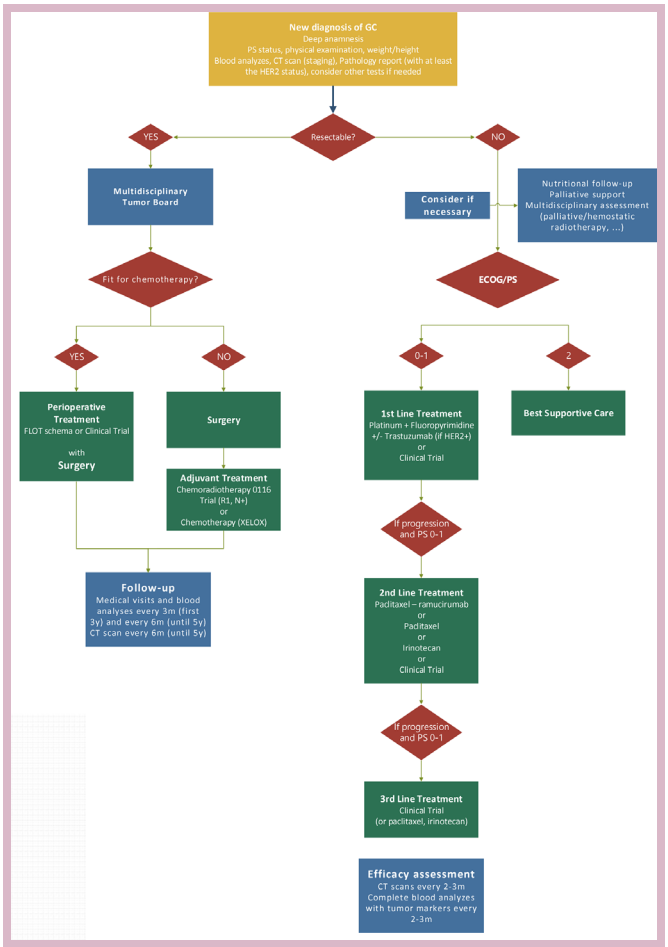

Figure 1 Algorithm for the treatment of GC. ECOG, Eastern Cooperative Oncology Group; FLOT, fluorouracil, leucovorin, oxaliplatin, docetaxel; GC, gastric and gastro-oesophageal junction cancer; HER-2, human epidermal growth factor receptor 2; PS, performance status.

HER2, epidermal growth factor receptor, MET, the tyrosine kinase receptor activated by the hepatocyte growth factor, fibroblast growth factor receptor 2, phosphatidylinositol 3-kinase-mammalian target of rapamycin, vascular endothelial growth factor (first line) and poly(ADP-ribose) polymerase-1 (table 1b).

Finally, comorbidities, organ function and performance status (PS) must always be taken into consideration when choosing a regimen.

Second-line treatment

Second-line treatment based at a minimum on chemotherapy (paclitaxel, docetaxel or irinotecan) should be considered in patients with PS 0–1, with the most robust evidence demonstrated for combined paclitaxel and ramucirumab (table 1c). This combination has demonstrated a benefit in both survival and also in quality of life.

Further lines

Further lines can be considered in fit patients (PS 0–1). Third lines with taxanes or irinotecan (depending on the second line) are acceptable, despite a lack of clear evidence. Trifluridine/tipiracil will likely be considered in the near future due to the benefit shown in a phase III clinical trial.[17]

INNOVATIVE STRATEGIES

The GC treatment paradigm may change in the near future. Recognition of the historic failure in molecular selection due to GC heterogeneity was an important first step. Liquid biopsies should help us to acquire important biomarker information.[18] Moreover, and taking into account the underlying gastritis that normally precedes GC tumorigenesis, the encouraging results showed by immune checkpoint inhibitors in the refractory setting[19] will hopefully be translated into the clinical setting from the ongoing phase III clinical trials, with a consequent significant improvement in the prognosis of patients with GC.

In GC tumours with microsatellite instability, pembrolizumab, although not approved by the Europena Medicines Agency, may be recommended, as well as in refractory programmed death-ligand 1-positive (combined positive score) patients.[19] In the Asian population, nivolumab has shown OS benefit in this refractory setting.[20]

CONCLUSIONS

Patients with GC should be discussed in multidisciplinary tumour boards. The particular fragility of these patients requires close monitoring by multiple specialists including nutritionists and supportive care professionals. Moreover, given the molecular complexity of these tumours, careful hierarchy when selecting a targeted treatment should be considered. Having established the standard practice in the clinic (figure 1), physicians should always consider a clinical trial as the first option to offer.

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