Optimal treatment in metastatic gastric cancer

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Speaker: Eric Van Cutsem

Scientific summary

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Faculty biography

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Eric Van Cutsem, MD, PhD, has been professor at the University of Leuven since 2000. He is head of the division of Digestive Oncology at the University Hospitals Gasthuisberg Leuven (UZ Leuven) and University of Leuven (KUL), a board member of the Department of Oncology at the University of Leuven and was a board member and secretary of the Leuven Cancer Institute (LKI) between 2010 and 2016.

He is a member of the Belgian Royal Academy of Medicine since 2015 and President of the Belgian Foundation Against Cancer since October 2016.

Professor Van Cutsem obtained his medical degree in 1983 from the University of Leuven, specialising in internal medicine and gastroenterology, and he was awarded his PhD in 1994. He has a mandate as clinical researcher of the Fund for Scientific Research (FWO) since 2003. Throughout his training he spent several months in England, Switzerland, the USA and the Netherlands and was involved in both clinical and research projects.

Professor Van Cutsem has published 481 peer-reviewed articles (PubMed – March 2017), 951 articles in WEB OF SCIENCE, Thomson Reuters (H-factor: 97; 43,934 citations – March 2017) and several chapters in books on gastrointestinal cancer. His work has been published in the most respected publications such as the *New England Journal of Medicine, The Lancet, Lancet Oncology, JAMA, Journal of Clinical Oncology, Nature Reviews Clinical Oncology, Annals of Oncology, European Journal of Cancer, British Journal of Cancer* and *Gastroenterology*. He is coeditor of the reference text book on gastrointestinal cancer: Principles and Practice of Gastrointestinal Oncology: second edition, 2008. He was mentioned in 2013 in Capital (French magazine) as being among the top 3 experts in the world in colon cancer and is mentioned in Thomson Reuters within the 1% highest impact in his domain (http://highlycited.com/). He also coordinates several European and worldwide trials investigating new drugs for gastrointestinal cancer and serves on many steering committees and advisory boards.

Eric Van Cutsem is a member of several scientific organisations. He is/was a member of the Scientific Program Committee and/or educational committee of ASCO, ASCO-GI cancers symposium, ESMO, UEG and ECCO. He served for ESMO as executive board member 2011-2013 and since 2014 has been on the ESMO press committee. He was secretary from 2000 to 2003 and chair of the EORTC-GI group from 2003 to 2007 and has been chairman of PETACC (Pan-European Trials on Adjuvant Colon Cancer) since 2008; he was a board member of the EORTC from 2009-2015, president of European Society of Digestive Oncology (ESDO) and is co-chairman of the European Neuro-Endocrine Tumour Society (ENETS) registry.

He was chairman of the governmental colon cancer prevention task force in Flanders, Belgium and was President of BGDO (Belgian Group Digestive Oncology) 2010-2016 and has been past-president since 2016. He was President of FAPA (Familial Adenomatous Polyposis Association) until 2016 and is now vice-president and a member of the general assembly of Kom tegen Kanker (Flemish Cancer Ligue). He is medical director of Europacolon (patient advocacy group).

Professor Van Cutsem was the founder (1999) of and is chair of the Scientific Committee of the ESMO GI/ World Congress on Gastrointestinal Cancer in Barcelona (in partnership with ESMO since 2005), the largest meeting on GI cancer with over 3500 participants.

Optimal treatment in metastatic gastric cancer

Eric Van Cutsem
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At the gastrointestinal cancers session at the 17th Pan Arab Cancer Conference (PACC), held in Algiers, Algeria, Professor Eric Van Cutsem discussed the treatment options for patients with metastatic gastric cancer, ranging from cytotoxic agents to targeted therapy, antiangiogenic agents and immune checkpoint inhibitors. In this report based on the talk, we provide an overview of the available therapies and the remaining challenges.

Cytotoxic agents

Cytotoxic drugs form the mainstay of advanced gastric cancer therapy, either administered in their own right or as a backbone for targeted therapy.

Five classes of anticancer agents – namely, fluoropyrimidines, platinums, taxanes, topoisomerase inhibitors and anthracyclines – have activity in or are used for the first-line treatment of patients with advanced gastric cancer.

They are used in different regimens and as part of different combinations, but mainly as doublets because research has shown that "two is better than one"[1], said Van Cutsem. The jury is still out, however, on whether three cytotoxics are better than two, he added, as although there is data to indicate higher efficacy with the triplet, it comes at the cost of increased toxicity [2], making physicians in Europe and the USA reluctant to use three cytotoxics concurrently.

There are geographical differences in the usage of cytotoxic regimens in the first-line metastatic gastric cancer setting, with, for instance, the combination of cisplatin and S-1 most commonly used in Japan, whereas cisplatin alongside either 5-fluorouracil (5-FU) or capecitabine is most common in Europe.

In the second-line, treatment with either a taxane or irinotecan has shown to increase median overall survival (OS) by "a modest but significant" 1.5 months relative to best supportive care in advanced gastric cancer patients with good performance status[3–5].

Altogether, cytotoxic regimens prolong OS by a median of 8–12 months in Western populations, said Van Cutsem, and although the median OS is a little longer in East Asian populations[6–11], at 11–18 months, "what this means is that there is a lot of room for improvement" and this is where other therapies come in.

Targeted therapy

Approximately 15% of gastric cancers overexpress HER2[12], making the anti-HER2 antibodies trastuzumab and pertuzumab an attractive option.

In the phase III ToGA trial, the addition of trastuzumab to doublet chemotherapy with cisplatin plus 5-FU or capecitabine led to a significant improvement in OS among 584 patients with HER2-positive gastric cancer, at 13.8 months compared with 11.1 months for those given chemotherapy alone[13]. An exploratory analysis showed particular benefit of trastuzumab addition for participants with strong HER2 expression, defined as either an immunohistochemical (IHC) score of 3+ or IHC2+ followed by confirmation by fluorescent in

situ hybridisation, with a median OS of 16.0 versus 11.8 months for the control group.

These results led to the approval of trastuzumab for patients with HER2-positive advanced gastric cancer by the European Medicines Agency (EMA), to be given alongside cisplatin plus 5-FU or capecitabine[14], and now it is common practice to test advanced gastric patients for HER2-positivity[15].

The phase III JACOB trial[16] evaluating the benefit of adding pertuzumab to trastuzumab plus chemotherapy in patients with metastatic HER2-positive gastric or gastro-oesophageal junction (GEJ) cancer is ongoing and the results are eagerly awaited, said Van Cutsem.

However, trials of other HER2 targeted agents have been less successful. The LOGiC trial[17], which assessed the addition of lapatinib to capecitabine–oxaliplatin in the first-line setting, and the TYTAN study[18], which evaluated the addition of lapatinib to paclitaxel in the second-line, were both negative, with no significant OS improvement in the lapatinib relative to the control arm.

Treatment with the antibody–drug conjugate trastuzumab emtansine also failed to improve OS relative to a taxane among patients with previously treated HER2-postive advanced disease in the GATSBY study[19], showing that trastuzumab emtansine is "not active in this situation", Van Cutsem commented.

And trials of other EGFR inhibitors, such as panitumumab and cetuximab, in patients with advanced gastric cancer have similarly failed to meet their primary endpoints[20,21].

Angiogenesis inhibitors

Click here to view the first clip from Professor Van Cutsem's presentation

The antiangiogenic approach has had different results depending on the agent in question. Bevacizumab, which binds to the circulating VEGFA ligand[22], has not been successful in the advanced gastric cancer setting, but the trials of ramucirumab, which binds directly to the VEGFR2 receptor[22], have been positive.

The AVAGAST trial[23] enrolled 774 individuals with locally advanced or metastatic gastric cancer and randomly assigned them to received front-line capecitabine and cisplatin either with or without bevacizumab. Addition of the angiogenesis inhibitor did not significantly improve the primary endpoint of OS, although progression-free survival (PFS) was significantly prolonged. As a result, bevacizumab was not approved and is not an option for this patient population.

There was a difference in OS by geographical region, such that Asian patients did not benefit from bevacizumab, but their European and Pan-American counterparts did. Van Cutsem said that the underlying reason is unlikely to be biological, with the difference being explained by differences in treatment patterns. Asian patients are more likely, for instance, to receive second and later-line therapies, which can have an impact on OS.

By contrast, ramucirumab has been approved, on the basis of the parallel REGARD and RAINBOW trials, by the EMA for patients whose disease has progressed after platinum- or fluoropyrimidine-based treatment, either alongside paclitaxel or as a single-agent if paclitaxel is not indicated[24].

In the phase III REGARD trial[25] comprising 355 participants with locally recurrent or metastatic gastric or GEJ adenocarcinoma, OS was significantly longer with ramucirumab than placebo, with median times of 5.2 and 3.8 months, respectively.

And in the phase III RAINBOW study[26], ramucirumab in combination with paclitaxel significantly prolonged the OS and PFS of 330 patients with previously treated gastric cancer relative to their 335 counterparts given placebo alongside the taxane, at a median of 9.6 versus 7.4 months and 4.4 versus 2.9 months, respectively.

Furthermore, when considering grade 3 or worse adverse events, ramucirumab had "very limited toxicity" in the single-agent study, the presenter pointed out. The incidence of neutropenia and other side effects was higher in RAINBOW, but the toxicities are "clearly manageable", he said. As an angiogenesis inhibitor, there are also class-specific effects, such as hypertension, associated with ramucirumab treatment, but the drug is "generally well tolerated".

Following the approval of ramucirumab in the second-line setting, the agent is now being investigated in the first-line – recruitment to the RAINFALL trial comparing the addition of ramucirumab or placebo to cisplatin plus capecitabine is ongoing.

Other agents have also shown promise – treatment with the VEGFR2 tyrosine kinase inhibitor apatinib led to an OS benefit of approximately 2 months relative to placebo in a phase III trial conducted in Chinese patients with disease progression after two prior lines of chemotherapy[27].

And in light of the PFS benefit offered by regorafenib in the placebo-controlled phase II INTEGRATE trial[28], also conducted among individuals refractory to first- or second-line chemotherapy, the team has initiated a phase III trial, named INTEGRATEII[29].

Click here to view the second clip from Professor Van Cutsem's presentation

Immune checkpoint blockers

Van Cutsem told the audience that we have seen interesting data with immune checkpoint inhibitors, but no drugs have been approved thus far. "What is clear, however, is that there are patients who derive benefit from checkpoint inhibition."

For instance, the phase Ib KEYNOTE-012 trial showed that among patients with PD-L1-positive advanced gastric cancer, approximately 20% responded to treatment with the anti-PD-1 antibody pembrolizumab[30]. Of note, as has been observed with checkpoint inhibition in other tumour types, patients who benefited tended to have a prolonged benefit, said the presenter, but the problem is we do not know how best to select these patients.

Also, the ONO-4538-12 investigators found that salvage treatment with the PD-1 blocker nivolumab resulted in significantly longer OS and PFS among heavily pretreated Japanese, Korean and Taiwanese patients than placebo[31].

The presenter noted that nivolumab is not yet approved in this setting, "but again it is clear that some patients benefit".

Many questions remain unanswered, however, including: can we improve the activity of immune checkpoint inhibitors; what is the best setting to use these agents; and can we combine immunotherapy with chemotherapy?

Next challenges

The field of metastatic gastric cancer has seen many advances in recent years and several new treatment options are available for patients, but challenges remain.

The key, Van Cutsem believes, is to "unravel the molecular taxonomy of gastric cancer", to not only better understand which individuals are likely to benefit from checkpoint inhibition, but also to identify other druggable targets. Our molecular understanding of gastric cancer is "rapidly progressing", he said, and this will help us to identify the different subgroups of gastric cancer that could potentially be targeted by different agents.

It is clear, however, that targeted agents, on top of cytotoxics, will play an important role in this setting, the presenter concluded.

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