Practical guidance for the treatment of patients with gastric or gastro-esophageal junction cancer

March 2020

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a Belgian expert consensus
Practical guidance for the treatment of patients with gastric or gastro-esophageal junction cancer: a Belgian expert consensus

INTRODUCTION
Currently there are no specific Belgian guidelines for the treatment of patients with advanced gastric or gastro-esophageal junction (GEJ) cancer. Therefore, the clinical practice guidelines for the diagnosis, treatment and follow-up of gastric cancer formulated by the European Society for Medical Oncology (ESMO) make up the guidebook for most centers in Belgium.1,2 However, at some points, these guidelines leave room for discussion and interpretation. Moreover, substantial heterogeneity exists into how gastric cancer patients are treated in Belgium. In an attempt to provide answers to some of the recurrent clinical questions encountered in daily practice, Eli Lilly assembled an advisory board of gastric cancer specialists coming from both the Northern and Southern part of the country. The scope of these advisory board meetings was to come up with practical guidance on the peri-operative management of patients with resectable gastric/GEJ cancer and to provide recommendations on the optimal treatment approach for patients with unresectable gastric/GEJ cancer, taking into account the specific Belgian reimbursement criteria.

STAGING AND RISK ASSESSMENT
All patients who are diagnosed with gastric or gastro-esophageal junction (GEJ) cancer should be discussed during a multidisciplinary tumor board (MDT). The core membership of the multidisciplinary team should consist of surgeons, gastro-intestinal or medical oncologists, radiation oncologists, radiologists and pathologists. Prior to any decision with respect to the treatment plan, adequate tumor staging is essential, and patients should undergo a thorough functional evaluation. This should include at least a physical examination, an evaluation of the blood count, liver and renal function tests, an endoscopy (plus echo-endoscopy), and contrast-enhanced computed tomography (CT) imaging of the thorax and the abdomen. In case of doubt, a dedicated MRI for the detection of liver and/or peritoneal metastases and a laparoscopy with or without peritoneal washing may be indicated.1

PERI-OPERATIVE TREATMENT FOR PATIENTS WITH RESECTABLE CANCER
Surgical resection of gastric cancer, specifically at early stages, is potentially curative. However, the majority of patients will eventually relapse after surgery. In an attempt to mitigate this relapse risk, peri-operative chemotherapy has become standard of care for patients with resectable gastric cancer, including GEJ tumors (for GEJ tumors also pre-operative chemoradiotherapy).3,6 According to the expert panel, peri-operative therapy is recommended in patients with ≥stage IB disease.1 For patients with resectable gastric cancer, the recommended peri-operative regimen consists of FLOT (4 pre- and 4 post-operative 2-week cycles of 50 mg/m² docetaxel, 85 mg/m² oxaliplatin, 200 mg/m² leucovorin and 2600 mg/m² 5-FU as 24-hour infusion on day 1), or a similar taxane-based triplet.7-9 For patients with resectable GEJ cancer, CROSS-trial based chemoradiotherapy (carboplatin [doses titrated to achieve an area under the curve of 2 mg/ml/min] + paclitaxel [50 mg/m²] for 5 weeks and concurrent radiotherapy [41.4 Gy in 23 fractions, 5 days per week]), is a feasible alternative for FLOT.5,6 In the absence of a randomized head to head comparison of CROSS and FLOT in this setting, it is impossible to make a firm recommendation for one or the other. However, the expert panel expressed a preference for CROSS-trial based chemoradiotherapy in patients with esophageal extension (Siewert type I and II), while FLOT is preferred in patients without esophageal extension (Siewert type III or lower).

While FLOT should be considered as the standard of care, a less intensive oxaliplatin/5-FU based peri-operative treatment schedule (e.g. FOLFOX, FLO) can be considered in frail patients. In this respect, the expert panel underscores the importance of assessing the frailty of patients in the light of the entire treatment sequence (i.e. consider both the peri-operative chemotherapy as the type of surgery). On a final note, it needs to be stressed that there is no longer a place for the use of anthracyclines (i.e. epirubicin, adriamy-
In the peri-operative treatment of patients with gastric/GEJ cancer.

INOPERABLE OR METASTATIC GASTRIC/GEJ CANCER

FIRST LINE TREATMENT

For all patients with palliative therapy intention (stage IV) a quality controlled HER2 testing is mandatory before the start of therapy. HER2 positivity is defined as HER2+++ on immunohistochemistry or HER2++ followed by a positive FISH test. However, in Belgium only positive FISH testing is accepted for the reimbursement of trastuzumab. According to the Belgian pathology guidelines, HER2-positivity is defined as having a HER2/CEP17 ratio of 2 or more with the HER2 in-situ hybridization test. For patients with a HER2-positive tumor, platinum + fluoropyrimidine (5-FU or capecitabine) chemotherapy in combination with trastuzumab is the recommended first-line treatment.

The standard of care for patients with HER2-negative tumors consists of doublet chemotherapy, including a platinum derivative and a fluoropyrimidine (5-FU or capecitabine). For patients in whom a rapid tumor response is needed, a taxane-based triplet regimen (e.g. DCF, FLOT, or other taxane-based triplets) can be considered in first line. However, the expert panel underscores that this applies to only a minority of selected symptomatic patients, mainly due to the significant increase in toxicity associated with taxane-based triplets, accompanied however by a small increase in efficacy and quality of life. Additionally, this also impacts their eligibility for future treatment options. Given the toxicity associated with triplet chemotherapy, the expert panel recommends to discontinue the taxane as soon as clinically possible and to closely monitor the patient for side effects.

SECOND LINE TREATMENT

Ramucirumab in combination with paclitaxel is the standard of care in the second line treatment of patients with metastatic gastric/GEJ cancer. In case of paclitaxel-related toxicity, de-escalation of the therapy to ramucirumab monotherapy can be considered. For patients who received a taxane-based regimen in first line (or in the peri-operative setting) and for patients with a contra-indication to taxanes, ramucirumab monotherapy or irinotecan-based chemotherapy (e.g. FOLFIRI) can be used in second line. Of note, the use of ramucirumab monotherapy in this setting is supported by results of a global double-blinded randomized phase III trial. Irinotecan-based treatments or taxane monotherapy are also validated options in second line and can be considered in case of a contra-indication for ramucirumab.

Of note, in patients where the taxane was de-escalated in the maintenance phase of a first-line treatment, a taxane can be re-introduced in a further treatment line. In case of de-escalation of the taxane in first-line due to side effect, re-introduction should be discussed with the patient (and should only be considered in case of resolution of the side effects). Finally, due to the high prevalence of cross-resistance between taxanes, it is not advised to use paclitaxel for those patients found with tumor progressive under docetaxel in first-line therapy.

THIRD LINE AND BEYOND

Recently, a randomized controlled trial demonstrated a survival benefit of trifluridine/tipiracil over placebo in patients with chemorefractory gastric cancer (third line and beyond). These results formed the rationale for the EMA approval of trifluridine/tipiracil in this setting, but this option is currently not yet reimbursed in Belgium. For the time being, irinotecan-based therapy (e.g. FOLFIRI) represents a feasible treatment alternative. In addition to this, participation in a clinical trial should always be considered.

FUTURE PERSPECTIVES

Recently, clinical studies have identified effective treatments for patients with MicroSatellite Instability (MSI)-high tumors (immune checkpoint inhibitors) and for patients with tumors harboring NTRK gene fusions (larotrectinib). However, as these treatments are not (yet) reimbursed in Belgium and given the fact that the exact position of these treatment options in the gastric/GEJ cancer treatment paradigm remains to be elucidated, these options will not be discussed in this article.

OLIGOMETASTATIC DISEASE

In recent years, oligometastatic disease has become a much-debated topic in many cancer types, including gastric cancer. Nevertheless, oligometastatic disease is a rare finding in gastric cancer patients and, as a result, it is difficult to make firm recommendations with respect to the management of these patients. As for all other patients with gastric cancer, oligometastatic patients need to be discussed in a multidisciplinary team. For some patients, metastasis-directed therapies such as surgery or radiotherapy can be considered.
**KEY MESSAGES FOR CLINICAL PRACTICE**

- All patients with gastric or gastro-esophageal junction (GEJ) cancer should be discussed during a MDT.
- Neoadjuvant or peri-operative therapy is recommended in patients with ≥stage IB disease.
- For patients with resectable gastric cancer, the recommended peri-operative regimen consists of FLOT.
- For patients with resectable GEJ cancer, chemoradiotherapy according to the CROSS regimen is a feasible alternative for FLOT.
- A less intensive oxaliplatin/5-FU based peri-operative treatment schedule can be considered in frail patients.
- For all patients with palliative therapy intention (stage IV) a quality controlled HER2 testing is mandatory before the start of therapy.
- For patients with a HER2-positive tumor, platinum + fluoropyrimidine (5-FU or capecitabine) chemotherapy in combination with trastuzumab is the recommended first-line treatment.
- The standard of care for patients with HER2-negative tumors consists of doublet chemotherapy, including a platinum derivative and fluoropyrimidine (5-FU or capecitabine).
- For a minority of selected, symptomatic patients in whom a rapid tumor response is needed, a taxane-based triplet regimen (e.g. DCF, FLOT) can be considered in first line.
- Ramucirumab in combination with paclitaxel is the standard of care in the second line treatment of patients with metastatic gastric/GEJ cancer.
- For patients who received a taxane-based regimen in first line (or in the peri-operative setting) and for patients with a contra-indication to taxanes, ramucirumab monotherapy or irinotecan-based chemotherapy (e.g. FOLFIRI) can be used in second line.
- Trifluridine/tipiracil will likely become a standard option in third line in addition to an irinotecan-based regimen. Until trifluridine/tipiracil is reimbursed irinotecan-based therapy (e.g. FOLFIRI) represents a feasible alternative.
- Oligometastatic disease is a very rare finding in gastric cancer, but for some of these patients, metastasis-directed therapies can be considered (after MOC discussion).

**REFERENCES**

1. NAME OF THE MEDICINAL PRODUCT

Cyramza 10 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of concentrate for solution for infusion contains 10 mg ramucirumab. Each 10 ml vial contains 100 mg of ramucirumab. Each 50 ml vial contains 500 mg of ramucirumab.

3. PHARMACEUTICAL FORM

Cyramza is a human IgG1 monoclonal antibody produced in mammalian cells (CHO) by recombinant DNA technology. Patients with IgE-mediated hypersensitivity reactions to any of the excipients listed in section 6.1. For patients with NSCLC, ramucirumab is contraindicated where there is tumour cavitation or tumour involvement of major vessels (see section 4.4). For patients with renal impairment, it is not necessary to adjust the maintenance dose of ramucirumab (see section 4.5.2). For patients with haemodialysis, it is not necessary to adjust the maintenance dose of ramucirumab (see section 4.5.2).

4. CLINICAL PHARMACOLOGY

4.1. Pharmacodynamic properties

4.1.1. Mechanism of action

Cyramza is a humanised monoclonal antibody directed against the VEGF receptor-2 (VEGFR-2) tyrosine kinase, which is a transmembrane protein that transduces signals from the VEGF ligand. The antibody covalently binds to VEGF receptors on the surface of tumour cells. Binding results in inhibition of the activation of VEGFR-2, a process that is essential for the growth and survival of cancer cells.

4.1.2. Pharmacodynamic profile

The primary mechanism of action of ramucirumab is to inhibit the binding of VEGF to VEGFR-2 and other VEGF receptors, thereby blocking the signal transduction required for the proliferation of cancer cells. Ramucirumab also inhibits the binding of VEGF to PDGFR and other PDGF receptors, which is involved in the migration and invasion of cancer cells.

4.2. Pharmacokinetics

Ramucirumab is cleared from the circulation through vascular endothelial growth factor (VEGF)-mediated internalisation and a second-order saturable process. The elimination half-life of ramucirumab is approximately 14 days.

5. INDICATIONS AND USAGE

5.1. ADVANCED HEPATOCELLULAR CARCINOMA

Ramucirumab is indicated for the treatment of patients with advanced HCC who have received prior sorafenib treatment and have progressed on or after sorafenib. The recommended starting dose is 8 mg/kg every 2 weeks via intravenous infusion. Ramucirumab therapy should be temporarily discontinued if the VEGF level returns to ≥2 mg/L or ≥2 x upper limit of normal (ULN) (see section 4.4). Once the urine protein level has decreased to ≤2 mg/L or ≤2 x ULN, therapy should be reinitiated at a reduced dose level (see section 4.4).

5.2. NON-Small Cell Lung Cancer

Ramucirumab in combination with paclitaxel is indicated for the treatment of patients with metastatic non-small cell lung cancer who have progressed on or after platinum-based chemotherapy. The recommended starting dose is 8 mg/kg every 2 weeks via intravenous infusion. Ramucirumab therapy should be temporarily discontinued if the VEGF level returns to ≥2 mg/L or ≥2 x ULN (see section 4.4). Once the urine protein level has decreased to ≤2 mg/L or ≤2 x ULN, therapy should be reinitiated at a reduced dose level (see section 4.4).

6. MODE OF DELIVERY

6.1. Administration

Ramucirumab should be administered intravenously over a period of 1 hour

6.2. Contraindications

Ramucirumab is contraindicated for patients with VEGF receptor-2 (VEGFR-2) and other VEGF receptors.

6.3. Precautions

6.3.1. Vascular access

6.3.2. Renal and hepatic impairment

6.4. Adverse reactions

6.4.1. Very common

6.4.2. Common

6.4.3. Uncommon

6.4.4. Rare

6.4.5. Very rare

6.5. Special populations

6.5.1. Elderly

6.5.2. Infants and children

6.6. Dilution

6.7. Administration site

6.8. Overdose

6.9. Disposal

7. POSOLOGY AND ADMINISTRATION

7.1. Intravenous infusions

7.2. Dose adjustments

7.3. Nausea and vomiting

7.4. Stomatitis and mucositis

7.5. Hypersensitivity reactions

7.6. Forteir and infestations

7.7. Gastrointestinal disorders

7.8. Cardiovascular disorders

7.9. Respiratory, thoracic and mediastinal disorders

7.10. Urogenital disorders

7.11. Skin and subcutaneous tissue disorders

7.12. Psychiatric disorders

7.13. General disorders

7.14. Laboratory test abnormalities

7.15. Positive and negative clinical findings

8. MARKETING AUTHORISATION

8.1. Marketing authorisation holder

8.2. Marketing authorisation number

8.3. Product licence holder

8.4. Authorised representative

9. PATIENT INFORMATION

9.1. Summary of the product characteristics

9.2. Summary of product characteristics (SPA)

9.3. Label and package information

9.4. Summary of safety profiles

9.5. Summary of product characteristics (SPA)

10. DATE OF REVISION OF THE TEXT 30th of September 2019

Acknowledgements

The authors wish to thank all the patients who participated in the studies and to the researchers who contributed to the development of this treatment.

References


10. DATE OF REVISION OF THE TEXT 30th of September 2019