ESMO 13th World Congress on Gastrointestinal Cancer

22-25 June, 2011
Barcelona, Spain

INTRODUCTION

The ESMO World Congress on Gastrointestinal Cancer took place in Barcelona from the 22nd until the 25th of June and hosted just over 3500 participants and faculty members from around the world, representing nearly 100 countries. The meeting mainly covered malignancies affecting the gastrointestinal tract, focusing on personalized therapy and the multidisciplinary approach. In addition, novel molecular prognostic and predictive tools were discussed. The scientific agenda included 'Meet the Expert' sessions, case discussions, and 24 oral abstract presentations selected from more than 400, which were published in a special supplement of Annals of Oncology. Furthermore, the scientific program presented special nurses' and surgeons' symposia, as well as young medical oncologist and satellite sessions.

The event was highly educational with an impressive list of invited speakers. The participants were able to attend state-of-the-art presentations while sharing the latest information and future directions of research and treatment of gastrointestinal malignancies, surrounded by the beautiful city of Barcelona.

The objective of this scientific report is to highlight the original data presented at the meeting and the new challenging topics raised during the sessions.

1. PANCREATIC CANCER

Advanced disease and molecular signature for selecting patients for chemotherapy

Prof. Tempero discussed the results of the phase III study PRODIGE/ACCORD 11-trial (Conroy et al. N Engl J Med 2011; 364: 1817-25), which randomized 342 patients with advanced pancreatic cancer (only eligible if bilirubin <1.5 upper normal limit (UNL), age 18-75 years, ECOG performance status (PS) 0-1/no cardiac ischemia) between gemcitabine (n=171) and 5-fluorouracil (5-FU), leucovorin,

irinotecan and oxaliplatin (FOLFIRINOX) (n=171). Overall, the characteristics of both groups were well balanced, but the study was unintentionally biased with a low number of lesions in the pancreas head and thus, fewer patients with biliary ductal obstructions and stents were included. Partial responses were observed, respectively, in 9.4 and 31% of patients. The hazard ratio (HR) of disease progression was 0.47 ($p<0.001$) and the HR of death was 0.57 ($p<0.001$), both in favor of the FOLFIRINOX arm. Quality of life (QoL) was better in the FOLFIRINOX arm, but the rate of grade 3/4 neutropenia and diarrhea was significantly higher, and prophylactic treatment with pegfilgrastim is therefore recommended.

Clinical practice point

FOLFIRINOX is a first-line option for patients with metastatic pancreatic cancer who are younger than 76 years and who have an excellent PS (ECOG 0-1), no cardiac ischemia and nearly normal bilirubin levels.

Future perspectives

It is necessary to investigate FOLFIRINOX in the adjuvant setting, where a regimen with more toxicity can be better tolerated, or in the neaodjuvant setting, where a higher response rate to the regimen is desired. Moreover, this study provides evidence that gemcitabine does not need to be the anchor drug and a new combination option in the therapeutic armory will be available.

In this context, future treatment decisions will depend on factors such as patient tolerance and predictive molecular signatures for chemotherapy (i.e. S100A2 may be a negative predictive biomarker for response to treatment with gemcitabine). As for the selection of patients for chemotherapy based on the molecular signature, Dr Marechal presented results on biomarker analysis conducted in 434 patients with resected pancreatic cancer, treated with adjuvant chemotherapy. The data demonstrated that hENT1 and dCK expression of the tumor predict benefit from gemcitabine after curative surgery.

A better understanding of tumor molecular features will lead to personalized medicine and more effective treatment decisions.

Another issue in treating advanced disease is the possible combination of chemotherapy with new agents. In this context, Dr Hidalgo presented the results of a phase II trial, comparing gemcitabine versus gemcitabine plus AGS-1C4D4, a fully human monoclonal antibody (MoAb) directed to a cell surface antigen (prostate stem cell antigen, PSCA) expressed in approximately 50% of pancreatic cancers. The data obtained from the primary analysis at 6 months of follow-up for the last randomized patient and the end point was the 6-months survival rate. Overall, 196 patients were enrolled (63 in

the gemcitabine arm, 133 in the combined arm) and a trend toward improvement in 6-months survival rate was observed in patients with tumors that revealed a strong or moderate staining for PSCA expression, and treated with gemcitabine in combination with the MoAb.

ESOPHAGEAL CANCER

Surgery and preoperative treatment

Dr Lanschot discussed the role of preoperative treatment in localized disease. Preoperative radiotherapy and chemotherapy have individually each been proven ineffective in randomized trials and in subsequent meta-analysis, and therefore are not considered as the standard of care. The role of preoperative chemo-radiotherapy has been explored in several randomized trials, with contrasting results. Meta-analysis showed benefits, but the studies were underpowered. Both sequential and concurrent chemo-radiotherapy were included in the meta-analysis. Furthermore squamous hystotypes were overexpressed and only medium-term survival data was considered (2 years). For these reasons, the conclusions were not acceptable to many institutes. A new multicenter randomized trial was performed in The Netherlands and data were presented at the 2010 ASCO Annual Meeting, definitively demonstrating a significant improvement in survival in favor of the combined treatment arm versus surgery alone. This also held true in primary resectable tumors. Consequently preoperative chemo-radiation is now considered as standard treatment for patients with potentially curable esophageal cancer.

Clinical practice point

For patients with early esophageal cancer (i.e. mucosal, T1a), where the risk for lymphatic dissemination is lower than the risk of postoperative mortality, endoscopic resection should be considered. In case of T1a tumors not amenable for local procedures, surgery without preoperative treatment is indicated. In case of T1b tumors, preoperative treatment is indicated in cases of clinical nodal involvement, while for T1bN0 tumors or for patients in poor general condition, the additional risks of the combined modality should be carefully discussed.

Clinical case discussion: GEJ tumors

An educational session focused on the controversy surrounding the treatment of tumors of the gastroesophageal junction (GEJ) with perioperative chemotherapy (as for gastric cancer), or for esophageal tumors, which addressed preoperative chemo-radiotherapy. Following this, an interactive clinical case discussion session was presented on a patient with a cT2N1 GEJ adenocarcinoma. As a result of the debate, an approach focused on esophageal cancer, rather than gastric, seemed to be

preferred by the audience and by the panel experts, supporting a preoperative chemo-radiotherapy treatment.

GASTRIC CANCER

Adjuvant treatment

Prof. Labianca discussed the recent results of the Asian phase III CLASSIC trial, presented at the 2011 ASCO Annual Meeting . The study identified a substantial improvement in disease-free survival (DFS) with adjuvant XELOX, compared with observation alone, in stage II and IIIA-B patients, following D2 resection. Although impressed by these findings, the speakers felt that the benefits of adjuvant XELOX identified in Asian patients with gastric cancer may not be easily transferrable to the Western patient population. This skepticism arose due to certain differences between Asian and Western patients, such as age (median 56 years, while Western patients are usually older), tumor location (mainly distant tumors, while in the West tumors are more likely to be proximal), and resection aggressiveness (median of 42 removed nodes in the study; for those Western centers performing subradical resection the addition of chemo-radiation still makes sense).

The differences in epidemiology and in the management of gastric cancer between Western countries and Asia were also pointed out by Dr Yang, who reported differences in the use of active agents in advanced disease. In Asia sequential therapy is preferred (a doublet in first line and a second line at the time of progression), while in Western countries a more aggressive strategy for an initial approach (triplets) is favored. Thus, the second line administration rates are lower in Western countries than in Asia.

Future perspective: how to reconcile these differences?

Diagnosis: more focus on praecox diagnosis in the West is needed.

Surgery: need for global consensus on D2 resections.

Locoregional disease: exploration of neoadjuvant chemotherapy in Asia is needed.

How to combine targeted agents with chemotherapy in advanced disease: global consensus on use of trastuzumab in HER2+ patients; while there are supposed ethnic differences seen in treatment with bevacizumab (in the AVAGAST study, the Japanese population has longer survival than others).

Intraperitoneal immunotherapy with catumaxomab

The trifunctional antibody catumaxomab (anti-EpCAM x anti-CD3) is approved in Europe for the treatment of malignant ascites, based on a pivotal study including patients with gastric cancer. Dr. Schuhmacher presented the results of a phase II study, on 54 patients evaluating a new multimodal approach combining neoadjuvant platinum-based chemotherapy, followed by gastrectomy and five administrations of intraperitoneal catumaxomab.

Pulmonary infections (17%), anastomosis insufficiency (11%) and abscess (7%) were the most frequent adverse events, and this pattern of complications is consistent with the surgical procedure, with catumaxomab probably having no impact. One-year follow-up efficacy data suggest a promising effect on DFS (74%, 95%CI: 61-86%). Overall survival (OS) data are not yet ready, as follow-up investigations will continue over an observation period of 4 years.

Future perspective

Intraperitoneal immunotherapy with catumaxomab after curative surgery for gastric cancer, although it remains an investigational procedure, merits further study for potential inclusion in the multimodal strategy options.

COLORECTAL CANCER

Towards personalization in advanced disease treatment

In several sessions, expert speakers addressed the issue of personalized treatment in advanced colorectal cancer, aiming to identify and select patients for biomarker platforms, and with the ultimate goal of offering personalized cancer medicine. In particular, Drs Ellis and Lenz focused on the mechanism of action of angiogenesis inhibitors and the way to improve their use and performance in the clinical setting. The complexity of developing a rational patients' selection is demonstrated by the lack of validated biomarkers in this field, due to the wide number of pathways involved. Biomarkers of angiogenesis are not determined only by the "genetic make-up" of the tumor. They correspond to an extremely complex loop of interactions, since tumor cells interact with stroma and endothelial cells, and not only with VEGF. In addition, the angiogenic pathway interacts also with EGFR signaling, and with drug-resistance mechanisms (TS, DPD, and ERCC1). Therefore, in light of the disappointing results with antiangiogenic agents in clinical practice, one must take a step back and re-evaluate the preclinical models of angiogenesis, in particular in colorectal cancer. A better understanding of the basic biology of angiogenesis and of the vasculature in promoting tumor growth should provide a foundation for more rational studies on therapeutic combinations.

Interestingly, two original abstracts highlighted the role of predictive biomarkers of response to anti-

EGFR agents. The first, presented by Dr. Stintzing, reported the positive role of amphireguline and epireguline. The second, discussed by Prof. Van Cutsem, presented the results of a pooled analysis from the CRYSTAL and OPUS studies, which demonstrated that patients carrying a KRAS 13D mutation have a worse prognosis, and show benefit from the addition of cetuximab to first-line chemotherapy.

Clinical practice point and future perspectives

To date, there are no validated markers for selecting patients for treatment with bevacizumab or other antiangiogenic therapies. In case of anti-EGFR treatment, KRAS mutations in codon 12 and 13 exon 2 represent a validated predictive biomarker of response to cetuximab or panitumumab. Further prospectively generated clinical investigations are necessary to confirm the role of additional features such as KRAS mutations, molecular alterations or protein expressions.

Cancer stem cells and tumor dormancy

Dr Lenz discussed the cancer stem cells theory, mainly developed in breast cancer (Naumov et al. Breast Cancer Res Treat. 2003; 82: 199-206), which could potentially be applicable to colorectal tumors. Cancer stem cells seem to remain in a dormant state most of the time and this is probably one of the reasons why they are resistant to many kinds of cytotoxic agents. If we are able to wake up these "sleepers" before patients receive treatment, we could also eliminate cancer stem cells and, thus, treat the disease much more effectively.

New combinations in advanced chemorefractory disease

Dr. Van Cutsem reported the new, intriguing data of the VELOUR study, a large phase III trial (1226 patients enrolled), in which patients with metastatic colorectal cancer, previously treated with oxaliplatin, were randomized to receive aflibercept (a recombinant human fusion protein, that acts as a decoy receptor preventing VEGF-A, VEGF-B and PlGF from interacting with their receptors) or placebo, in combination with FOLFIRI. The addition of aflibercept significantly improved both OS (HR=0.817; p=0.0032) and progression free survival (PFS) (HR=0.758; p=0.00007). A similar effect was seen with aflibercept whether or not patients had received prior bevacizumab therapy. The safety profile was acceptable and consistent with other anti-VEGF adverse events, even though aflibercept appears to increase chemotherapy-specific complications, such as diarrhea, neutropenia and stomatitis.

Dr. Samalin presented the results of a French phase II study exploring the activity and the efficacy of sorafenib in combination with irinotecan (NEXIRI) as second or later-line treatment in 54 patients with KRAS mutated tumors. Observed grade 3 toxicities were hand-foot syndrome (15%), diarrhea (39%),

and neutropenia (19%). The disease control rate was 65%, with median PFS and OS of 3.5 and 7.7 months, respectively.

In a randomized phase II trial, presented by Dr Peeters (144 patients), another new antiangiogenic drug, AMG 386 (a selective angiopoietin 1/2-neutralizing peptibody that inhibits angiogenesis by preventing interaction between angiopoietins and Tie2 receptors), in combination with FOLFIRI did not prolong PFS versus FOLFIRI alone, although higher response rates were obtained. In the pharmacokinetics analysis, the levels of irinotecan and 5-FU metabolites were approximately 50% lower with AMG 386 co-administration, possibly suggesting an intriguing drug-drug interaction, which merits further investigation.

Clinical practice point and future perspectives

The results from the phase II study with sorafenib show promising activity in a selected subgroup of patients. Therefore, further randomized phase II/III studies are justified to confirm the efficacy of this combination. Sorafenib could represent a new light in the darkness of the treatment of KRAS mutated tumors.

New antiangiogenic strategies are under development, and the positive results of the phase III trial with aflibercept in second-line should be further investigated in earlier phases of advanced disease.

Rectal cancer: neoadjuvant chemoradiation

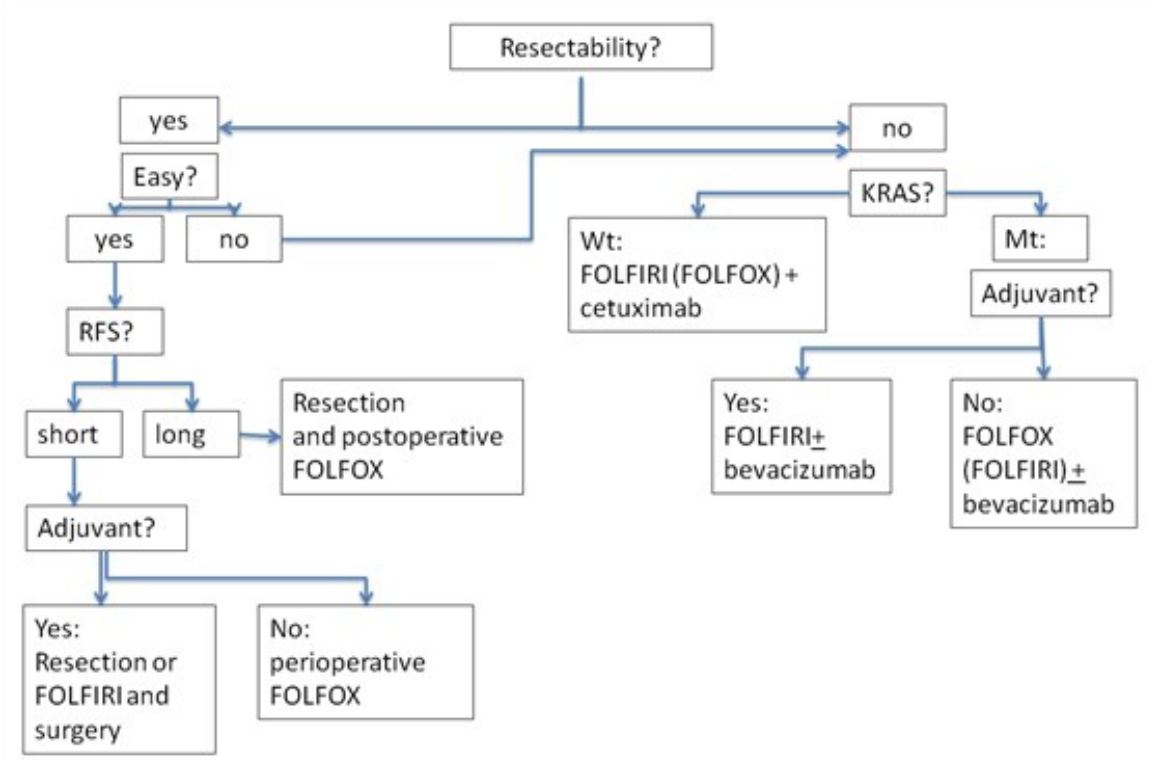
Original data from the Swiss SAKK 41/07 study was reported by Dr Helbling, concerning the addition of panitumumab to chemoradiotherapy in KRAS wild type patients, affected by cT3-4 N+/- rectal cancer. Sixty-eight patients were enrolled in this phase II randomized trial. The addition of panitumumab to chemoradiotherapy seems to be feasible but results in increased toxicities (in particular, up to 20% of patients experienced grade 3-4 diarrhea versus 6% with chemoradiotherapy alone, and, interestingly, anastomotic leaks, 15% versus 4%). However, the addition of panitumumab to chemoradiotherapy resulted in a higher pathological complete response rate (56% versus 44%), mostly due to grade 3 regression, according to the Dworak classification.

Clinical practice point and future perspectives

Since none of the pathological parameters are considered valid surrogate endpoints for survival, further investigations of this active regimen in KRAS selected patients are needed for newer generations of chemotherapeutics (oxaliplatin and irinotecan), and targeted therapies (cetuximab and bevacizumab).

Multidisciplinary approach to liver metastases

Several speakers discussed the optimal strategy for patients with isolated hepatic metastasis. In particular, Dr. Sobrero gave a presentation on the optimal neo-adjuvant treatment, suggesting an extremely practical and useful algorithm for patient evaluation and for developing the treatment plan:



EPILOGUE

Overall, the meeting was successful in providing highly educational and multidisciplinary presentations in the field of gastrointestinal malignancies. Moreover, the speakers were exceptionally prepared and discussions were oriented towards standardized approaches to gastrointestinal neoplasms, with a special emphasis to future perspectives based on novel molecular targets.

RELATED INFORMATION

The congress webcasts will soon be available and Abstracts are now available at http://annonc.oxfordjournals.org/content/22/suppl.

Save the date: 14th ESMO World Congress on Gastrointestinal Cancer 27-30 June 2012.

Visit the Congress website (www.worldgicancer.com) for updated information.

AFFILIATION AND DISCLOSURE

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Dr. De Dosso has reported no conflicts of interest.