

Scientific Meeting Report

Hendrik K. van Halteren · ESMO Publishing Working Group
ESMO 12th World Congress on Gastrointestinal Cancer

12TH WORLD CONGRESS ON
Gastrointestinal
CANCER



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From June 30th until July 3rd 2010,

the **ESMO 12th World Congress on Gastrointestinal Cancer (WCGIC)**, was hosted by Mario Dicato and Eric van Cutsem in the beautiful city of Barcelona. Excellent speakers provided perfectly updated overviews of state of the art treatment for the broad spectrum of gastrointestinal cancers. Furthermore, related topics, such as the increasing costs of cancer research and cancer treatment, were discussed.

ESMO's 12th World Congress on Gastrointestinal Cancer was an unquestionable success and beneficial for all who participated!

- Record attendance, with more than 3,400 attendees from 95 countries
- Extensive coverage in the international press
- Endorsement from major societies and organizations

The scientific agenda of the 2010 Congress made it the most comprehensive and most effective in addressing the educational needs of physicians.

- 72 international expert specialists led high quality sessions on a wide array of topics and met with participants in small, targeted groups.
- Special sessions for young medical oncologists and nurses, plus 7 satellite symposia, provided targeted educational opportunities

Presentation of cutting-edge research is one of the highlights of the World Congress. More than 400 abstracts were presented in the expansive poster sessions and published in a special supplement to the Annals of Oncology, representing the latest research from across the globe in colon, esophageal, gastric, liver, pancreatic and rectal cancer. 16 travel grants were awarded to abstract submitters from developing nations.

- Significant new data on neuroendocrine tumors
- New Phase 3 studies
- Updated information on new treatment in colorectal cancer

- Updates on molecular profiling of colon cancer
- Updates on new targeted agents in gastric cancer
- Updates on large trials on colorectal cancer

The future of research in gastrointestinal malignancies

The time course from drug development through preclinical research and phase I, II and III studies to drug reimbursement is a long and expensive one. Many possible potent compounds take too long to reach the cancer patient. There is a great need for adjustment of the present system and several speakers came with creative solutions. John Marshall proposed moving from large scale phase III trials that have a possible benefit for a minority of included patients to smaller randomized Phase II trials aimed at finding the best predictive markers. These trials could be repeated until the patients who really benefit can be sorted out. In ongoing Phase III trials this subgroup of patients could be identified by means of a pair wise comparisons analysis, as Marc Buyse explained, based upon his recent article in *Statistics in Medicine* (DOI: 1002/sim.2923, 2010). Trial researchers should not redefine the predefined aims of the study, when the results appear poorer at analysis than previously expected, as Alberto Sobrero stated. He pleaded for a system in which the study aim (for instance; at least 30% of patients should have a ≥ 6 months survival gain due to the experimental treatment) is directly connected with a go/no go-option for reimbursement. Such a reimbursement model could avoid difficult discussions between doctor and patient about new agents, which bring some clinically irrelevant benefit. Again, the pair wise comparisons analysis mentioned by Buyse would fit well in this drug reimbursement model. And how should treatment benefit be measured? With the improved outcome due to palliative treatment, recurrence-free survival may lose its role as surrogate marker for overall survival in adjuvant cancer trials. Also examined was whether progression-free survival should remain the first choice primary endpoint in trials on palliative systemic treatment. In certain treatment settings duration of disease control (DDC) and time to failure of strategy (TFS) may turn out to be more suitable surrogates for overall survival. Another very good initiative was initiated by the ARCAD Clinical Trials program, a forum of oncologists, statisticians and trial professionals. They have created a huge database, which contains complete data of almost all recently performed randomized clinical trials (RCTs) on advanced colorectal cancer, according to *J Clin Oncol* (2010; 4: 527- 30). This database may show the way to go and even indicate (trial calculator) the possible increment of future studies. Hopefully, identical initiatives will be initiated for other gastrointestinal malignancies.

Future perspective: The process, which leads from cancer research towards actual drug reimbursement, will be thoroughly revisited in the upcoming years.

Esophageal cancer

The session started with state of the art lectures on Barrett's esophagus screening and treatment of early cancer, but there have not been breakthroughs since last year. These lectures were followed by a pro/con debate concerning the additive value of surgery in locally advanced esophageal cancer. Both presenters quoted the results of the FFD9102 trial. In this trial, patients with locally advanced esophageal cancer and a favorable response to chemoradiation appeared not to benefit from subsequent surgical resection. This trial, however, included a majority of squamous cell cancers and a minority of adenocarcinomas, whereas the incidence of squamous cell cancer has decreased and the incidence of adenocarcinoma has increased 4-fold. Nevertheless, it is generally accepted that surgery should only be offered to fit patients who are either unresponsive to or progressive after chemoradiation.

Gastric cancer

Surgery

Van der Velde pleaded for centralization of gastric cancer surgery, as it has been shown that peri-operative mortality and oncological outcome depend heavily on the yearly number of performed gastrectomies. The cut off point appears to be around 10. A D2-resection is advised for fit patients, as it has been shown to improve survival, although peri-operative morbidity was higher even in the absence of a splenectomy. In (neo) adjuvant studies, it has been shown that adjuvant chemotherapy yields the highest gain in local recurrence-free and overall survival in D1 patients, which again underlines the value of a D2-resection. A recent meta-analysis performed by Gertler et al. has shown that additional pouch formation leads to a better quality of life (QOL) (less dumping and heartburn, better food intake) without an increase in morbidity or mortality. Additionally, it neither extends operating time or hospital stay.

(Neo) adjuvant treatment

Three RCTs have shown that peri-operative chemotherapy (either epirubicin, cisplatin, and 5-fluorouracil (5-FU)(ECF) or epirubicin, cisplatin and capecitabine (ECX)) for patients with stage II/III gastric cancer leads to a reduction of local and distant recurrences and an increase in overall survival. The reduction of local recurrences may be partly explained by a higher rate of R0 resections. In a recently performed meta-analysis, patients with an esophagogastric junction tumor appeared to benefit more from peri-operative chemotherapy than patients with a true gastric tumor.

The question of whether postoperative radiotherapy can further increase life expectancy when added to peri-operative chemotherapy is currently addressed by the CRITICS-study. Drawbacks of neoadjuvant chemotherapy are toxicity, overtreatment due to overstaging (20% of patients) and further progression (6% of patients). The MUNICON-study has shown that positron emission tomography (PET)-response measured 2 weeks after the first neoadjuvant chemotherapy course can accurately predict pathological response after 3 peri-operative chemotherapy courses. In case of a poor (less than 35%) reduction in standardized uptake value (SUV)-uptake, patients should proceed to surgery. For the introduction of PET evaluation in everyday practice rigorous standardization of the procedure would be needed.

Definition of 1st line palliative chemotherapy

Three presenters from the USA, Asia and Europe were invited to comment on the ideal standard 1st line regimen. All presenters agreed to an extent that ECF is a suitable first choice. Furthermore, as shown in the REAL-study cisplatin could be replaced by oxaliplatin and 5-FU could be replaced by capecitabine. D(ocetaxel)CF is a good, although more toxic, alternative. Europe and Asia both pleaded for a doublet without epirubicin, as an additive value of this drug has never been shown in previous trials. Several recently performed international studies already contain a control arm with a doublet of cisplatin and 5-FU.

Twenty percent of patients have a Her2-positive tumor (3+--staining at immunohistochemistry and/of positive fluorescence in situ hybridization (FISH) and should be offered the combination of 5-FU, cisplatin and trastuzumab.

Clinical practice point: epirubicin can be omitted in 1st line palliative chemotherapy.

Targeted therapy for advanced gastric cancer

Dr Ohtsu reported the results of the AVAGAST-study, previously reported also at ASCO 2010, which randomized 774 patients between treatment with capecitabine and cisplatin and treatment with capecitabine/cisplatin/bevacizumab. The latter combination resulted in a slightly increased progression-free survival, but there was no significant difference in overall survival.

Gastrointestinal Stromal Cell Tumors (GIST)

Dr. Zalberg provided a thorough overview of tumor biology, genetics and treatment of GIST. GIST have a shared ancestry with the interstitial cells of Cajal, which are involved in peristalsis. Sixty percent of GIST originates from the stomach and 25% from the small intestine, but GIST may occur anywhere in the gastrointestinal tract.

Prior to operation, neoadjuvant treatment with imatinib could be considered to facilitate an R0 resection. C-Kit and platelet-derived growth factor receptor (PDGFR)- α , two receptors belonging to the tyrosine kinase family, are often mutated. Patients with Exon 9 mutations in C-Kit or the C-Kit wild type fare significantly worse than patients with a mutation in exon 11.

A treatment nomogram has been developed to identify high-risk patients who could be offered adjuvant treatment with imatinib, but there is no solid evidence for a relevant beneficial effect. In the ACOSOG Z9001-trial 12 months of adjuvant treatment with imatinib (400 mg daily) led to a significantly improved recurrence-free survival as compared with placebo (hazard ratio (HR) of recurrence 0.35, but a survival advantage was not seen. The EORTC 62024-trial, which randomizes patients between 2 years of imatinib and observation, may provide more insight. Eventually, 40% of operated patients will have recurrence within 5 years. In case of local recurrence, imatinib may cause considerable tumor shrinkage. There is no place for radiotherapy.

In case of distant metastases imatinib is the 1st treatment choice and a meta-analysis has previously shown that dose escalation (800 mg instead of 400 mg daily) does not lead to longer progression-free or overall survival.

C-Kit and PDGFR- α mutational status appear to be related with imatinib response. There are phase III data suggesting that a double dose (800 mg) leads to a higher response rate in patients with exon 9 mutated GIST. Another example is GIST with a PDGFR D842V mutation, which is virtually resistant towards all targeted compounds available. To date, there is no clear proof that patients with progressive disease may benefit from escalation of the imatinib dose. In case of imatinib resistance, sunitinib should be offered in 2nd line (HR for disease progression 0.33).

Clinical practice point: Mutational analysis of GIST has only limited therapeutic consequences in current daily practice.

Neuroendocrine tumors (NET)

Radionuclide treatment for advanced disease

Toumpanakis reported the outcome of patients who had undergone ⁹⁰Yttrium-DOTA-octreotate treatment as second line therapy. The NET's differed considerably in terms of primary location, but the majority were well differentiated. In every patient, ⁹⁰Yttrium-DOTA-octreotate was administered 3 times via the intravenous route, in case of metastasis, and via the arterial route in case of locally advanced tumors. Subjective and radiological responses were observed in 72.9% and 87% of patients, consecutively. Only 11.7% of patients developed transient bone marrow depression.

In his presentation on radionuclide treatment with ⁷⁷Lutetium-DOTA-octreotate, Dr. Kwekkeboom mentioned that such treatment significantly improves overall survival in comparison with historical controls. Although radionuclide treatment has been available since the early nineties, it still has not come out of Phase II and there is without doubt considerable selection bias. A phase III study is urgently needed to point out pros and cons of radionuclide therapy.

Targeted therapy for well-differentiated pancreatic NET's

Doublets of chemotherapy (e.g. 5-FU and streptozotocin) can induce up to 60% responses. Several targeted agents have been tested in patients with advanced well-differentiated NET and the results of two studies were reported.

The NCT00428597-study randomized 171 patients between sunitinib/best supportive care (BSC) and placebo/BSC for patients with disease recurrence after prior surgery. Median progression-free survival was 11.4 versus 5.5 months in the control group. There was also a significant survival gain (HR 0.418, 95%CI 0.187-0.894). It is, however, difficult to interpret the relevance of these results for 1st line systemic treatment since this study contained a no treatment arm.

The RADIANT3-study could be interpreted as a second-line study; 410 patients, of whom the majority had received previous systemic treatment (78% in the experimental arm and 84% in the treatment arm), were randomized to receive either everolimus/BSC or placebo/BSC. Median progression-free survival increased from 4.60 to 11.04 months (P<0.0001). Most commonly observed side effects were stomatitis, rash and diarrhea. Grade III/IV side effects were rare. As 75% of patients crossed over, progression-free survival was anticipated as the primary endpoint.

Pancreatic cancer

Hereditary pancreatic cancer

Pancreatic cancer risk is increased in cancer syndromes, such as BRCA2 (relative risk (RR) 6), Peutz Jeghers (RR 130) and Lynch syndrome (RR 8). It is also clustered within families. Moreover, the risk is increased 15-fold in case of chronic pancreatitis. Magnetic resonance cholangiopancreatography (MRI/MRCP) and endoscopic ultrasonography (EUS) are most suitable for screening, but laborious. There are only small studies on the cost-effectiveness of screening in high-risk groups. Vasen reported the results of an analysis among 79 members of a pancreatic cancer clustered family. Seven tumors were detected and 5 patients underwent a resection. 40 MRI's were needed to detect 1 cancer case.

Neoadjuvant therapy

Dr. Mornex discussed the results of a recently performed systematic review and meta-analysis of response and resection percentages after neoadjuvant therapy, according to a recent article in PLoS med (May, 2010). The analysis included 111 retrospective and prospective studies (n= 4,394) on neoadjuvant chemoradiation, chemotherapy and radiotherapy. The study cohort was divided into patients with initially resectable and initially non-resectable pancreatic cancer. For the latter group averaged complete/partial response probabilities were 4.8% (95%CI 3.5- 6.4) and 30.2% (95%CI 24.5- 36.3), which led to an estimated resectability of 33.2%. The estimated median survival following resection was 20.5 months. Combination therapy resulted in a higher estimated response and resection rate than monotherapy. Patients with locally non-resectable tumors should be included in neoadjuvant protocols, but a uniform definition of (non)resectability is required.

Clinical practice point: There is a strong scientific rationale for neoadjuvant treatment, if the pancreatic adenocarcinoma is initially considered non-resectable, but a uniform definition of (non)resectability is required. Such treatment should ideally be given within the context of a randomized prospective trial.

Advanced pancreatic cancer

Conroy presented the results of a Phase III study (PRODIGE/ACCORD 11-trial), which randomized 342 patients with advanced pancreatic cancer (only eligible if bilirubin < 1.5 upper normal limit (UNL), ECOG performance status (PS) 0-1/absence of cardiac ischemia/ absence of stent) between gemcitabine (n=171) and 5-FU, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) (n=171). Both groups were well-balanced.

Complete responses were observed in 0 and 0.6%, respectively. Partial responses were observed in 9.4 and 31% of patients. The HR of disease progression was 0.47 (95%CI 0.37- 0.59). The HR of death was 0.57 (95%CI 0.45- 0.73). QOL was significantly better in the FOLFIRINOX arm, but the rate of grade III/IV neutropenia and diarrhea was significantly higher. Prophylactic treatment with peg-filgrastim is therefore recommended. The full paper is eagerly awaited, for this study appears to be the first one which clearly shows a benefit of polychemotherapy in comparison with gemcitabin alone.

Clinical practice point: In fit patients with advanced pancreatic cancer FOLFIRINOX significantly improves QOL and survival in comparison with gemcitabin monotherapy.

Targeted therapy for advanced pancreatic cancer

The only targeted agent which has passed Phase III successfully is erlotinib. In the PA.3-study, the addition of erlotinib to gemcitabine in 1st line led to a 2-week gain in median overall survival (6.4 vs. 5.9 months), which was not considered to be of clinical significance.

Pancreatic cancer has been genotyped completely. Tumor biology depends largely on 12 signaling pathways/processes. Hedgehog signaling appears to be particularly important, as it mediates tumor-assisted fibroblast activation and loss of vascularity. Hedgehog inhibition may render the tumor more sensitive to other therapeutic strategies. It has, however, not yet passed Phase I-

Hepatocellular cancer

Palliative systemic therapy

The results of the EACH-study, which have previously been presented at ASCO 2010, were addressed in an oral presentation by Dr. Qin. 216 Asian patients with either locally advanced or metastatic hepatocellular cancer were randomized to receive either doxorubicin or FOLFOX4. Response rates were 2.7% and 9.6%, respectively for doxorubicin and FOLFOX-4. Treatment with FOLFOX4 resulted in a 1.2 months increase (5.7 vs. 4.5 months; $P=0.028$) in median overall survival.

Sorafenib should therefore not be considered the only way to go with hepatocellular cancer and other agents should still be tested in 1st line.

Colorectal cancer

Screening

Patient compliance in colorectal cancer (CRC)-screening is hampered by the burden of colonoscopy.

The aim of a study presented by Dr. Rosenthal was to develop a blood test with high sensitivity and specificity for early CRC. White blood cell RNA expression patterns were measured with an Affymetrix U133 2.0 Plus array. A case control design was adopted and patients were recovered from two prospective trials. The training set consisted of 55 CRC cases and 64 controls. A 202-gene signature (Detector-C) was identified. In the validation set of 343 patients, 90% sensitivity and 88% specificity for early colorectal cancer were achieved. The high specificity ensures that available endoscopy resources will not be exhausted by large-scale use of this blood-based test. Confounder analysis did not reveal confounders. The false negative rate was 1/872 compared to 1/154 in fecal occult blood testing.

Adjuvant chemotherapy for stage III colon cancer

Results of the ACCENT study and the MOSAIC study have suggested that patients older than 69 years with stage III colon cancer do not benefit from adjuvant chemotherapy with bolus 5-FU/leucovorin or FOLFOX4. As Dr. Twelves reported, the X-ACT trial-results (an equivalence trial comparing 5-FU/leucovorin and capecitabine) did not show a relation between age and treatment outcome. The same holds for adjuvant treatment with XELOX (NO 16968-study), as Dr. Schmoll stated in his presentation. The addition of bevacizumab to adjuvant chemotherapy has been shown not to be beneficial.

Adjuvant chemotherapy for stage II colon cancer

At present, adjuvant chemotherapy can save the lives of 4% of patients with stage II colon cancer, whereas 40% of treated patients will experience serious side effects. There is a great need for prognostic markers, and previous studies have provided microsatellite instability/mismatch repair deficiency, B-RAF and 18q loss of heterozygosity (LOH). A B-RAF mutation, which is found in approximately 8% of patients, is correlated with worse overall survival (HR 3.61 (95%CI 2.24- 5.81 Roth et al. this congress)). The same counts for microsatellite instability and chromosome 18q allelic imbalance, but the impact of these aberrances appears to be smaller. Both are being used for treatment stratification in the ongoing E5202-trial.

The evidence for a detrimental effect of adjuvant fluoropyrimidine treatment in patients with MSI-H-tumors is not considered compelling enough to justify routine MSI-determination prior to adjuvant chemotherapy.

Finally, two prognostic gene signatures, ColoPrint and the continuous recurrence score, were presented. According to the validation study, ColoPrint can distinguish a low-risk (5 year distant-metastasis-free survival (DMFS)-rate 95%) and a high-risk (5-year DMFS-rate 79.9%)-group. The low-risk group comprised 74% of patients. ColoPrint is currently tested in a prospective clinical trial. In the QUASAR-study, 761 candidate genes were tested in 1,851 stage II colon cancer patients treated in randomized trials (enrollment in 1994 - 2003). A continuous recurrence score (RS) was calculated. Every 25-points RS-increase was related with a 1.42 HR for disease recurrence and a 1.33 (1.01- 1.76) HR for death.

Future perspective: Apart from the usual risk factors (T4 stage, bowel obstruction, less than 12 lymph nodes examined), a tumoral genetic signature may soon be included in the treatment selection guidelines for stage II colon cancer.

First line systemic therapy for advanced colorectal cancer

In his presentation, Dr. Sobrero stated that there is no standard 1st line regimen. Treatment decisions should be based on performance status and treatment goal. If preservation of QOL and increased survival are the main goals, 1st line treatment with capecitabine and bevacizumab could be justifiable. If a combination of XELOX (or FOLFOX) with bevacizumab is chosen, oxaliplatin can be safely omitted after 6 courses (OPTIMOX 1).

The MACRO-TTD-study (results presented by Dr. Aranda) randomized 479 patients between XELOX/bevacizumab until progression and 6 courses of XELOX/bevacizumab followed by maintenance therapy with bevacizumab. There was no significant difference in response rate, progression-free or overall survival between both treatment arms. The SAKK trial and the CAIRO 3-trial will eventually answer the question of whether a complete chemotherapy holiday (without bevacizumab maintenance) can be safely applied.

If the primary tumor and/or metastases can be down staged to a resectable size, a combination of a chemotherapy doublet or triplet and an epidermal growth factor receptor (EGFR)-inhibitor is expected to offer the highest response rate. Bevacizumab is not known for its downstaging capacity. Both K-ras and B-RAF have predictive value regarding response to treatment with EGFR-inhibitors (cetuximab/panitumumab). Patients with mutated K-ras and/or B-RAF fare significantly worse. Lacopetta provided one of the explanations for a relation between B-RAF and aggressive tumor biology; B-RAF mutated tumors all appear to have hypermethylated DNA, which leads to inactivation of suppressor genes.

Treatment of isolated hepatic metastases

Based on current criteria for resectability (all metastases are resectable with adequate margins, adequate future remnant liver (30%), and preservation of functional liver anatomy) and improvement of operation techniques, 20% of patients with advanced CRC are expected to be operable. This figure could become far more optimistic in the case of effective downstaging by means of systemic therapy. In the process of downstaging, a complete response should be avoided.

Adjuvant chemotherapy should not be given outside clinical trials. Dr. Ruers reported the final results of the EORTC 40004-trial which randomized 119 patients with up to 9 irresectable isolated hepatic metastases between chemotherapy (CT)/radiofrequency ablation (RFA) and chemotherapy only. The median progression-free survival was 16.8 months in the CT/RFA-arm (95%CI, 11.7-22.1) and 9.9 months (95%CI 9.3- 13.7) in the chemotherapy arm (P=0.025), but there was no difference in overall survival.

Epilogue

The congress delivered a unique mix of diagnostic and multidisciplinary therapeutic aspects of gastrointestinal cancer care. It was the perfect place to be for multidisciplinary teams working in this field.

The Congress webcast will soon be available. Look for the link on: www.worldgicancer.com.

Mark your calendars for **22 – 25 June 2011**, and visit the Congress website (www.worldgicancer.com) for updated information.

Dr. Hendrik K. van Halteren has reported no conflicts of interest.