6125 POSTER

Two Polymorphisms of the Endothelin Axis in Colorectal Cancer

A.G. Antonacopoulou[1], A. Mathiopoulou[1], F.I. Dimitrakopoulos[1], A. Kottorou[1], C.D. Scopa[2], H.P. Kalofonos[2]. [1]*University of Patras, Molecular Oncology Laboratory, Patras, Greece;* [2]*University of Patras, Department of Pathology, Patras, Greece*

Background: Endothelin (ET) is a vasoconstricting peptide that mediates its effects through the endothelin receptors (ETA and ETB). This sytems gains increasing importance in cancer. Previous studies have associated the ET-1 isoforms and ETA receptor with mitogrenic effecs on tumour and stromal cells, tumour cell survival, invasion and metastastis as well as modulation of tumour-infiltrating immune cells. The ET-1 +1383A/4A polymorphism results in altered ET-1 levels while the role of the ETA receptor rs 5333 polymorphism remains unknown. In this pilot study we asked whether these 2 polymorphisms influence relapse status in patients with colorectal cancer (CRC).
Material and Methods: DNA was extracted from formalin-fixed paraffin-embedded tissue samples from 89 patients with CRC. Genotyping was performed using real time PCR. The +1383A/4A polymorphism was genotyped with a taqman assay on 68 samples while the rs5333 polymophism was genotyped on 89 samples using a sybr green approach. Statistic analysis was performed using pasw18.
Results: Regarding the ET-1 +138 3A/4A polymorphism, the majority of patients (45.4%) were homozygous for 3A. The homozygous 4A genotype was observed in 20.1% and heterozygosity in 34.3% of patients. The 3A allele frequency was lower in patients who remained disease free compared to patients who relapsed (0.525 *vs* 0.654, respectively). Accordingly, the 4A allele was more frequent in patients who remained disease free compared to those who relapsed (0.475 *vs* 0.346, respectively). However, statistical significance was not reached.
Regarding the ETA receptor rs5333 polymorphism, the majority of patients were TT (60%) while only 9% of patients were CC. The remaining 31% comprised the heterozygotes. Both T and C allele frequencies were similar between patients who relapsed and patients who remained disease free (T: 0.737 *vs* 0.755 and C: 0.262 *vs* 0.245).
Conclusions: The ET-1 and the ETA receptor polymorphisms studied are unrelated to disease relapse in patients with colorectal cancer.

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Thymidylate Synthase as Biomarker in Rectal Cancer Patients After 5-FU-based Radiochemotherapy − Evaluation of the Prognostic Capacity in Pre-treatment Biopsies and Resected Adenocarcinoma

L.C. Conradi[1], A. Bleckmann[2], T. Sprenger[1], M. Schirmer[3], K. Homayounfar[3], H.A. Wolff[4], H. Becker[1], B.M. Ghadimi[1], T. Beissbarth[5], T. Liersch[1]. [1]*University of Göttingen, Surgery, Goettingen, Germany;* [2]*University of Göttingen, Oncology, Goettingen, Germany;* [3]*University of Göttingen, Pharmacology, Goettingen, Germany;* [4]*University of Göttingen, Radiationoncology, Goettingen, Germany;* [5]*University of Göttingen, Medical Statistics, Goettingen, Germany*

Purpose: Fluorouracil (5-FU) remains the backbone of neoadjuvant radiochemotherapy (RCT) as well as adjuvant therapeutic strategies in multimodal treatment of rectal cancer patients. Due to its central role as the major target of 5-FU thymidylate synthase (TS) is a promising biomarker in rectal cancer. We assessed TS in 208 patients with regard to its predictive/prognostic capacity for disease free DFS and overall cancer specific survival (CSS).
Patients and Methods: 167 patients cUICC stages II (28%) and III (72%) received preoperative 5-FU based RCT followed by total mesorectal excision (TME) A comparison group n = 41 received postoperative RCT after primary TME. All patients were treated after standardized protocols within phase-II/-III trials of the German Rectal Cancer Study Group. TS levels from pre-treatment biopsies and corresponding resection specimens were assessed by immunohistochemical staining for their impact on DFS and CSS. Additionally, a TS gene polymorphism (28 bp repeat) was analysed in respect to intracellular protein expression levels and prognostic significance.
Results: Patients with low TS expression in pre-treatment biopsies showed a correlation with impaired CSS (p = 0.015). After neoadjuvant RCT there was evidence of lymph node metastases ypUICC stage III in 32.6%. Complete histopathologically confirmed tumour regression TRG 4 was achieved in 16 patients (9.5%). During follow-up (median 57 months) patients with low intratumoral TS expression and positive nodal status were at high risk for local and/or distant metastatic recurrence (p = 0.040). Analysis of the 28bp repeat revealed a correlation of *3/*3 genotype with high TS expression in pretherapeutical biopsies (p = 0.05).
Conclusion: TS represents a prognostic biomarker in locally advanced rectal cancer indicating an unfavourable outcome for patients with low TS expression and might help to adapt adjuvant therapy regimens by stratifying patients according to their risk for cancer recurrence.

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What About Risk Factors KRAS, BRAF and PI3K in a French Translational Study OMIT of 325 Patients Traited With Cetuximab Based-regimen in Real Practice

A. Morel[1], M. Boisdron[2], J. Metges[3], O. Capitain[4], J. Douillard[5], J. Ramée[6], J. Raoul[7], I. Cumin[8], P. Etienne[9], F. Grude[4]. [1]*Centre Paul Papin, Pharmacogenetic, Angers, France;* [2]*Centre Paul Papin, Oncopharmacology, Angers, France;* [3]*CHU Brest, Oncology, Brest, France;* [4]*Centre Paul Papin, Oncology, Angers, France;* [5]*Centre René Gauducheau, Oncology, Nantes, France;* [6]*Centre Catherine de Sienne, Oncology, Nantes, France;* [7]*Centre Eugène Marquis, Oncology, Rennes, France;* [8]*CH Lorient, Oncology, Lorient, France;* [9]*Clinique Armoricaine Radiologie, Oncology, Saint Brieuc, France*

Background: The OMIT (Drugs and Emerging Therapeutics Observatory) is a French structure created in 2003 by the Regional Health Agencies of Western France (Bretagne and Pays de la Loire). This network gathers clinical data from 50 public and private institutions. Its medical staff (oncologists, surgeons, pharmacists, biologists, etc) has a global reflection on drugs management in cancer patients and represents a task force for French Health Authorities.
K-RAS mutation status is a strong predictive marker of cetuximab efficacy in advanced colorectal cancer. However, a subset of wild-type K-RAS patients do not respond, suggesting the existence of additional markers of resistance, such as other EGFR downstream signaling molecules like B-RAF and PI3K.
Methods: K-RAS, B-RAF and PI3K mutation status were retrospectively analysed in a large group (n = 341) of mCRC patients treated with cetuximab based-regimen.
The aim of this study was to determine their role as prognostic markers.
Statistical analysis used the χ^2 test, linear regression analysis, and the Kaplan–Meier method.
Results: The sex ratio (male to female) of the population was 1.69 and the mean age was 63.8 IC95% [62.7–65.0]. 75% of the patients received the cetuximab-based regimen as second or third-line therapy. Mutations in MAP kinase pathway were found in 39% (Kras: 36%; BRAF: 3%) and PI3K mutations in 9%. 6.5% of the patients had simultaneous PI3K and KRAS mutations. Median Progression Free Survival (PFS) and Overall Survival (OS) were significally lower (p = 0.0031 & p = 0.0253) in patients with tumours presenting K-Ras mutation. The OS was significantly lower only in patients with codon 13 K-RAS mutant tumours while the PFS was significantly lower only in patients with codon 12 K-RAS mutant tumours. B-RAF and Pi3K mutation status did not affect the PFS and OS. However, in patients with K-Ras wild type tumours, the presence of B-RAF mutation or PI3K mutation leads to significantly decreased PFS (B RAF p = 0.0078; PI3K p = 0.05) and OS (B-RAF p = 0.079; PI3K p = 0.0029).
Conclusion: Our study confirms that K-RAS is a predictive biomarker of the response of metastatic colorectal cancers to anti-EGRF monoclonal antibody cetuximab. K-RAS codon 12 and 13 mutation status affect differently the response to cetuximab. In patients with wild-type K-RAS, B-RAF and Pi3K mutation status are relevant to predict cetuximab efficacy.

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Frequency and Importance of KRAS Mutations in Inoperable Cholangiocarcinoma Patients Referred for Systemic Therapy

L.H. Jensen[1], N. Pallisgaard[2], A.H. Mellergaard[1], K.E. Aaroee[1], J. Lindebjerg[3], J. Ploen[1], A. Jakobsen[1]. [1]*Vejle Hospital, Oncology, Vejle, Denmark;* [2]*Vejle Hospital, Clinical Biochemistry, Vejle, Denmark;* [3]*Vejle Hospital, Pahology, Vejle, Denmark*

Background: The purpose of the present study was to investigate KRAS in an unselected population of cholangiocarcinoma patients eligible for oncologic treatment. There are no curative options for inoperable cholangiocarcinoma. Systemic therapy with chemotherapy has proven to increase survival and, furthermore, combination chemotherapy is superior to monotherapy. There is, however, plenty of room for improvement and this may be achieved by adding biologic agents. In other gastrointestinal cancers supplemental effect is seen when adding EGFR inhibiting treatment to chemotherapy, but the effect depends on KRAS wild-type. The frequency of KRAS mutations in cholangiocarcinoma patients eligible for oncologic treatment is largely unknown and this is a prerequisite for designing marker driven clinical trials.
Material and Methods: From October 2008 to December 2010 all patients with inoperable cholangiocarcinoma referred to our department of oncology were included. DNA was isolated from tumour tissue and analysed with quantitative PCR for the 7 most frequent activating mutations in the KRAS gene. Data about chemotherapy and participation in clinical trials were extracted from patient records and case report forms. Date of death was verified in a central register.
Results: During 27 months 148 patients were referred with inoperable cholangiocarcinoma. 109 patients received chemotherapy and most of