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First line treatment with FOLFIRI-Bevacizumab for advanced colorectal cancer (ACRC): a single institution experience with 127 consecutive unselected patients

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Background: Bevazicumab (BV) combined with IFL (Irinotecan, bolus 5FU and Leucovorin) improves response rate (ORR) and overall survival (OS) in patients (p) with ACRC. Nowadays, infusional 5FU based combinations are considered the optimal schedules. In EU, only irinotecan based combinations are approved for the use in combination with B in the first line setting. We analysed the efficacy and toxicity of a consecutive cohort of unselected patients with ACRC treated with FOLFIRI-BV.
Materials and Methods: From Aug-05 to Aug-08, 127 p with unresectable ACRC received BV 5 mg/kg d1, Irinotecan 180 mg/m^2 d1, Leucovorin 200 mg/m^2 d1 y 2, 5FU 400 mg/m^2 bolus and 600 mg/m^2 CI of 22 h d1 and 2, every 14 days (FOLFIRI-BV). There were 87 males and the mean age was 63 y (29−83). ECOG 0/1/2: 60/64/3. Primary tumour: colon 73 p, rectum 52 p, 2 p double primary. Median number of metastatic sites was 1 (1−4). According to Khöne risk classification, there were 60% low risk patients, 33% intermediate risk and 7% high risk.
Results: A total of 1417 courses were administered (median 12, range 1−29). Intention to treat ORR was 55% (95% CI: 46.3−63.6), with 12 CR, 58 PR and 44 SD. Two patients progressed at the first evaluation and 4 were not evaluated due to early withdrawal. Salvage surgery was performed in 31 p (24%), 23 p liver 1 p lung and 6 p other sites. Grade 3/4 toxicity per patient: anaemia 3/1, thrombopenia 1/1, neutropenia 13/8, febrile neutropenia 5/0, emesis 15/0, diarrhoea 20/0, mucositis 5/0, intestinal subocclusion 4/0. BV-related grade 2/3/4 toxicities: hypertension 12/2/0, proteinuria 9/0/0, headache 2/0/0, hemorrhage 6/3/0, wound complication 1/0/0, GI/GU fistula 1/2/1, anastomosis leak 0/1/0, GI perforation 0/2/0, venous thromboembolic 1/7/1 and arterial thromboembolic events 0/3/3. There were two toxic deaths because of septic shock without neutropenia. Sixty days mortality rate was 3.9%. Median progression free survival was 11.6 months (95% CI: 10.5−12.7), and median OS was 24 months (95% CI: 19.7−28.4).
Conclusions: FOLFIRI-BV is a safe and very active regimen for unselected patients with ACRC. This activity is correlated with a large rate of surgical rescue and with a long survival. BV toxicity profile seems similar to the described in clinical trials.

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Pathways of oxaliplatin/5-fluorouracil resistance in colorectal cancer

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Background: The development of drug resistance limits the effectiveness of current chemotherapeutic agents used to treat colorectal cancer. The discovery of the underlying mechanisms of resistance and the development of novel agents to target these pathways is a priority.
Materials and Methods: Transcriptional profiling of pre-treatment metastatic colorectal cancer liver biopsies and HCT116 parental, oxaliplatin and 5-Fluorouracil resistant cell lines was performed. A panel of chemotherapy resistant HCT116 CRC cell lines were previously generated by repeated exposure to increasing concentrations of drug over a period of several months. The parental and drug resistant cell lines were treated for 6, 12 and 24 hours and analyzed using the Affymetrix HGU133 Plus 2.0 array. Profiling of the in vitro and clinical samples was also carried out using the Almac Diagnostics Colorectal Cancer Disease Specific Array (DSA) which contains 61,528 probesets encoding 52,306 transcripts, 40% of which are not represented on the Affymetrix platform. Pathway analysis of the microarray data was performed using Metacore and Gene Set Enrichment Analysis (GSEA) was employed.
Results: Data analysis identified panels of in vitro and clinical genes whose expression is acutely altered in the parental setting following drug treatment and also basally deregulated in the resistant cells. The correlation between the in vitro and clinical samples in relation to gene expression and pathway analysis was examined. The significant pathways involved in these panels of genes were compared with the results of the GSEA to produce a final ranked gene list of pathways. This list included groups of Cell Cycle, Focal Adhesion, Insulin and MAPK signalling genes. A candidate gene approach was used to select individual genes from these pathways for incorporation into siRNA screens.
Conclusions: This study demonstrates the utility of microarray expression data analyzed by pathway and Gene Set Enrichment Analysis to identify pathways of Oxaliplatin/5-Fluorouracil resistance in colorectal cancer.

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European audit on cancer treatment outcome: an international, multidisciplinary, outcome-based quality improvement project of the European CanCer Organisation

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Background: In recent years there have been significant improvements in rectal cancer treatment. Both new surgical techniques as well as effective neoadjuvant treatment regimens have contributed to these improvements. Throughout Europe there are several national audit programs that have proved to facilitate the spread of up to date knowledge and skills among medical professionals resulting in improved treatment outcome. These quality assurance programs have resulted in improvements that have a greater impact on survival than that of any of the adjuvant therapies currently under study. Despite these laudable efforts there is still a wide variation in treatment outcome between countries, regions and institutions. Urged by these considerable differences the European Society of Surgical Oncology (ESSO) initiated an International, Multidisciplinary, Outcome-Based Quality Improvement which is fully embraced by the European CanCer Organisation (ECCO).
Material and Method: Initially, the focus will be on colorectal cancer. In the first period of 2 years the registration will make use of currently existing audit systems for colorectal cancer as in Norway, Sweden, Denmark, the United Kingdom, the Netherlands and Belgium, and start a benchmarking process. The national audit coordinators will provide access to their national databases and will form a multidisciplinary Steering Committee. The second period starts after the development of the European registration system. The data will be continuously used for benchmarking and internal feedback among participants. Afterwards, this experience will be used to extend the audit to other solid malignancies such as breast, gastric and oesophageal cancer.
Results: An overview of the structure of the European colorectal audit will be presented with a template for outcome registration on the basis of striking similarities and differences between institutions and nations.
Conclusion: A European audit could lead to further rapid improvements in outcome for cancer patients. The ECCO has recognized the importance of quality assurance for outcome of cancer patients and has created a framework to develop a European audit. We present the need, structure and progress of this European colorectal audit project.

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Pattern of bevacizumab use in 1st-line therapy metastatic colorectal cancer (mCRC) in real-life practice: results of the ETNA cohort study

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Added to combination chemotherapy regimen, targeted therapies are innovative treatment strategies in oncology. Bevacizumab (BV) was demonstrated to improve survival outcome in mCRC in the pivotal clinical trial (PCT), Hurwitz et al. 2004. It was approved in France as 1st-line therapy for mCRC in Jan 2005. The ETNA study aimed to describe BV use and survival outcome in real practice and to compare results to the PCT. We present BV usage patterns and safety with chemotherapy in 1st-line mCRC therapy and how these compare to the PCT.
ETNA is a cohort study conducted in 28 French centers that included patients initiating BV between Jan 2006 and Dec 2007. Patients treated with BV for mCRC as 1st-line therapy were followed for 12 months.
A total of 1551 patients were identified, 943 (61%) had CRC and 375 (24%) were treated for mCRC as 1st-line therapy. Their main characteristics were: age (mean) 65 yrs, male 57%, ECOG status 0−1: 51%. Thirty-eight per cent (n = 142) of patients complied with the PCT inclusion criteria for medical data and 166 (44%) for laboratory data. BV was combined with FOLFIRI/XELIRI in 334 patients (89%) FOLFOX/XELOX in 40 (11%) and FOLFIRINOX (n = 1). Onset of BV treatment was delayed in 99 patients