The EORTC Gastrointestinal Tract Cancer Group: 50 years of research contributing to improved gastrointestinal cancer management

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ABSTRACT

During the last decades, the evolution of treatment – including radiotherapy, chemotherapy and targeted agents – has improved the cure and survival of patients with gastrointestinal (GI) cancer. Within the past 50 years of the EORTC’s existence, significant progress has been made in the fight against cancer. During this time several cancer clinical trials were completed, and through these we are able to identify the most notable advances in GI cancer research done by the EORTC Gastrointestinal Tract Cancer Group (GI Group). Several EORTC clinical trials results have changed practice (e.g. standard of care of liver metastases of colorectal cancer has been changed by the EPOC trial) or have helped to support new treatment strategies in either early- or advanced-stage GI cancers. In addition to its clinical activities the group has started an extensive program of translational research. This changed strategy towards a translational, multidisciplinary program regarded as the basis for future developments. This review of the major achievements of the GI Group shows that it has played an important role in the scientific development of the understanding and treatment of GI cancer over the last 50 years.

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1. Introduction

During the last decades, the evolution of treatment – including radiotherapy, chemotherapy and targeted agents – has improved cure and survival of patients with gastrointestinal (GI) cancer. Within the past 50 years of the EORTC’s existence, significant progress has been made in the fight against cancer. During this time several cancer clinical trials were completed, and through these we are able to identify the most notable advances in GI research done by the GI Group.

Since the beginning of the new millennium, the GI Group has been well aware that translational research (TR) and biobanking would be a major issue in the EORTC strategy for the future. Translational research was implemented into the agenda of the GI Group as early as 2002 by integrating pathologists into the group and into the translational research discussions of studies. As a result, initiatives such as biobanking, screening platforms for molecular pathway driven trials, and biomarker driven clinical trials have been launched with the objective of improving cancer therapy outcomes.

Optimizing treatment for each individual patient by tailoring it to the patient’s molecular profile or by using imaging for early prediction of response/non-response to specific drugs are ways towards a more efficient management of GI cancer and are therefore priorities for the GI Group. Designing clinical trials will become more complex in the future. It will require multidisciplinary team efforts. Methodologists will have to face the challenge of having to screen a large number of patients in order to enroll only some with the desirable features in a given clinical trial. New innovative designs and imaging techniques will have to be pushed forward for screening drugs in more complex phase II trials in order to identify the more promising drug for the targeted population at an early stage. The capability for rapid accrual of a sufficient number of patients having some desirable molecular features for the testing of a targeted therapy will be key to obtain convincing results.

In this report we summarize only studies that significantly altered the way GI cancer is understood or that had a direct effect on patient care.

2. Major Gastrointestinal Tract Cancer Group achievements in the last 50 years

2.1. Colorectal cancer

2.1.1. Early-stage and locally advanced disease

The GI Group was one of the leading groups in oncology to test the hypothesis of neoadjuvant treatment for rectal cancer in the 1980’s. At that time the value of preoperative radiotherapy was unknown, and surgery techniques such as total mesorectal excision (TME) were not yet established. Thanks to joint collaborations with other groups, the EORTC participated actively in the evolution of the treatment of rectal cancer.

Preoperative radiotherapy decreases the risk of developing local recurrence after surgical resection of rectal adenocarcinoma. In the 1980s, a phase III EORTC study included 466 patients to assess the effectiveness of radiation therapy administered before radical surgery for rectal cancer. This trial failed to demonstrate a significant benefit of radiation therapy in terms of overall survival (OS), but importantly demonstrated a decrease in the risk of developing local recurrence after surgical resection of rectal adenocarcinoma. The GI Group joined the Dutch Colorectal Cancer Group (DCRCG) trial which showed that short-term preoperative radiotherapy reduces the risk of local recurrence in patients with rectal cancer who undergo a standardized total mesorectal excision.

In parallel, other EORTC groups published key studies in this area, such as EORTC trial 22921 which showed that in patients with stage T3 or T4 resectable rectal cancer treated with preoperative radiotherapy, adding fluorouracil-based chemotherapy preoperatively or postoperatively has no significant effect on survival. Regardless of timing, chemotherapy provides a significant benefit with respect to local control. Moreover, the GI Group is currently recruiting patients in the PETACC6 trial (EORTC 40054) which is evaluating the addition of perioperative oxaliplatin to preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine in locally advanced rectal cancer.

Investigating the benefit of adjuvant chemotherapy in colon cancer: the Pan-European Trials in Adjuvant Colon Cancer (PETACC) initiative. The GI Group launched the Pan-European Trials in Adjuvant Colon Cancer (PETACC) effort which had the objective of investigating the treatment of CRC in early-stage disease. The first study (PETACC1) started in 1998 and evaluated raltitrexed to the standard leucovorin/bolus 5-FU. Following it, other PETACC trials were initiated that tested different drugs and regimens such as high-dose infusional 5-FU, irinotecan, celecoxib and cetuximab. One of the most important trials, despite having negative results, was PETACC3 (EORTC 40993) trial that has shown that the addition of irinotecan to adjuvant 5FU/LV regimen increases toxicity and has no significant benefit in the adjuvant treatment of stage III colon cancer, even if combined with a modern 5-FU schedule. The trial was initiated when oxaliplatin and irinotecan were regarded as equally effective first-line combinations for advanced CRC when combined with 5-FU/FA. The success achieved with such regimens in the treatment of advanced disease prompted their examination in the adjuvant setting. The PETACC-3 study included 2094 stage III patients from 368 sites in 31 countries.
The GI Group has performed important research in treatment for resectable liver metastasis of CRC. The with 5-fluorouracil/leucovorin (FOLFOX4) regimen as part of perioperative chemotherapy with oxaliplatin combined (EORTC 40983) was designed to evaluate the efficacy of this regimen. In up to 75% of patients, the phase III EPOC trial contributed to one of the current standard chemotherapy backbones – infusional 5-FU/leucovorin in combination with irinotecan – in first-line treatment of metastatic colorectal cancer.

Irinotecan added to 5 fluorouracil/leucovorin regimen improves PFS in metastatic CRC. EORTC trial 40986 was a phase III study that included 430 patients with the objective to demonstrate that adding irinotecan to a standard weekly schedule of high-dose, infusional fluorouracil (FU) and leucovorin (folinic acid) can prolong PFS in metastatic colorectal cancer. The median PFS in the experimental group (irinotecan) was 8.5 months compared to 6.4 months in the standard arm (P < 0.0001), and the objective response rate was high in the experimental arm, 62.2% versus 34.4% (P < 0.0001). No significant difference in survival was noted. The results of this study, together with the cooperative group trial V303, confirmed that irinotecan in combination with high-dose infusional 5FU/LV is a reference first-line treatment for metastatic CRC.

2.1.3. Palliative treatment of metastatic disease

The GI Group has also developed clinical trials for patients in advanced-stage disease considered to be incurable (e.g. unresectable liver metastases) with several chemotherapy combinations. EORTC trials 40983 and 40986 contributed to one of the current standard chemotherapy backbones – infusional 5-FU/leucovorin in combination with irinotecan – in first-line treatment of metastatic colorectal cancer.

Liver metastasis of colorectal cancer improves DFS. Liver metastases occur in approximately 40% of patients with CRC and are the principal cause of death in these patients. In spite of progress observed in chemotherapy for advanced colorectal cancer, survival rates remain very low in patients with unresectable liver metastasis of CRC (LMCRC). Surgical resection is presently the only treatment offering potential cure when liver metastases are resectable; long-term survival following resection is in the order of 25–30%. Despite the benefit of resection of liver metastasis, relapse is common and occurs in up to 75% of patients. In order to improve the outcome of these patients, the phase III EPOC trial (EORTC 40983) was designed to evaluate the efficacy of perioperative chemotherapy with oxaliplatin combined with 5-fluorouracil/leucovorin (FOLFOX4) regimen as part of treatment for resectable liver metastasis of CRC. The study demonstrated that perioperative chemotherapy with FOLFOX4 is compatible with major liver surgery and reduces the risk of events of progression-free survival (PFS) in eligible and resected patients. The three-year PFS rate was improved by 7.3% (35.4% vs. 28.1%; HR 0.79; P = 0.058) in all randomized patients, by 8.1% (P = 0.041) in eligible patients, and by 9.2% (P = 0.025) in resected patients. It is to date the largest phase III clinical trial organized in this indication and has set the new international standard of care in patients who are candidates for resection of liver metastasis from CRC.

In the same way, a less invasive approach such as radiofrequency ablation (RFA) has been applied in metastatic CRC to reduce the survival gap between resectable and unresectable disease. This strategy was tested in a recent EORTC prospective study described below.

RFA together with chemotherapy improves PFS in patients with unresectable liver metastases of CRC. The CLOCC trial (40004) was the first study that prospectively investigated the efficacy of RFA in combination with CT in patients with unresectable CRC liver metastases (LM). This phase II study randomized patients between CT alone (FOLFOX for six months) or RFA plus CT. Of the 119 patients included, 60% had >4 LM, 85% received CT in the RFA+CT arm and all in the CT arm. Patients in the RFA+CT arm had a 30-months OS rate of 61.7% (95% CI: 48.2–73.9). RFA plus systemic treatment resulted in a significant benefit on PFS; at a median follow up of 4.4 years the median PFS was 16.8 months and 9.9 months (HR = 0.63, 95% CI: 0.42–0.95; P = 0.025) for RFA+CT and CT alone, respectively. This study does not allow a formal survival comparison between treatment arms but contributes in showing the efficacy of local tumor ablation by RFA for patients with unresectable colorectal liver metastases.

2.1.2. Curative treatment of liver metastases

The GI Group has performed important research in advanced colorectal cancer where cure can be achieved by treatment of liver metastases. The EORTC 40983 (EPOC) trial was a landmark in this field and established perioperative chemotherapy as a standard of care for patients with stage IV CRC with potentially resectable disease. This strategy was the collection of biomaterial that allowed further translational research as outlined below.

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2.2. Esophagogastric cancer

Carcinomas of the stomach and gastroesophageal junction are among the top five leading cancer types worldwide. In recent years, multimodal strategies combining neoadjuvant and/or adjuvant protocols and palliative chemotherapeutic protocols combined with new targeted agents have clearly improved the treatment options and prognosis in advanced esophagogastric cancer. Over the past two decades, the GI Group has continuously contributed to this scientific process and inspired the further development of new therapeutic strategies for this still often fatal disease.
2.2.1. Early-stage and locally advanced disease

The concept of neoadjuvant treatment is based on several theoretical advantages, such as treatment of tumor and surround tissue intact vascularization, monitoring response, less radical surgery, and better tolerability among others. Additionally, because of the food intake difficulties linked to gastrectomy, chemotherapy is less likely to be well tolerated after surgery in this disease. On the other hand, inaccurate clinical staging, peritoneal carcinomatosis, bleeding or obstructive complications, and progressive disease during treatment with consequent inoperability are all challenges in applying the concept of neoadjuvant treatment in esophagogastric cancer. The EORTC ran an important study to evaluate the role of neoadjuvant chemotherapy in the treatment of gastric cancer.

Neoadjuvant chemotherapy for locally advanced cancer of the stomach and cardia significantly increased R0 resection rate. In spite of radical surgical R0 resections being the basis of cure of gastric cancer, surgery alone provides long-term survival in only ~30% of patients with locally advanced UICC stages in Western countries because of a high risk of recurrence and metachronous metastases. Patients with locally advanced gastric cancer benefit from combined pre- and postoperative chemotherapy, although fewer than 50% could receive postoperative chemotherapy. The EORTC 40954 trial examined the value of purely preoperative chemotherapy in a phase III trial with strict preoperative staging and surgical resection guidelines. Patients with locally advanced adenocarcinoma of the stomach or esophagogastric junction (AEG II and III) were randomly assigned to preoperative chemotherapy with cisplatin, leucovorin and fluorouracil (PLF) for 12 weeks followed by surgery or to surgery alone. This trial showed a significantly increased R0 resection rate (81.9% after neoadjuvant chemotherapy as compared with 66.7% with surgery alone, \( P = 0.036 \)) but failed to demonstrate a survival benefit. Although this study could not demonstrate a significant survival advantage for neoadjuvant chemotherapy over surgery alone, the results indicate that sophisticated staging, including endosonography, CT and laparoscopy followed by quality-controlled surgery with D2 lymphadenectomy leads to a much better outcome than seen in other contemporary randomized European trials. In contrast to the previous studies, EORTC trial 40954 leaves us with some doubt as to whether one preoperative chemotherapy concept fits all gastric tumors. Our perception is that we still have to know more about tumor biology and learn how to select the right patients for the appropriate treatment.

Preoperative chemoradiotherapy improves DFS and local recurrence in patients with esophageal cancer. The GI Group participated in a randomized trial comparing preoperative chemoradiotherapy followed by surgery versus surgery alone in patients with squamous-cell esophageal cancer. Preoperative chemoradiotherapy did not improve OS, but it did prolong DFS and survival free of local disease.

2.2.2. Metastatic disease

For a long period of time, gastric carcinoma was considered to be a poorly chemoresponsive tumor. The so-called ‘first-generation’ drug combinations, designed before the introduction of cisplatin for the treatment of this disease, gave disappointing results. The EORTC has participated in the evolution of chemotherapy regimens from FAM in the 1980s to FAMTX in the 1990s and then to cisplatin-based regimens in this decade.

Establishing the best chemotherapy regimens for metastatic gastric cancer: from FAMTX to 5-FU/FA/cisplatin regimen. The GI Group has developed the FAMTX regimen and has shown that FAMTX is superior to the FAM regimen that was considered the standard regimen in the 1980’s and early 1990’s. Consequently, in the mid-1990’s FAMTX was considered the standard regimen for patients with advanced gastric cancer. EORTC trial 40902 later showed that FAMTX is not better than 5-FU/cisplatin in advanced gastric cancer. Today, 5-FU- and cisplatin-based regimens are considered as standard regimens in advanced gastric cancer. The most recent GI Group trial has contributed to this knowledge; we have shown that 5-FU/FA/cisplatin is better than 5-FU/FA and infusional 5-FU.

In the last few years, the discovery of tumor-specific biomarkers has provided the basis for the development of targeted therapies in esophagogastric cancer.

Individualization is on the way to becoming key in the treatment of advanced esophagogastric cancer. Very recently it was shown that a subgroup of 20% of gastric cancers exhibit overexpression of Her2neu. This subgroup of patients has a benefit from adding trastuzumab, an anti-Her2 directed monoclonal antibody to cisplatin and fluorouracil chemotherapy. Laptinib is a small molecular tyrosine kinase inhibitor that targets both EGFR1 and HER2, is active in HER2+ gastric cell lines, and has shown clinical activity in uncontrolled phase II gastric cancer trials. In the recently started EORTC 40071 study, about 350 patients with advanced esophagogastric adenocarcinoma will be screened centrally for HER2/EGFR1 by fluorescence-in-situ hybridisation (FISH) and immunohistochemistry (IHC). Patients will be enrolled into one of three strata: (1) HER2 FISH+ and IHC 2/3+, (2) HER2 FISH− and IHC 2/3+, or (3) HER2 IHC 0/+ and EGFR1 FISH+ or IHC 2/3+. This is the first trial to analyze prospectively and separately the role of HER2 and EGFR1 by FISH and IHC for lapatinib combined with chemotherapy in gastric cancer. Hence one of the main questions of this trial is whether the tumor EGFR over-expression will translate into lapatinib benefit in clinical practice.

Thus, coming from an active history with successful clinical studies, the group will further continuously
2.3. Pancreatic cancer

World-wide the incidence of pancreatic ductal adenocarcinoma (PDAC) continues to increase and ranks as the fourth commonest cause of cancer death. In patients with resectable disease, adjuvant chemotherapy more than doubles the 5-year survival rate, from about 10% with surgery alone to around 25% with post-operative chemotherapy. On the other hand, level I evidence for adjuvant chemoradiotherapy is lacking and its role is still controversial, especially in Europe. One of the biggest studies ever in this setting was done by the GI Group.

Adjuvant chemoradiation (with 5-fluorouracil) does not improve OS in patients with resected pancreatic cancer. A phase III trial (EORTC 40891) was performed to test adjuvant radiotherapy and 5-FU after curative resection of cancer of the pancreas or the peri-ampullary region. No survival benefit of adjuvant chemoradiation over observation was noted (19 vs. 24.5 months, \( P = 0.208 \)), also no reduction of locoregional recurrence rates was apparent in the groups. Later on, a long-term follow-up of this trial confirmed no benefit of adjuvant chemoradiation over observation and enforced the bad prognosis of this disease showing a 10-year OS of 18% in the study population. Although this trial was basically negative, it served as a background for the preparation of a future trial.

Improving strategies in pancreatic cancer research. Although adjuvant chemotherapy is now considered as standard after resection, the GI and RO groups have completed a randomized phase II trial showing the feasibility of combining adjuvant gemcitabine and chemoradiation. This concept was further incorporated in the design of a large intergroup US-RTOG/EORTC 40084 phase III trial currently evaluating the benefit of adding quality-controlled radiation therapy to a 6-month course of adjuvant gemcitabine-based treatment. The group continues to commit to the design of new strategic trials in improving the management of pancreatic cancer and has recently organized a consensus meeting which aimed to delineate specific guidelines for a better research in this dismal cancer.

2.4. Translational research

In addition to its clinical activities the group has started an exhaustive program of translational research based mainly on the PETACC2, PETACC-3 and EPOC trials. This changed strategy towards a translational, multidisciplinary program is regarded as the basis for the next developments.

2.4.1. International network of pathologists and laboratories

The group has also established an international network of pathologists and laboratories with decentralized tissue processing. At ASCO 2005 the group presented the use of a so-called quality-control tissue array with which the impact of different fixation times on immunohistochemical and molecular assays can be determined. This quality-control tissue array has been used ever since to determine the influence of fixation times on the results of immunohistochemical analyses in the PETACC2 study. Further, researchers evaluated the prognostic value of KRAS and BRAF in stage II and III resected colon cancer as results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. The results of this study showed that the KRAS mutation status does not have major prognostic value in stage II–III CRC. However, the BRAF mutation was prognostic for OS, particularly in patients with microsatellite instability low (MSI-L) and stable (MSI-S) tumors. The same markers were tested for survival after relapse in 392 of 990 patients, who experienced disease relapse in the PETACC-3, EORTC 40993, SAKK 60-00 studies. The authors found that, although BRAF gene status and tumor site had no prognostic value on relapse-free survival, both, along with time to relapse (TTR), were strong determinants of OS of patients with colon cancer after disease relapse. Patients with BRAF mutated tumors had a median survival of 7.5 months compared with 25.2 months for patients with BRAF wild-type tumors. The researchers suggested these markers should be used in stratifying patients with metastatic colon cancer for clinical trials.

Moreover, the group will concentrate its efforts in the next three years on the following TR projects:

2.4.2. Interaction with the EORTC virtual tumor bank

Interaction with the EORTC virtual tumor bank has been developed so that it can function as backbone for this collaborative research. Among the ongoing TR projects we can mention the examination of oxaliplatin-induced liver toxicity, the pharmacogenomic profiling of patients receiving fluoropyrimidine-based therapy, expression analysis of CXCR4, Hif-1a, VEGF-C and VEGF-D, VEGFR3, Src family kinases and in-depth examination of the ‘serrated pathway’ and its associated gene modifications during colorectal carcinogenesis.

2.4.3. Screening platform

Due to the better knowledge of molecular pathology not only KRAS was integrated as the first molecular marker in the prescription label of EGFR− antibodies and promoted the research in further molecules in the EGFR pathway. The better understanding and the availability of specific inhibitors or antibodies requires also a new trial structure, as the current routine diagnostic does not allow indentifying the right patients...
for trials with new inhibitors. Highly targeted treatment also means that only a small subgroup is planned to be enrolled, increasing the efforts for the screening procedure. As an example, to enroll 40 patients in a phase I/II trial for BRAF mutant patients will require to screen 500–700 patients with metastatic colorectal cancer, a patient number similar to phase III trials in other indications. Therefore, a common screening platform for all patients with colorectal cancer is a key project for the group as well as the EORTC itself, and is currently in development in partnership with the European Society of Pathology (ESP). The vision in this project is that all patients at the participating centers are first characterized according to the molecular markers, and then – based on this information – are enrolled in different, parallel phase II trials. This concept has already been applied in the BATTLE and I-SPY programs in lung and breast cancers.

3. Conclusion

In conclusion, this review of the major achievements of the GI Group shows that the group has played an important role in the scientific development of understanding and treatment of GI cancer over the last 50 years. The statements written 10 years ago in the 40th EORTC anniversary GI paper – “in the near future, treatment of gastrointestinal tract cancer will be tailored to the characteristics of tumours”, “our group is assessing the possibility of doing some translational research”, “we will now preserve resected specimens in all of the new trials” – become reality and demonstrate the ability of the group to foresee the future and to integrate and apply new concepts in its scientific programs. The development of the screening platform with the ESP in CRC described above constitutes a major challenge and a turn in the ways of collaboration with both individual cancer centers and industry. If successful, this model might be extended to other malignant tumors and set up a new era of clinical investigations at the EORTC.

4. Conflict of interest statement

Gustavo Werutsky, Murielle Maurer, Jean-Luc Van Laethem, Theo Ruers, and Bernard Nordlinger declare no conflicts of interest. Markus Moehler consulted for and received honoraria from Roche and Amgen, and consulted for and received research funds from Merck. Gunnar Foilprecht consulted for and received honoraria from Roche and Sanofi-Aventis, consulted for and received honoraria and research funds from Merck KGaA, received honoraria from Amgen, and consulted for Bristol Myers Squibb. Florian Lordick consulted for and received honoraria and research funds from Merck, Sanofi, Fresenius, consulted for and received honoraria from Amgen, consulted for Ganymed, and received research funds from GSK. Manfred Lutz consulted for Celgene, Sanofi-Aventis, and Bayer, and received honoraria from Falk. Eric Van Cutsem received research funds from Amgen, Novartis, Pfizer, Merck Serono, Sanofi, and Roche. Arnaud Roth received honoraria and travel reimbursement from Roche, Sanofi, Amgen and Bayer, and travel reimbursement from Pfizer Oncology. Daniela Aust received honoraria from Roche, Merck, Falk, and Amgen. Michel Ducriveau received grants, honoraria and travel support from Merck Serono, honoraria for lecturing from Roche, Amgen and Pfizer, received grants from Roche, is board member of Roche, Pfizer, Amgen and Fresenius Biotech, and is married to an Oncology Marketing Director in an affiliate of GlaxoSmithKline.

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