REVIEW ARTICLE

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Locally Advanced Gastric Cancer: Current and Future Strategies to Improve Outcomes with Multimodality Approach

Elisabete Couto, Ana Marques, Diana Freitas, Rui Nabiço

Medical Oncology Department, Hospital de Braga, Portugal

Corresponding author:
Elisabete Maria Oliveira Couto
Hospital de Braga
Sete Fontes 4101-901Braga
(São Vítor)
Phone: 00351253027144
Fax: 00351253027999
E-mail: elisabetemocouto@gmail.com

INTRODUCTION

Gastric cancer is the sixth most common cancer and the fourth most common cause of cancer- related death in Europe, causing 107.000 deaths every year. Locally advanced gastric cancer (LAGC) can be defined as clinical T2 disease and beyond with or without confirmed nodal involvement. Surgery is the cornerstone of therapeutic strategies with curative intent, but a significant amount of patients relapse after surgery and 5-year survival rates remain poor (1). Active research on multimodality approach, adding chemotherapy and/or radiotherapy to optimal surgery allowed improvement of survival in the past two decades.

Diagnostic and Staging Workup

The American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumour, node and metastasis (TNM) staging system has been extensively used in defining gastric cancer stage and is the most relevant tumour-related prognostic factor. Since January 2018 it is mandatory to use the 8th edition of the TNM staging system (2).

Prior to any treatment, patients should undergo an upper endoscopy with biopsy to provide definitive diagnosis and histological type, tumour extension, as well as other important features such as bleeding, ulceration and stenosis. This study should be complemented with an endoscopic ultrasound (EUS) to accurate assessment of T and N stage. A CT scan of the thorax, abdomen and pelvis is critical to detect distant metastasis (3).

To exclude radiologically occult metastatic disease, a staging laparoscopy is also recommended in all stage IB–III gastric cancers, according to the current ESMO guidelines that assume, however, a greater benefit for patients with T3/T4 disease. Patient's characteristics (age, comorbidities, performance status and treatment expectations) should be considered simultaneously with the definition of the optimal treatment strategy (4).

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Therapeutic Strategies in LAGC

Currently, patients with LAGC are candidates to multimodality treatment: either perioperative chemotherapy (standard approach in Europe) or upfront

surgery followed by adjuvant chemotherapy or chemoradiation therapy (if there is a compelling reason to do surgery first).

Perioperative chemotherapy

The aims of neoadjuvant (and perioperative) chemotherapy are to downstage the tumour, increase R0 resection rate, treat micrometastatic disease and to improve overall survival (OS). Neoadjuvant chemotherapy also has the advantage of better tolerance compared with the adjuvant setting (perhaps due to a better performance status) and has no impact on postoperative morbidity or mortality. In 2006, the MAGIC trial demonstrated the benefit of 3 cycles of chemotherapy with epirrubicin (50 mg/m^2 on day 1), cisplatin (60 mg/m^2 on day 1) and 5-fluorouracil (200 mg/m^2/day on continuous intravenous infusion from day 1 to 21 of each three-week cycle), followed by surgery and 3 more cycles of the ECF regimen, versus surgery alone (5). Later, the FFCD/FNCLCC trial showed a survival benefit from 2-3 cycles of cisplatin (100 mg/m^2 on day 1) and a continuous intravenous infusion of fluorouracil (800 mg/m^2/day) from day 1 to 5 of every 4 weeks cycle (CF), followed by surgery and 3-4 cycles of CF chemotherapy (6). These trials highlighted important aspects of this perioperative strategy: there is a better compliance in the neoadjuvant setting (since only approximately 10% of the patients did not complete the pre-planned number of cycles), which gives the patients the opportunity to benefit from systemic treatment, since half of the patients did not tolerate any adjuvant chemotherapy. They also showed similar improvements in five-year survival rates (MAGIC trial: 23% in the surgery arm versus 36% in the perioperative treatment arm; FFCD trial: 24% in the surgery arm vs 38% in perioperative arm) (5,6).

Modifications to standard perioperative treatments were evaluated in the MAGIC-B/ST03 trial, which assessed the safety and efficacy of adding bevacizumab to standard perioperative chemotherapy with ECX (epirrubicin 50 mg/m^2 day 1, cisplatin 60 mg/m^2 day 1 and capecitabine 1250 mg/m^2 day 1 to 21). The results of this trial did not provide any evidence for the use of bevacizumab and it also might be associated with impaired wound healing (higher rates of anastomotic leaks in patients who underwent oesophagogastrectomy) (7).

CRITICS is a phase III trial that explored the combination of perioperative chemotherapy and adjuvant chemoradiation. Randomisation was done before patients were given any preoperative chemotherapy. Surgery consisted of a radical resection of the primary tumour and at least a D1+ lymph node dissection. Chemotherapy consisted of three preoperative 21-day cycles and three postoperative cycles of standard ECX or EOX (with oxaliplatin). Chemoradiation consisted of 45 Gy in 25 fractions of 1.8 Gy, for 5 weeks, five daily fractions per week, combined with capecitabine (575 mg/m^2 orally twice daily on radiotherapy days) and cisplatin (20 mg/m^2 intravenously on day 1 of each 5 weeks of radiation treatment). This trial concludes that postoperative chemoradiation did not improve overall survival compared with postoperative chemotherapy in patients with resectable gastric cancer treated with adequate preoperative chemotherapy and surgery (median OS was 43 months in the chemotherapy group and 37 months in the chemoradiation group) (8).

Recently, the FLOT4-AIO trial investigated a new treatment option for patients with gastric adenocarcinoma with cT2 or higher and/or positive lymph nodes. This study enrolled 716 patients, randomized to 4 cycles of docetaxel (50mg/m^2 day 1), 5-FU (2600 mg/m^2 on a 24h continuous infusion), leucovorin (200mg/m^2 day 1) and oxaliplatin (85 mg/m^2 day 1) every 2 weeks, followed by surgery and 4 post-operative cycles of the same regimen versus 3 cycles of ECF or ECX (epirrubicin, cisplatin and capecitabine), followed by surgery and 3 cycles of ECF/ ECX. In terms of toxicity, patients in FLOT arm experienced more grade 3/4 neutropenia, while patients in ECF/ECX arm had more grade 3/4 nausea and vomiting. In spite of this, treatment was well tolerated regardless of the treatment arm (around 90% completed preoperative chemotherapy) but more patients treated with FLOT were able to complete the pre-planned postoperative cycles (46% versus 37%). R0 resection rate was slightly higher in the FLOT arm (84% versus 77%) and the surgical morbidity and mortality were comparable in both arms. Progression free survival (PFS) and OS were increased in the FLOT group compared with the ECF/ECX group. Median PFS was 30 months in the FLOT arm versus 18 months in the ECF/ ECX arm; median overall survival was 50 months in the experimental arm versus 37 months in the ECF/ ECX arm. The benefit of FLOT was observed in all groups, regardless of T and N-stage and the presence of signet cells (9). FLOT is the new gold standard treatment for patients who receive perioperative chemotherapy and surgery for resectable gastric cancer. In the case of a formal contraindication for the use of any of its components or the patient is not suitable for triplet chemotherapy, perioperative chemotherapy should be based on fluoropyrimidine–platinum doublet (4). At this moment, oncologists need to carefully select patients to FLOT chemotherapy, as

real-world practice data are reporting higher rates of grade 3/4 toxicities, treatment discontinuations and dose reductions than those reported in clinical trial population (10).

Adjuvant treatment

Patients with a pathological stage ≥ IB who did not receive any preoperative treatment are candidates for adjuvant therapy: chemoradiation (CRT) or chemotherapy.

Chemoradiation (CRT)

The North American Intergroup-0116 trial was the first randomized study evaluating the benefit of adjuvant CRT. Adjuvant therapy with 5-FU/leucovorin plus conventionally fractionated radiotherapy (45 Gy in 25 fractions) resulted in improved OS rates compared with surgery alone (50% 3-year survival in the CRT arm versus 41% in surgery alone arm) and is currently considered standard therapy in the USA (11). However, CRT has not gained wide acceptance in Europe, mostly due to concerns about the quality of surgery within the trial (more than 50% of patients underwent less than D1 lymphadenectomy), suggesting that benefits of CRT are mainly compensating for suboptimal surgery (4). These concerns are supported by retrospective data from the Dutch D1D2 trial, demonstrating that CRT reduces local recurrence rates following D1 resection and improves survival after R1 resection (12).

This subject is still under investigation, since there are other randomised and non-randomised data suggesting potential benefits from postoperative CRT even after optimal D2 dissection (4).

Adjuvant Chemotherapy

The use of adjuvant chemotherapy in Europe remains limited due to the routine use of perioperative chemotherapy and lower postoperative treatment tolerance in western patients. Evidence of benefit from adjuvant chemotherapy comes mostly from Asian studies. The phase II, randomised, CLASSIC trial included 1035 patients with stage II–IIIB gastric cancer who underwent curative D2 gastrectomy that were randomly assigned (1:1) after surgery to receive adjuvant chemotherapy with capecitabine and oxaliplatin (eight 3-week cycles of oral capecitabine 1000 mg/m^2 twice daily on days 1–14 plus intravenous oxaliplatin 130 mg/m^2 on day 1) for 6 months or observation alone. Estimated 5-year disease-free survival was 68% in the adjuvant capecitabine and oxaliplatin group versus 53% in the observation alone group. Estimated 5-year overall survival was 78% in the adjuvant capecitabine and oxaliplatin group versus 69% in the observation group (13). The ACTS-GC trial also demonstrated an OS survival benefit with adjuvant chemotherapy with S-1 following D2 resection in Asian patients (14).

An individual patient-level meta-analysis of randomized controlled trials to quantify the potential benefit of chemotherapy after complete resection over surgery alone, concluded that postoperative chemotherapy based on fluorouracil regimens was associated with reduced risk of death in gastric cancer compared with surgery alone, and five-year overall survival increased from 49.6% to 55.3% with chemotherapy (15).

Future Therapeutic Options

One possible future option is the reinforcement of preoperative treatment. The TOPGEAR trial is an international phase III trial in which patients with gastric adenocarcinoma are randomized to perioperative chemotherapy alone (3 preoperative and 3 postoperative cycles of ECF) or perioperative chemotherapy plus preoperative chemoradiation. In the chemoradiation arm, patients receive 2 cycles of ECF plus chemoradiation (continuous infusional 5-fluorouracil 200 mg/m^2/day, throughout the entire period of radiotherapy or capecitabine 825 mg/m^2, oral tablet twice daily, days 1-5 of each week of radiotherapy and 45 Gy of radiation in 25 fractions, five days per week for five weeks) prior to surgery, and then 3 further cycles of ECF. Results from an interim analysis demonstrate that preoperative chemoradiation can be safely delivered to the vast majority of patients without a significant increase in treatment toxicity or surgical morbidity (16).

Molecular targeted therapy has already been demonstrated in the palliative setting and is under investigation in the perioperative treatment. The INNOVATION trial is a randomized, open-label, phase II trial that evaluates the role of adding trastuzumab and/or pertuzumab to perioperative chemotherapy in patients with HER2+ gastric cancer (17). The MAGIC-B/ST03 trial is also evaluating the possible benefit of the addition of lapatinib to the subgroup of HER2+ patients treated with perioperative ECX (18). In HER2-negative gastric cancer, RAMSES/ FLOT7 trial is recruiting patients to perioperative FLOT with or without ramucirumab, a VEGFR2 monoclonal antibody that is already approved in the metastatic setting (19).

Precision medicine probably will play a major role in

the selection of the optimal treatment, but also to provide prognostic and predictive markers. Large-scale studies on genomic and proteomic profiling of gastric carcinomas define four molecular subtypes: microsatellite instability (MSI), Epstein-Barr virus (EBV)-associated, chromosomal instability (CIN) and genomically stable (GS) tumours. The application of these signatures to large patient's datasets with long follow up allowed to understand the different prognosis of each subtype: EBV subtype has the most favourable prognosis, followed by MSI, CIN and GS. Besides these survival differences, it is possible to observe that adjuvant chemotherapy has the greatest benefit associated with the CIN subtype and the smallest with the GS subtype. So, besides giving relevant prognostic information, these four subtypes will possibly be used as predictive markers of response to treatment (20). Similarly to the implications of MSI status on the benefit of adjuvant therapy in stage II colorectal cancer, a secondary post hoc analysis of the MAGIC trial examined the association among mismatch repair deficiency (MMRD), MSI, and survival in patients enrolled in this study. It concluded that MMRD and high MSI were associated with a positive prognostic effect in patients treated with surgery alone and a negative prognostic effect in patients treated with chemotherapy (21). Tumour MSI status may also be important in ongoing trials investigating the benefit of immunotherapy in non-metastatic patients (20).

CONCLUSIONS

Multimodality treatment strategies in locally advanced gastric cancer achieved important improvements in survival rates and perioperative chemotherapy is the standard of care in Europe. FLOT4-AIO trial came to encouraging and practice-changing conclusions, but there are still some concerns. It is undoubtedly the most effective regimen in this setting but it cannot be proposed to every patient, due to toxicity profile, and there is also the uncertainty of subsequent treatments in the case of disease progression under FLOT. Several ongoing phase III trials are trying to improve the perioperative chemotherapy (molecular targeted therapy and immunotherapy) and we await further investigation on molecular profiling to better tailor treatments in the future.

Conflicts of interest and Source of Funding

None

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