Poster ID: P-141
Category: Basic Colon Cancer

The contribution of White Blood Cells' gene expression in prediction of gastrointestinal cancer

Apostolou P.[1], Parsonidis P.[1], Iliopoulos A.C.[1], Papasotiriou I.[2]

[1]Research Genetic Cancer Centre S.A.,Florina, 53100, Greece

[2] Research Genetic Cancer Centre International GmbH, Zug, 6300, Switzerland

Background: Gastrointestinal cancer (GI) remains one of the most deadly and common types of cancer worldwide. The early detection of GI cancer contributes in designing more efficient treatment algorithms and therefore reduction in mortality rates. The present study aimed to introduce and evaluate a non-invasive and sensitive technique, able to distinguish between normal and GI cancer samples. The recommended assay is based on the synergy of molecular biology with artificial neural networks.

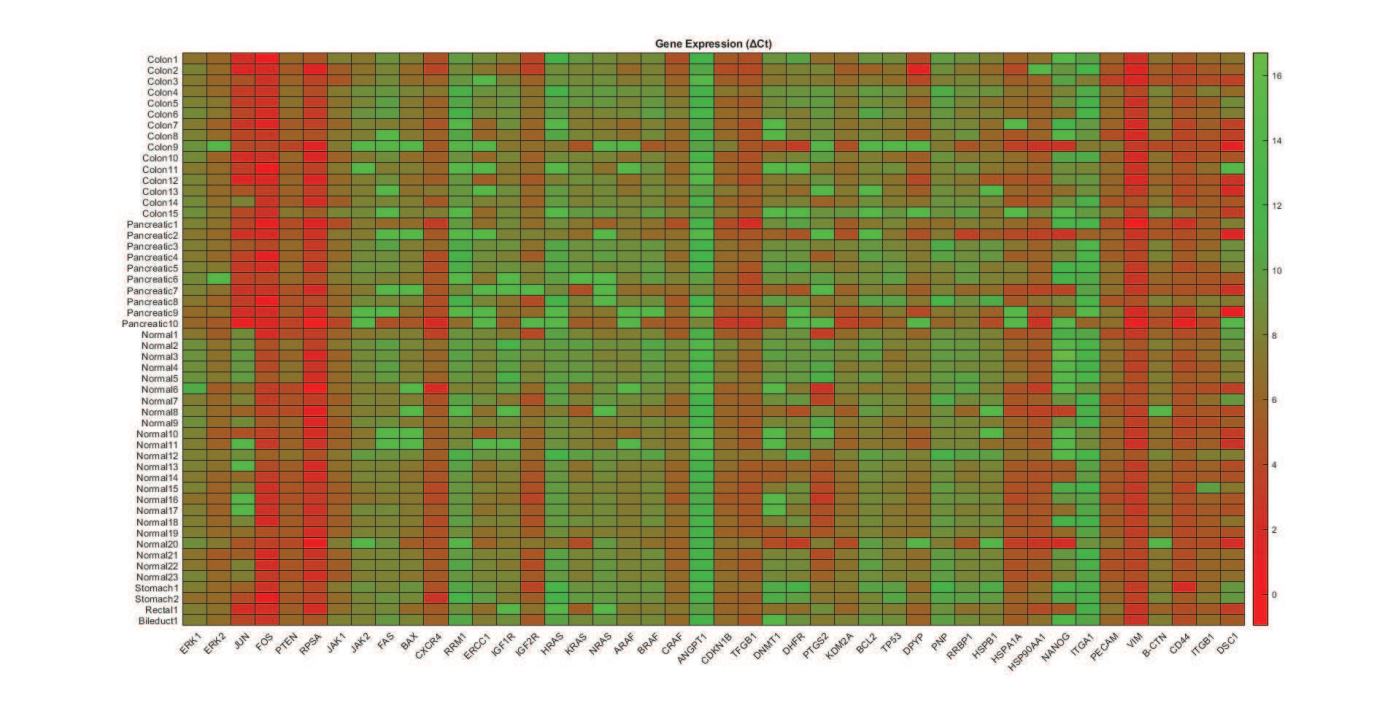

Figure 1: Delta Ct qPCR Data among all samples. The higher the DeltaCt the lower the gene expression.

Methods: The data set included healthy samples as well as GI cancer patients from a variety of cancer types (colon, pancreatic, stomach etc.) at different stages. In particular, from 60 samples (in a ratio of healthy-cancer approximately 1:1), a small quantity of whole blood was removed, and white blood cells were further isolated. Then, total RNA extracted and qRT-PCR reactions for more than 50 different genes were performed. The chosen genes consist of common oncogenes, tumor suppressor genes, and/or genes associated with key cellular processes (metastasis, apoptosis, signaling pathways etc.). The calculated DeltaCt values were provided as input to a supervised pattern recognition model for the classification between healthy subjects and cancer patients. The model was an artificial neural network ensemble, designed and built deploying the Bagging (Bootstrap Aggregating) method, while its performance was evaluated by 10-fold cross validation.

Results: The average accuracy of the ensemble was 90.24% (±13.95), achieving a high rate of identification, namely the ensemble predicted the correct class (healthy or GI cancer) in almost all cases. The specificity and sensitivity of the method calculated at 87.5% and 90.63% respectively.

Conclusions: These preliminary results indicate that the proposed system, namely the exploitation of qPCR data by neural network ensembles, can be very helpful towards a more accurate and less time consumable prognostic method of GI cancer. The above system is not affected by the stage or particular type of cancer. Further studies in more samples and different types of cancer, are required for the verification of this method at clinical level.

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and selection pressure from treatment. In select cases, there may be potential to exploit CMS subtype switching for therapeutic benefit.

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P-139 Comparison of cost-effectiveness of anti-epidermal growth factor receptor monoclonal antibody and anti-vascular endothelial growth factor monoclonal antibody in K-RAS WT, RAS WT, and RAS WT left-sided metastatic colorectal cancer

S. Lee[1], C. Chiang[2], K. Lam[2], V. Lee[2], I. Wong[3], S. Chan[2], H. Choi[2]

[1]Department of Clinical Oncology, Tuen Mun Hospital, Hong Kong, China; [2]Department of Clinical Oncology, University of Hong Kong, Hong Kong, China; [3]School of Public Health, University of Hong Kong, Hong Kong, China

Background: Metastatic colorectal cancer (mCRC) is a significant global health burden. Combination chemotherapy plus targeted therapy, either anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibody (mAb) or anti-vascular endothelial growth factor (anti-VEGF) mAb have become the current standard first-line treatment. Both kinds of targeted therapy have demonstrated their efficacies as first-line therapies in K-RAS wild-type (WT) patients. We aimed to compare the economic value of chemotherapy plus anti-EGFR mAb against chemotherapy with bevacizumab (an anti-VEGF mAb) in K-RAS WT, RAS WT, and RAS WT left-sided mCRC patients from a Hong Kong societal perspective.

Methods: We reviewed standard literature databases (PubMed, Cochrane library, ASCO and ESMO congress database). Phase II or phase III randomized controlled trials (RCTs) comparing chemotherapy and anti-EGFR mAb versus chemotherapy and anti-VEGF mAb as first-line treatment in mCRC patients were selected. Included studies must have had survival data from K-RAS WT, RAS WT, and RAS WT left-sided tumour populations. We then modeled a hypothetical cohort of patients with K-RAS WT mCRC with the same characteristics as those patients enrolled in the screened RCTs as a base case. We developed a three-state Markov model and 10-year horizon to estimate and analyze costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratio (ICER) of chemotherapy plus anti-EGFR therapy against chemotherapy plus Bev in K-RAS WT, RAS WT, and RAS WT left-sided mCRC respectively. There were three transition probabilities, namely from progression-free to progressive disease, from progression-free to death, and from progressive disease to death. All transition probabilities for each treatment strategy were estimated based on the survival curves reported in the RCTs assessing the respective treatments. We considered three times the local gross domestic product per capita (GDPpc) as the willingness-to-pay (WTP) threshold (3x GDPpc; i.e., US$146,748). The cost threshold of anti-EGFR therapy was also to be evaluated.

Results: Based on these criteria, we identified three trials in comparing anti-EGFR mAb versus anti-VEGF mAb (FIRE-3, CALGB 80405, and PEAK). Compared with chemotherapy plus bevacizumab, anti-EGFR mAb to chemotherapy provides additional 0.177 (0.092 to 0.333), 0.252 (0.104 to 0.479), and 0.334 (0.154 to 0.695) QALY compared to anti-VEGF mAb in K-RAS WT, RAS WT, and left-sided RAS WT mCRC population respectively. The corresponding ICER is $147,282 (69,067 to 377,371), $111,735 (50,460 to 277,226), $125,263 (52,786 to 291,639) per QALY gained, respectively. For RAS WT and left-sided RAS WT mCRC, adding anti-EGFR mAb to chemotherapy is cost-effective under the WTP threshold. However, in right-sided tumours, anti-EGFR mAb provides worse QALY of −0.106 (−0.390 to 0.094) compared to anti-VEGF mAb, and therefore it would not be a cost-effective one. Probability sensitivity analysis with Monte-Carlo simulation did not alter our main findings.

Conclusion: Anti-EGFR therapy is more cost-effective than bevacizumab as front-line targeted therapy in RAS WT, in particular left-sided RAS WT mCRC tumours, but not in the K-RAS WT population. Biomarkers-based selection of patients improves the cost-effectiveness of targeted therapy and should be advised.

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P-140 Targeted NGS panel of epigenetic regulators genes: Application results for gastric cancer patients

A. Kalinkin[1], E. Kuznetsova[1], E. Alekseeva[1], I. Bure[2], D. Mikhaylenko[2], A. Tanas[1], V. Strelnikov[1], M. Nemtsova[2]

[1]FSBSI Research Centre for Medical Genetics, Moscow, Russia; [2]I.M. Sechenov First Moscow State Medical University, Moscow, Russia

Background: Epigenetic processes play a significant role in carcinogenesis, cancer recurrence and metastasis, and may serve as useful clinical biomarkers. According to GLOBOCAN 2018 data, gastric cancer (GC) is the third most lethal cancer with about 783000 deaths in 2018. Therapeutic drugs that are effective in the treatment of various types of tumors have a weak therapeutic effect in the treatment of GC due to the lack of genetic variants in known driver genes. Analysis of epigenetic regulator genes mutation landscape in GC samples may reveal novel genetic variants and therapeutic targets. This study presents an application of epigenetic regulators targeted NGS panel to GC patients.

Methods: We designed the NGS-based targeted panel of 25 genes whose products are involved in epigenetic processes and determined somatic alterations in 52 tumor samples of the GC. This panel consists of genes that regulate DNA methylation: DNMT1, MBD1, TET1, DNMT3A, DNMT3B ; genes involved in the modification of histone proteins: EZH2, UTX, EP300, JARID1B, CREBBP, HDAC2, SIRT1, KMT2A, KMT2D, KMT2C ; chromatin remodeling genes: SMARCB1, SMARCA2, SMARCA4, ARID1A, ARID2, BRD7, PBRM1, CHD5, CHD7, CHD4 . For the selection of genes, we took into account the frequency of somatic variants in GC according to the COSMIC cancer database. Prediction of somatic variants pathogenicity and impact on structure were carried out using PolyPhen2, SIFT, PROVEAN, MutPred2, I-Mutant 3.0 and HOPE3D tools. All identified somatic variants were verified in tumor tissue by Sanger sequencing.

Results: In 52 GC samples, targeted NGS sequencing revealed 50 nonsynonymous substitutions, 20 frameshift indels, 5 nonsense variants. We selected only known variants with minor allele frequency (MAF) lower than 0.0001 and no available information about clinical significance or novel genetic variants, which have never been described in any database. Of these selected variants, 11 are known with low MAF, and 14 are novel. Based on results of in silico pathogenicity prediction, substitutions in genes ARID1A (p.R2236C, p.Q152*, p.S1828*), KMT2A (p.W1909*), KMT2D (p.D3419G), KMT2C (p.Q462*, p.P959I, p.R973G), SMARCA4 (p.P913L) and CHD4 (p.R1943Q) are of interest due to pathogenicity prediction and disruption of various molecular mechanisms such as ligand binding, molecular recognition and relative solvent accessibility.

Conclusion: In this study, we present novel results on somatic mutation profiling in epigenetic regulators for GC patients. The identified pathogenic variants can be used as prognostic markers or new drug targets, but further investigation is needed. Deep target sequencing of epigenetic regulators makes it possible to acquire novel alterations and resolve true mutation frequencies of such genes. Subsequently, results of mutational landscape studies can be used to form risk groups among patient, confer significant prognostic information and improve clinical decision-making.

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P-141 The contribution of white blood cell gene expression in the prediction of gastrointestinal cancer

P. Apostolou[1], P. Parsonidis[1], A. Iliopoulos[1], I. Papasotiriou[2]

[1]Research Genetic Cancer Centre S.A., Florina, Greece; [2]Research Genetic Cancer Centre International GmbH, Zug, Switzerland

Background: Gastrointestinal (GI) cancer remains one of the most deadly and common types of cancer worldwide. The early detection of GI cancer contributes to designing more efficient treatment algorithms and therefore reduction in mortality rates. The present study aimed to introduce and evaluate a non-invasive and sensitive technique, able to distinguish between normal and GI cancer samples. The recommended assay is based on the synergy of molecular biology with artificial neural networks.

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Results: The average accuracy of the ensemble was 90.24% (±13.95), achieving a high rate of identification; namely, the ensemble predicted the correct class (healthy or GI cancer) in almost all cases.

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P-142 Early gastric cancer: Identification of molecular markers able to distinguish penetrating lesions with different prognosis

C. Molinari[1], G. Tedaldi[1], F. Rebuzzi[1], P. Morgagni[2], L. Capelli[1], S. Ravaioli[1], M. Tumedei[1], E. Scarpi[3], A. Tomezzoli[4], C. Castelli[4], M. Ambrosio[5], A. D'Ignazio[5], L. Solaini[2], F. Limarzi[1], P. Ulivi[1], L. Saragoni[6]

[1]Biosciences Laboratory, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; [2]Department of General Surgery, Morgagni-Pierantoni Hospital, Forlì, Italy; [3]Biostatistics and Clinical Trials Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; [4]Department of Pathology, University of Verona, Verona, Italy; [5]Pathology Unit, University of Siena, Siena, Italy; [6]Pathology Unit, Morgagni-Pierantoni Hospital, Forlì, Italy

Background: Early Gastric Cancer (EGC) represents 25% of the gastric cancers surgically treated and is usually characterized by a good prognosis (5-year survival >90%). However, some patients show a significantly worse prognosis. In particular, among penetrating EGCs classified according to Kodama's criteria, Pen A tumors are characterized by extensive submucosal invasion, lymph node metastases, and worse prognosis, whereas Pen B tumors seem to be associated with a better prognosis.

The aim of the study was to characterize the differences between Pen A, Pen B and locally advanced gastric cancers (T3N0) in order to identify biomarkers involved in aggressiveness and clinical outcome of such tumors.

Methods: Formalin-fixed paraffin-embedded (FFPE) tissues were obtained from 87 patients (33 Pen A, 34 Pen B, and 20 T3N0 tumors), matched for age, gender and lymph nodes status. Mucins analysis (MUC2, MUC6, MUC5AC) was performed by immunohistochemistry; copy number variation (CNV) analysis by multiplex ligation-dependent probe amplification (MLPA); TP53 mutational status by Sanger sequencing; TP53 loss of heterozygosity (LOH) and microsatellite instability (MSI) evaluations by fragment analysis.

Results: MUC6 expression significantly distinguished Pen A and Pen B tumors, being overexpressed in 33.3% and 2.9% of the two subgroups, respectively (p=0.014). CNV evaluation of PIK3CA, EGFR, CDK6, MET, GATA4, FGFR1, MYC, PTP4A3, FGFR2, CCND1, KRAS, KLF5, ERBB2, TOP2A, GATA6, and CCNE1 genes showed that amplification was the most frequently observed alteration, but the only gene that was significantly different between tumor groups was the GATA6 gene (p=0.02), amplified in 33.3% and 66.7% of Pen A and Pen B, respectively. The evaluation of MSI showed no significant differences between Pen A and Pen B. Finally, TP53 gene analysis showed that 34.0% of Pen tumors have a mutation in TP53 exons 5-8 and 38.5% has LOH, suggesting the early onset of alterations of this gene in gastric carcinogenesis. No differences between Pen A and Pen B tumors were observed in terms of TP53 mutation frequency and site of mutation, even if a different frequency of TP53 missense variants was detected (78% of Pen A and 67% of Pen B tumors). Preliminary data showed that TP53 mutation and LOH co-occur mainly in Pen A tumors with respect to Pen B (p=0.001).

Conclusion: Overall, our analyses revealed that clinicopathological parameters, microsatellite status and frequency of TP53 mutations do not seem to distinguish Pen A and Pen B tumors. Alternatively, the overexpression of gastric mucin MUC6 significantly characterized Pen A tumors, as well as the amplification of the GATA6 gene was associated with Pen B tumors. The co-occurrence of TP53 mutations and LOH in EGC needs further investigations.

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Disclosure: The presenting author has declared no conflicts of interest.

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P-143 Lack of expression of CDX2: Prognostic biomarker in stage IV colorectal cancer

A. Soares[1], D. Rodrigues[2], E. Cipriano[3], A. Tavares[1], M. Vilaca[1], D. Silva[1], J. Santos[1], A. Mesquita[1], M. Salgado[1], C. Sottomayor[1], R. Almeida[4]

[1]Hospital Pedro Hispano, Matosinhos, Portugal; [2]Centro Hospitalar São João, Porto, Portugal; [3]Hospital Pedro Hispano, Matosinhos Local Health Unit, Matosinhos, Portugal; [4]IPATIMUP/I3S, Porto, Portugal

Background: Lack of expression of caudal homeobox 2 transcription factor (CDX2) is associated with a high risk of relapse in patients with stage II / III colon cancer after complete surgical resection, but its role in metastatic colorectal cancer (CRC) remains uncertain.

Methods: Patients with metastatic CRC at diagnosis treated at our institution and with available histological material from the primary tumor were selected. Patient tissue microarrays were performed and the samples analyzed by immunohistochemistry. We defined CDX2 negativity as an absence of expression of CDX2 in IHC in archived tumor tissue. Retrospective analysis of all patients diagnosed with RCC between January 2011 and December 2017 was performed. Demographic, clinical and survival data were analyzed using SPSS v24. A multivariate analysis was performed using the Cox proportional hazard regression model.

Results: We included 125 patients, with male predominance (n=73). The median age at metastatic diagnosis was 65 years and 105 patients had colon cancer. In total, 52.8% (n=66) of the patients had liver metastasis. Median overall survival was 17,66 months (95%CI 11,98-23.34) for a median follow up time of 17,66 months (0.03-91.81 months). 38 patients had a loss of CDX2 expression, and 87 patients had CDX2 positive. We have found that the CDX2 positive correlates with a lower risk of death (HR 0.44 (95%CI 0.26-0.73) p=0.002) as well as a decreasing trend in the likelihood of progression with first-line chemotherapy (HR 0.86 (95%CI 0.44-1.66) p=0.942). In total, 19% of patients CDX2 negative versus 12.1% CDX2 positive were grade 3 (p = 0.540). 53% of CDX2 negative were women versus 47.4% men (p = 0.073). Focusing on the metastasization sites, 22.75% of CDX2-negative had hepatic metastasis and 50% had peritoneal metastasis. 77.3% of patients with CDX2 positive tumours had liver metastasis. Partial responses were more frequent in CDX2 positive patients. We detected a negative predictive value (NPV), about 75-80%, for death/progression in the first 6 months after metastatic diagnosis.

Conclusion: CDX2 negativity was associated with a higher risk of death and a trend for increased risk of progression after first-line ChT. Due to the high NPV, patients are less likely to die or progress at 6 months when they have CDX2 positive mCRC.

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P-144 Infigratinib versus gemcitabine plus cisplatin as first-line therapy in patients with advanced cholangiocarcinoma with FGFR2 gene fusions/translocations: phase 3 PROOF trial

G. Abou-Alfa[1], I. Borbath[2], A. Cohn[3], L. Goyal[4], A. Lamarca[5], T. Macarulla[6], D. Oh[7], S. Roychowdhury[8], S. Sadeghi[9], R. Shroff[10], M. Howland[11], A. Li[11], T. Cho[11], A. Pande[11], M. Javle[12]

[1]Memorial Sloan Kettering Cancer Center, Weill Medical College at Cornell University, New York, United States; [2]Cliniques Universitaires Saint-Luc Université Catholique de Louvain, Brussels, Belgium; [3]Rocky Mountain Cancer Centers, Denver, United States; [4]Massachusetts General Hospital, Boston, United States; [5]University of Manchester / The Christie NHS Foundation Trust, Manchester, United Kingdom; [6]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [7]Seoul National University Hospital, Seoul, South Korea; [8]CLIA Cancer Genomics Laboratory, Comprehensive Cancer Center and The James Cancer Hospital at The Ohio State University, Columbus, United States; [9]David Geffen School of Medicine at UCLA, Santa Monica, United States; [10]University of Arizona Cancer Center, Tucson, United States; [11]QED Therapeutics Inc., San Francisco, United States; [12]The University of Texas MD Anderson Cancer Center, Houston, United States

Background: Treatment options for metastatic or unresectable cholangiocarcinoma are limited with a need to provide increased disease control, improved outcomes, and targeted therapy that is less toxic than standard chemotherapy. As the understanding of the molecular landscape of cholangiocarcinoma has increased, the fibroblast growth factor receptor (FGFR) family has been found to play an important role in cholangiocarcinoma. FGFR translocations (i.e. fusion events) represent driver mutations in cholangiocarcinoma. They are present in 13−17% of intrahepatic cholangiocarcinomas (IHC) and may predict tumor sensitivity to FGFR inhibitors. Infigratinib (BGJ398) is an ATP-competitive, FGFR1−3 selective oral tyrosine kinase inhibitor that demonstrated excellent preliminary anti-tumor activity in patients with relapsed/refractory cholangiocarcinoma with FGFR2 fusions/translocations in a phase 2 study (CBJG398X2204) [Javle et al. J Clin Oncol 2018]. The PROOF trial is evaluating infigratinib versus current standard-of-care gemcitabine + cisplatin in front-line patients with advanced cholangiocarcinoma with FGFR2 gene fusions/translocations (ClinicalTrials.gov identifier: NCT03773302).

Trial design: PROOF is a multicenter, open-label, randomized, controlled, phase 3 trial. Patients with previously untreated advanced/metastatic or inoperable cholangiocarcinoma with FGFR2 gene fusions (determined by local CLIA-certified or central laboratory) are randomized 2:1 to oral infigratinib 125 mg once daily for 21 days of a 28-day treatment cycle versus intravenous standard gemcitabine (1000 mg/m^2) + cisplatin (25 mg/m^2) on days 1 and 8 of a 21-day cycle. Treatment will continue until confirmed progressive disease by central review, intolerance, withdrawal of informed consent, or death. Patients assigned to the gemcitabine + cisplatin arm who progress can cross-over to infigratinib. The primary endpoint is progression-free survival (PFS, RECIST v1.1 by blinded central review). Secondary endpoints include overall survival, PFS (investigator determined), overall response rate, disease control rate, duration of response, and safety. Quality of life, pharmacokinetics and exploratory genetic alterations/biomarkers will also be assessed. The trial will have sites in the US, EU, and APAC, including Australia. The target population size is 384 patients. Recruitment started in December 2019, and the study has an estimated primary completion date of September 2023.