



11th World Congress on Gastrointestinal Cancer



Meeting Report

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Introduction

From the 24th until the 27th of June more than 3400 participants enjoyed 4 days of high quality education regarding a broad spectrum of gastrointestinal cancers. The scientific agenda contained a motivating mix of in-depth reviews by expert speakers, oral presentations of recently analyzed trial results and case discussions. This meeting report has been divided into general issues and tumor-specific chapters.

The quest for early surrogate endpoints in oncologic trials

Dr. Marc Buyse provided insight into the statistics of adjuvant and palliative randomized controlled trials (RCTs).

In palliative RCTs overall survival (OS) appears to lose its premier position as primary endpoint because of barriers such as the high patient number needed for a sufficiently powered trial or the high crossover rate after disease progression. In fact, it may be difficult for the most effective new agent to display a survival benefit in prospective RCTs. If progression-free survival (PFS) is to be chosen as primary endpoint, only a post-hoc analysis of the study or a meta-analysis of all studies on a certain agent may tell whether the correlation coefficient between PFS and OS is high enough.

Breakthroughs in the treatment of recurrent cancer may weaken the correlation between disease-free survival (DFS) and OS in adjuvant RCTs. A good example was provided by Dr. Axel Grothey. In a dataset of 20,898 colon cancer patients (ACCENT dataset) who had undergone adjuvant chemotherapy within RCTs, the association between 3-years disease free survival (DFS) and 5-years overall survival (OS) appeared to decrease, especially in the subgroup of patients with stage II colon cancer.

Preservation of nation-wide high quality cancer surgery by means of professional-based auditing

Gastrointestinal cancer surgery should be performed by experienced surgeons in order to keep complication risk and recurrence risk as low as possible. Surgical skills depend on talent and patient volume. A good example is rectal cancer surgery. On behalf of the European Society of Surgical Oncology (ESSO) Drs. Lars Pålman and Cornelius J.H. van de Velde stressed the importance of auditing. ESSO welcomes all national initiatives aimed at the development of auditing programs. In the future, ESSO strives to play a coordinating role in the international harmonization of operation-specific quality standards.

Pancreatic cancer

Adjuvant chemotherapy for resected pancreatic cancer Based on the results of the CONKO trial (6.5 months benefit in median DFS) 6 cycles of adjuvant gemcitabine (day 1, 8, 15, every 28 days) are considered to be the gold standard.

Chemoradiation for unresectable pancreatic cancer

Pancreatic cancer is well known for a high stromal content and relatively poor vascularization, which may explain its resistance to radiotherapy and chemotherapy. Response rate, however, increases if both modalities are given concurrently. In the case of presumed inoperability without distant metastases chemoradiation could be considered. When operability is uncertain, chemoradiation may aid the clinician to observe the biological behavior of the tumor and it may lead to avoidance of ineffective surgery in rapidly growing tumors. On the other hand, it could lead to down-staging. In a study by Evans et al. (JCO 2008) among

patients with borderline resectable pancreatic cancer neoadjuvant chemoradiation (7 weekly doses of gemcitabine followed by 10 radiotherapy doses of 3 Gy) followed by surgery resulted in a 5-year survival percentage of 33%. Up to now, targeted agents have not shown additive value in this setting.

Chemotherapy for distant metastases

First-line therapy with gemcitabine has been shown to improve overall survival (1-year survival 18% vs. 2%, Burns et al. JCO 1997) in comparison with best supportive care. Most studies on combination therapy with cisplatin have reported negative results. However, a recent meta-analysis of all RCTs (Heinemann et al. BMC Cancer 2008) showed a significant survival benefit for patients with a good performance status (PS) who had been treated with gemcitabine and cisplatin (HR 0.76).

Based on this meta-analysis it was assumed that fit patients fared better with combination therapy. At ASCO 2009, Dr. Guiseppi Colucci reported the results of a large RCT, which also failed to show a survival benefit for gemcitabine-cisplatin in comparison with gemcitabine. Gemcitabine monotherapy therefore remains the 1st line therapy of choice. Genome studies of pancreatic adenocarcinomas have shown that these tumors harbor a wide variety and high number of gene mutations which may make it difficult to determine the right target for targeted therapy.

Biliary tract cancer

Surgical intervention

Resectability and prognosis depend on tumor stage and location (intrahepatic bile duct, extrahepatic bile duct, gall bladder). At the time of diagnosis less than 20% of patients are considered operable. Patients with intrahepatic biliary cancer tend to do better after liver transplantation than after resection. In case of a borderline resectable perihilar tumor, neoadjuvant chemoradiation could be considered.

Management of bile duct obstruction

In the case of bile duct stenosis, stenting should be performed. Metal stents stay open for a longer time than plastic stents, but they cost ten times as much. The stent choice could be based on life expectancy. Photodynamic therapy prior to stent positioning has been shown to preserve stent continuity with an increase in survival. In case of bilateral hepatic duct stenosis bilateral drainage has been shown to increase survival in comparison with unilateral drainage.

Palliative chemotherapy

Advanced gallbladder cancer bears a worse prognosis than advanced bile duct cancer. Monotherapy studies have shown response rates around 20% in patients with advanced gallbladder cancer. Combination therapy is, however, the treatment of choice. Dr. H. Wasan reported results of the ABC-O2 trial. In this trial the addition of cisplatin added to gemcitabine resulted in comparable toxicity and a

significant survival benefit (median OS 11.7 vs. 8.2 months). Other comparable combinations are gemcitabine/capecitabine and gemcitabine/oxaliplatin. The hedgehog pathway has been shown to play an important role in the development of biliary tract cancer and trials on related targeted therapy are underway.

Liver cancer

Prognosis and treatment options are guided by tumor stage and the degree of liver cirrhosis. Practical treatment algorithms can be found in recent publications (for instance Llovet et al. JNCI 2008) or in the internet (NCCN guidelines 2009).

Local intervention

The optimal treatment is liver transplantation and the best candidates are patients with a single nodule and Child Pugh stage A cirrhosis. Alternatively, resection and/ or radiofrequency ablation can be performed. Postoperative transarterial chemoembolization (TACE) has not been shown to be beneficial. For larger tumors TACE (if liver function allows) is the treatment of choice with a clear survival benefit in comparison with best supportive care (level 2 evidence). Dr. Riccardo Lencioni reported the results of a recently performed randomized phase II trial, which compared traditional TACE with TACE delivered with a drug eluting bed (DEB). DEB has been developed to enhance drug delivery to the tumor and to decrease systemic toxicity. The DEB-TACE was significantly more effective in terms of response rate and significantly less toxic.

Palliative therapy

In patients with advanced disease, sorafenib has shown a significant survival benefit (median OS benefit in Sharp trial 3.2 months and in Asia Pacific trial 3.7 months). There is no clearly defined second-line alternative.

Neuro-endocrine tumors (NET's) originating from the gut

Therapeutic options depend on the location of the primary tumor, hormonal activity, tumor extent, grade of tumor differentiation and proliferation index (measured by % Ki67-expression). For example, pancreatic NETS's generally grow faster than midgut NET's. Classification according to World Health Organization guidelines distinguishes between well-differentiated endocrine tumors, well-differentiated endocrine carcinomas and poorly differentiated endocrine carcinomas.

The European Neuro-endocrine Tumor Society (ENETS) has recently proposed a complementary grading system (Grade 1–3) based on tumor differentiation and Ki67 percentage, which appears to have a higher prognostic relevance than traditional TNM-staging. Nowadays, inclusion in RCTs is guided by location of primary tumor and the ENETS grading system.

Treatment with the somatostatin analogue (SSA) octreotide LAR used to be limited to patients with the carcinoid syndrome. In the case of octreotide-refractory carcinoid syndrome pasireotide, a new generation SSA has shown symptomatic improvement in 27% of patients. In the PROMID study (patients with midgut NET's randomized between octreotide and placebo) octreotide LAR also showed anti-proliferative action (median PFS 14.3 vs. 6.0 months). Radioactive labeling strongly increases the anti-proliferative activity of octreotide (Kwekkeboom et al., JCO 2008). In high-grade NET's (mostly originating from the pancreas) combination chemotherapy (usually cisplatin and etoposide) could be given. In the case of chemoresistance, targeted therapy within RCTs should be considered. Agents of particular interest are everolimus and sunitinib. In a double blind RCT among patients with advanced well-differentiated pancreatic islet cell tumors (n=154) sunitinib appeared to prolong PFS in comparison with placebo (median PFS 11.1 vs. 5.5 months). Analysis on survival is ongoing, but patients on placebo have been allowed to cross over to sunitinib.

Gastrointestinal Stroma Cell Tumors (GIST)

Curative treatment

Complete surgical resection (R0) without clinically negative lymph nodes dissection is mandatory and laparoscopic resection should reach a comparable goal.

One year of adjuvant therapy with imatinib is considered as a treatment standard for patients with a tumor larger than 3 cm based on the results of the ACOSOG Z9001 study. The 1-year PFS percentage rose from 83% to 97% in comparison with no treatment. Two other adjuvant trials are ongoing to sort out the optimal treatment duration. There is a clear correlation between GIST genotype, optimal imatinib dosing and treatment outcome, which will guide future treatment in the adjuvant and palliative setting.

Palliative treatment

There is level 2 evidence that an imatinib break leads to a worse prognosis and it is advised to maintain treatment until progression. In the presence of progressive disease, treatment compliance should be checked. Approximately one in every 4 patients has a compliance problem which may negatively influence imatinib exposure. Dose escalation from 400 mg to 800 mg daily can be considered. In the case of advanced GIST and mutated kit exon 9, dose escalation to 800 mg per day has been shown to improve median PFS and OS, whereas dose escalation has not shown any benefit in patients with unmutated kit exon 9. The available data suggest that maintenance of imatinib beyond progression in order to continue the blockade of sensitive clones improves prognosis.

Treatment with sunitinib can be considered first choice for second-line therapy. Two RCTs have shown an almost fourfold increase in PFS compared to best supportive care (Casali et al., ASCO 2006; Judson et al., ESMO 2006).

Esophageal cancer

Treatment of dysplasia and early malignancy in Barret's esophagus

With the current concept of screening endoscopies and random biopsies the sensitivity for detecting early cancer is 81%. With endocytoscopy or endomicroscopy a sensitivity of at least 92% can be achieved with a specificity of 95% or higher. The inter-observer variability between experienced endoscopists has been shown to be very acceptable (kappa value 0.843). In the absence of signs of venous or lymph node invasion early cancer can be treated by endoscopic surgery, as long as the resection margin does not extend beyond the first 3rd of the submucosal layer. Other local therapy modalities are photodynamic therapy, laser therapy and radiofrequency ablation. But the more aggressive the surgery, the higher the stricture rate. Dr. Ell reported on a prospective series of 1,059 patients who had been treated by endoscopic resection or photodynamic therapy in a tertiary referral hospital. The rate of long-term complete response was 88.3%.

Treatment of localized cancer

If the tumor is considered resectable, preoperative chemoradiation should be given first. Several meta-analyses have shown a survival benefit in comparison with preoperative chemotherapy or sequential chemotherapy/radiotherapy.

In case of presumed irresectability, upfront chemoradiation is the treatment of choice. Two RCTs have shown that sequential surgery and continuation of combined modality therapy produce similar results in case of a partial remission.

Gastric cancer

Preventive Helicobacter pylori eradication

Gastric cancer risk increases 20-fold in case of a Helicobacter pylori (HP) infection and a causal relationship between the two is supported by clinical data. Several placebo-controlled RCTs have shown that cancer risk decreases in case of HP eradication. Based on a systematic review of these RCTs the number needed to treat (NNT) in order to prevent one cancer case is 227. The NNT could be smaller if eradication were performed in an early phase, i.e. before atrophic gastritis has developed. For most patients, this phase would correspond with an age of 40 years or younger. A future preventive program should combine a high patient compliance and acceptable costs per life year saved.

Surgical intervention

An R0-resection is considered standard and should be performed by a skilled surgeon. In N0 disease a D1 resection is sufficient, in N1-2 disease a D2 resection has been shown to improve survival. A D2-resection can induce more complications and should be performed in selected cases and selected centers. Surgical skills depend on talent and volume of gastrectomies. In a study by Birkmeyer et al. (N Engl J Med 2003) surgical mortality was lower among surgeons who performed at least 21 gastrectomies per year.

These results underline the importance of regional centers of excellence.

Perioperative treatment

Since the publication of the MAGIC trial results perioperative chemotherapy is recommended. In this trial 90.7% of patients completed preoperative chemotherapy, whereas only 49.7% fully completed pre- and postoperative chemotherapy. A further improvement in treatment compliance is one of the goals of future trials. Another issue is the additive value of postoperative combined modality treatment, which is currently evaluated in the CRITICS-trial. Postoperative combined modality therapy has been shown to improve prognosis if lymphadenectomy was inadequate (level 2 evidence).

Treatment of advanced disease

Small randomized trials performed in the 90ies suggest that patients with peritoneal metastases benefit from cytoreduction and hyperthermic intraperitoneal chemotherapy (CHIP)(Fujimoto et al, Cancer 1999). Based on these results a treatment proposal has been made which includes 3 months of neoadjuvant chemotherapy followed by D2 gastrectomy and CHIP.

Concerning chemotherapy, there is no consensus regarding a unique first-line combination. Many targeted therapy trials are currently being performed. Dr. Y. Bang reported the results of the ToGA-trial, in which patients with Her2-positive gastric cancer had been randomized between 6 cycles of cisplatin/fluorouracil and 6 cycles of cisplatin/fluorouracil/trastuzumab. There was no crossover in the case of progressive disease. The addition of trastuzumab resulted in a higher response rate (47.3 vs. 34.5%), a higher median OS(13.5 vs. 11.1 months) without an increase in (serious cardiac) toxicity. The rate of Her2 positivity has been shown to be related to tumor location and tumor histology. Her2-positive gastric cancers are expected to become a separate entity regarding treatment and future trials.

Colorectal cancer

Local treatment of isolated hepatic metastases

Several speakers discussed the optimal treatment of patients with isolated hepatic metastases. New irradiation techniques enable radiotherapy of 5 or less metastases with a diameter of up to 8 cm, as long as 700 cc of liver is preserved. Most patients are however treated by surgical resection and/or radiofrequency ablation (RFA).

Dr. Hans-Joachim Schmoll held a presentation on the optimal down-staging combination of cytotoxic agents prior to surgery. He concluded that a backbone of fluorouracil, oxaliplatin and irinotecan is obligatory (to obtain a high response rate) and that future trials should point out which targeted agents can provide additive clinical benefit.

Another question is whether RFA can improve prognosis in patients with isolated unresectable hepatic metastases who undergo chemotherapy. This question was evaluated

ina randomized phase II trial coordinated by the EORTC and Dr. Theo J. Ruers presented the first results. Patients treated with RFA and FOLFOX had a significantly higher 1-year PFS percentage (60.06 vs. 39.35%; $P=0.0267$), but the number of events was still small and there were no data regarding survival. Toxicity profiles were comparable.

Local treatment of metastatic disease confined to the peritoneum

Regarding patients with peritoneal metastases, approximately 10% of all patients with advanced colorectal cancer usually have a poor prognosis. For selected patients hyperthermic intraperitoneal chemotherapy (HIPEC) has been shown to improve survival in comparison with systemic chemotherapy (level 2 evidence) in spite of considerable co-morbidity. Dr. Andre D'Hoore discussed the optimal work-up needed to estimate operability. Retrospective analyses have shown that patients with a Peritoneal Cancer Index (PCI) of less than 16 fare best after HIPEC. However, contrast-enhanced computed tomography (CT), positron emission tomography (PET) and even laparoscopy lack sufficient sensitivity to provide a reliable estimate of the extent of disease. Therefore, an explorative laparotomy is often needed.

Systemic treatment of advanced disease

Sequential or combined chemotherapy?

Dr. Axel Grothey mentioned in his presentation that the highest survival figures have been obtained in studies where first-line treatment with doublets or triplets have been given. In the CAIRO 1 study and the FOCUS study patients had been randomized between sequential and combined chemotherapy. In the sequential treatment arm median OS was considerably lower than the usual median OS of 20 months or longer obtained in combination therapy trials. Although this difference in OS could partly be explained by differences in patient characteristics, the general opinion is that combination therapy should be the standard and sequential treatment should be limited to selected cases. The old paradigm of non-cross resistant therapy initiated at each disease progression should be replaced by a continuum of care aimed at optimal exposure to all agents.

Chemo-holidays

Dr. Aimery de Gramont addressed the important question whether systemic therapy can be stopped before disease progression, if the advantage of further treatment does not outweigh the treatment burden. Previous RCTs have shown that fixed duration fluorouracil-based chemotherapy with oxaliplatin (OPTIMOX-trials) or irinotecan (GISCAD-trial) does not lead to a poorer OS than treatment until progression. The median chemotherapy-free interval (CFI) was 6 months. A therapy break can however only be achieved in a subgroup of patients, who usually have a favorable prognosis (median OS 30 months). There are no reliable predictive factors, which can identify this subgroup. Posthoc

analysis of the OPTIMOX results suggests that CFI is highest in patients who have received chemotherapy for at least 6 months. Reintroduction of FOLFOX after a chemo-holiday

Dr. Aimery de Gramont discussed the outcome of patients treated within the OPTIMOX1 and 2 trials who had been re-challenged with FOLFOX in case of disease progression ($n=330$). Response rate was highest in patients with a CFI of 12 months or longer (35% complete response (CR)/partial response (PR), 35% stable disease (SD)). There was also a significant positive correlation between CFI duration and PFS/OS.

EGFR antibodies

Cetuximab and panitumumab have shown a reliable increase in response rate and single agent activity, independent of line of therapy. Patients with unmutated K-RAS live significantly longer if they are treated with one of these EGFR antibodies. The most suitable advanced colorectal cancers for treatment would have normal PTEN and high epidermal growth factor receptor (EGFR) ligand expression and contain unmutated K-RAS and B-RAF. A disadvantage of treatment with EGFR antibodies is the toxicity profile.

Bevacizumab

Bevacizumab has not shown single agent activity or a reliable increase in response rate, but it has been shown to significantly prolong PFS. Its use is limited to first-line therapy and several RCTs failed to show a survival percentage. The latter could be explained by a high crossover rate. The effect of treatment with bevacizumab beyond progression is currently tested in RCTs.

Rectal cancer

Transanal endoscopic microsurgery

This surgical mode can be performed in case of T2 or aggressive T1 tumors with a diameter of 3 cm or less. As many lymph nodes as possible should be removed. In study reports based on these surgical principles a local recurrence rate of around 5% has been reported.

Neoadjuvant treatment for rectal cancer

Neoadjuvant chemoradiation is indicated in the case of T4-disease and/or enlarged loco-regional lymph nodes, as shown by means of magnetic resonance imaging (MRI). The primary goal of chemoradiation is down-sizing of the tumor to improve operability. Anal sphincter preservation should not be the goal. In RCTs chemoradiation has not been shown to increase the percentage of patients in which the anal sphincter can be preserved. Fluorouracil and capecitabine are considered equally active. Preliminary results of the STAR-trial and the PRODIGE-2 trial, which were reported at ASCO 2009, suggest that the addition of oxaliplatin improves DFS.

Roth et al. compared the incidence of molecular markers, such as P53, K-RAS and microsatellite instability (MSI), in stage II and III colon cancer and tested their prognostic

value per stage. Tumor material and data were derived from the PETACC-3 trial. In this adjuvant RCT patients had been treated with either fluorouracil/irinotecan or fluorouracil only. For most molecular markers tested, except K-RAS and B-RAF, significant differences per stage were found. They also showed a stage-specific prognostic value. In patients with stage II colon cancer high MSI (at least 3 out of 10 markers present) was independently related with shorter recurrence-free survival (HR 0.26, 95% CI 0.11-0.65) and OS (HR 0.153, 95% CI 0.037-0.631). Dr. Hernando Salazar presented the results of a study performed to develop a genomic signature (ColoPrint) for high-risk stage II and III colon cancer. In a multivariate analysis the high-risk group detected by ColoPrint had a hazard ratio of 2.95, independent of tumor stage ($P=0.015$). These promising results have been reproduced in a training set of 322 tumor samples.

Surgical resection

Global improvement in surgical techniques has brought an improvement in the pathological examination of the resection specimen, including the mesorectum. This variable has proved more valuable than T-stage. Several multivariate analyses have shown that patients with a completely resected mesorectal fascia have a lower recurrence risk than their incompletely operated counterparts. But the worst prognosis is found in patients with a circumferential resection margin contaminated by tumor. As long as not all patients undergo transmesorectal excision (TME) including the entire mesorectal fascia, this variable should be discussed by a multidisciplinary team with a mode of adjuvant treatment as a possible consequence.

Adjuvant treatment for rectal cancer

This issue was addressed in an oral presentation by Dr. James Arnold. The only RCT (EORTC 22921), which has evaluated whether patients treated with preoperative chemoradiation benefit from adjuvant chemotherapy (fluorouracil/leucovorin) failed to show a survival benefit at 5-year follow up. The survival curves however diverged late and, at 10-year follow up, a survival gain of 4% was found. In a post hoc analysis, patients in whom downsizing to T0, T1 or T2 had been achieved appeared to benefit most from adjuvant chemotherapy, but patient samples were small and differences non-significant. At present, there are no routine markers, which can select a subgroup of patients that benefits more from adjuvant therapy. Yet, it is considered obvious that rectal cancer patients can benefit from systemic chemotherapy if a more active regimen is used. Recent RCTs that compared adjuvant chemotherapy with no further therapy have been closed prematurely due to poor accrual. Therefore, RCTs with a no treatment arm are no longer considered feasible, which leaves room for adjuvant chemotherapy outside clinical trials. Currently ongoing trials – such as the PETACC 6 – have incorporated a control arm of fluorouracil-based therapy.

Colon cancer

What is the gold standard for adjuvant chemotherapy?

In many countries FOLFOX is advocated, whereas some countries have already switched to CAPOX for treatment of colon cancer. Results of RCTs addressing the additive value of cetuximab and bevacizumab are expected within the next 3 years.

Definition of high-risk stage II tumors

A T4 stage and/or less than 12 pathologically examined lymph nodes are generally accepted as clinical factors, which indicate a high-risk stage II tumor. These factors do not, however, suffice to detect all stage II patients at high-risk of recurrence or patients who will benefit most from adjuvant therapy. Therefore, a lot of translational research is being performed to identify prognostic and predictive markers in the tumor genome or at the molecular level.

Epilogue

The 11th World Congress on Gastrointestinal Cancer provided a multidisciplinary overview of achieved goals and goals to be achieved. The positive chemistry between surgeons, medical oncologists, radiotherapists, radiologists and pathologists was inspiring for all attendants. The 12th congress in 2010 is the place to be, that is for sure.

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