6067 POSTER

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

A. Ruiz de Lobera Martinez[1], I. Marrodan Ciordia[1], E. Azkona Uribelarrea[1], A. Sancho Gutierrez[1], A. Muñoz Llarena[1], A. Martinez Bueno[1], G. Lopez de Argumedo Esnarrizaga[1], N. Fuente Fernandez[1], R. Casas Cornejo[1], G. Lopez Vivanco[1]. [1]*Cruces Hospital, Medical Oncology, Barakaldo-vizcaya, Spain*

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.

6068 POSTER

Pathways of oxaliplatin/5-fluorouracil resistance in colorectal cancer

R. Turkington[1], W. Allen[1], L. Stevenson[1], V. Coyle[1], P. Jithesh[1], I. Proutski[1], C. Fenning[1], G. Stewart[1], D. Longley[1], P. Johnston[1]. [1]*Queen's University Belfast, Centre for Cancer Research and Cell Biology, Belfast N. Ireland, United Kingdom*

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.

6069 POSTER

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

M. den Dulk[1], W. van Gijn[2], V. Valentini[3], C.J.H. van de Velde[2]. [1]*Haga Hospital, Surgery, The Hague, The Netherlands;* [2]*Leiden University Medical Center, Surgery, Leiden, The Netherlands;* [3]*Università Cattolica del Sacro Cuore, Radiation Therapy, Rome, Italy*

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.

6070 POSTER

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

D. Smith[1], M. Rouyer[2], A. Balestra[2], D. Jayles[2], R. Guimbaud[3], P. Michel[4], O. Bernard[5], A. Ravaud[1], N. Moore[6], A. Fourrier-Réglat[6]. [1]*Hôpital St. André – CHU Bordeaux, Oncologie Médicale, Bordeaux, France;* [2]*INSERM CIC 0005 – Université V Segalen, Pharmacologie, Bordeaux, France;* [3]*CHU Toulouse – Institut C. Regaud, Oncologie Médicale, Toulouse, France;* [4]*Hôpital Charles Nicolles – CHU Rouen, Hépato-Gastroentérologie, Rouen, France;* [5]*Clinique Dr Calabet, Oncologie Médicale, Agen, France;* [6]*INSERM U657/CIC0005 – CHU Bordeaux – Université V Segalen, Pharmacologie, Bordeaux, France*

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

(26%, median delay: 28 days), motivated by recent surgery in 26 cases (26%) and co-morbidities in 8 cases (8%). Median duration of BV treatment was 5.4 months. Treatment discontinuation was observed in 150 patients (40%): 106 (28%) had treatment-free interval, 44 (12%) had a maintenance therapy (16 with BV alone). Among those receiving irinotecan-based regimens, the incidence of any events (grade 3/4) was 48% (vs 85% in PCT; $p < 0.0001$): neutropenia (17 vs 37%; $p < 0.0001$) and diarrhea (11 vs 32%; $p < 0.0001$). In line with the known safety profile of BV (any grade), hypertension was observed in 21 vs 22% ($p = 0.58$), arterial/venous thrombosis (11 vs 19%; $p = 0.0009$), proteinuria (32 vs 27%; $p = 0.10$) and gastrointestinal perforation (0.3 vs 1.5%; $p = 0.097$).
ETNA is one of the first real-life, post-marketing cohort study conducted to compare results of real practice with those of the PCT. Primary data indicated that patients differed to those included in the PCT with regard to several aspects. Common BV-associated effects were similar to those observed in the PCT. The safety profile of FOLFIRI regimen seems more manageable than that of IFL regimen but the lower frequency of neutropenia and diarrhea could also be related to an under-reporting of these in real-life.

6071 POSTER

Radioembolization with 90Y-resin microspheres as a salvage treatment for refractory liver-dominant colorectal metastases: a matched-pair analysis

M. Seidensticker[1], R. Rühl[1], P. Kraus[1], T. Denecke[2], A. Pethe[1], M. Pech[1], H. Amthauer[1], J. Ricke[1]. [1]*Universitätsklinikum Magdeburg, Klinik für Radiologie & Nuklearmedizin, Magdeburg, Germany;* [2]*Universitätsmedizin Berlin, Charité Klinik für Strahlenheilkunde, Berlin, Germany*

Background: Despite advances in systemic chemotherapy and biological agents, liver metastases continue to present a life-limiting prognosis for colorectal cancer (CRC) patients. This prospective study assessed the safety and efficacy of radioembolization (RE) with ^{90}Y-resin microspheres as a salvage therapy in patients with progressive liver-dominant CRC metastases compared with matched historical controls who received best supportive care (BSC).
Materials and Methods: A matched-pair analysis for overall survival was conducted in patients who presented after multiple lines of systemic chemotherapy/biological agents with extensive (>20%) liver involvement and tumour progression as confirmed by imaging (CT/MRI), alkaline phosphatase (ALP), tumour markers (CEA) and/or clinical symptoms. Patients treated with RE were matched with historical controls by tumour load, synchronous/metachronous metastases, ALP and CEA >200 U/mL. Overall survival from the date of progression prior to salvage treatment was calculated using Kaplan-Meier analysis. The relationships between baseline covariates (including Karnofsky performance status, tumour load, number of lines chemotherapy) and overall survival were examined by multivariate Cox proportional hazard model (SAS, Carey, NC).
Results: 58 patients (29 RE; 29 BSC) were recruited with extensive liver tumour involvement: median (range) 30% (20−50%) and 25% (10−75%) respectively. Patients in both cohorts received a median of 3 (2−6) prior lines of chemotherapy. RE was a significant predictor of survival (Hazard Ratio = 4.8; 95%CI 2.4−9.5) and the only parameter found to be a significant contributor to the prognosis. Compared with BSC, patients receiving RE survived significantly longer (median: 8.3 vs. 3.5 months; $p < 0.001$). This benefit was clearly evident at 3 months (97% vs. 59% survival) and sustained through 12-months follow up (24% vs. 0% survival). Progression-free survival was 5.5 and 2.1 months with RE and BSC, respectively ($p < 0.001$). Adverse events following RE included thrombocytopenia and sepsis (3%), and abdominal pain (3%). Three possible cases of radiation-induced liver disease were medically managed and not considered life-threatening (median survival: 9.8 months; range: 9.0−16.6 months).
Conclusions: RE provides substantial clinical benefit as evidenced by significant increased liver disease stabilization and prolonged overall survival in patients for whom there are limited treatment options.

6072 POSTER

Bevacizumab related adverse events in patients affected by metastatic colorectal cancer: a meta-analysis

E. Galfrascoli[1], M. Cinquini[2], A. Rossi[3], A. Manazza[4], G. Damia[5], G. Banna[6], A. Tosoni[7], M. Tiseo[8], G. Farina[9], M. Garassino[9]. [1]*Ospedale Fatebenefratelli e Oftalmico, Hospital Pharmacy, Milano, Italy;* [2]*Mario Negri Institute, New Drug Development Strategies Lab., Milano, Italy;* [3]*S.G. Moscati Hospital, Oncology, Avellino, Italy;* [4]*CeRMS, Molecular Oncology Lab., Torino, Italy;* [5]*Mario Negri Institute, Molecular Pharmacology Lab., Milano, Italy;* [6]*Vittorio Emanuele Hospital, Oncology, Catania, Italy;* [7]*Maggiore Hospital, Oncology, Bologna, Italy;* [8]*Maggiore Hospital, Oncology, Parma, Italy;* [9]*Fatebenefratelli and Ophthalmic Hospital, Oncology, Milano, Italy*

Background: Bevacizumab, a recombinant humanized monoclonal antibody targeting the vascular endothelial growth factor, is widely used in patients with metastatic colorectal cancer. Bevacizumab suffers by several adverse events which may be different according to the diverse kind of treated tumours. We performed a systematic review and meta-analysis of published randomized clinical trials (RCTs) investigating bevacizumab in the treatment of patients affected by advanced colorectal cancer to better understand the overall risk of side effects.
Methods: PubMed, Medline, CancerLit, and Embase databases were searched for RCTs, comparing chemotherapy plus bevacizumab *versus* chemotherapy alone in metastatic colorectal cancer patients. Also abstracts presented at the main international meetings until April 2009 were analyzed. Odds ratios (ORs) and Number Needed to Harm (NNH) for main side effects were calculated with their 95% confidence intervals (CI) using fixed-effects model.
Results: Nine controlled trials encompassing 7,132 patients, were eligible for the present analysis. Patients receiving bevacizumab plus chemotherapy have a risk twice superior (OR 1.92 95% CI 1.51−2.44) of developing all-grade hypertension corresponding to a NNH 9 and seven times superior of developing grade 3−4 hypertension (OR 6.94 95% CI 5.07−9.52; NNH 11). Moreover, the risk of the other grade 3−4 toxicities were: bleedings (OR 1.83 95% CI 1.11−3.01 NNH 83), proteinuria (OR 4.20 95% CI 2.17−8.12 NNH 73), thromboembolic events (OR 1.19 95% CI 0.98−1.45 NNH 77), cardiac events (OR 1.72 95% CI 0.72−4.13 NNH 167), and oxaliplatin-related neuropathy events (OR 1.55 95% CI 1.29−1.87 NNH 17).
Conclusions: Patients affected by metastatic colorectal cancer and treated with chemotherapy plus bevacizumab have a significant increased risk of developing severe hypertension, proteinuria, and bleedings. Surprisingly, in our analysis, bevacizumab is not associated with higher onset of thromboembolism events, but it increases the oxaliplatin-related neurotoxicity.

6073 POSTER

Interim analysis of epidermal-growth factor receptor (EGFR) expression in a single-arm, phase II, first-line study (20060314) of panitumumab with FOLFIRI in the management of metastatic colorectal cancer (mCRC)

C. Koehne[1], R. Hofheinz[2], L. Mineur[3], H. Letocha[4], R. Greil[5], J. Thaler[6], E. Gamelin[7], E. Fernebro[8], L. Wright[9], M. Karthaus[10]. [1]*Onkologie Klinikum Oldenburg, Klinik für Onkologie und Hämatologie, Oldenburg, Germany;* [2]*Klinikum Mannheim, III. Medizinische Klinik, Mannheim, Germany;* [3]*Institut Sainte-Catherine, Oncologie Radiothérapie, Avignon, France;* [4]*Central Hospital Västerås, Department of Oncology, Västerås, Sweden;* [5]*Universitaetsklinik f. Innere Medizin III, Onkologie, Salzburg, Austria;* [6]*Klinikum Wels-Grieskirchen, Hämatologie und internistische Onkologie, Wels, Austria;* [7]*Centre Paul Papin, Service d'Oncologie Médicale, Angers, France;* [8]*Lund University, Department of Oncology, Lund, Sweden;* [9]*Amgen Limited, Biostatistics, Uxbridge, United Kingdom;* [10]*Klinikum Neuperlach, Department Hämatologie und Onkologie, München, Germany*

Background: The fully human anti-EGFR monoclonal antibody panitumumab (Vectibix®) is an important monotherapy treatment option for chemotherapy-refractory patients (pts) with EGFR-expressing, *KRAS* wild-type mCRC. Preclinical data show sensitivity of EGFR inhibitors to be linked to EGFR expression as determined by immunohistochemistry (IHC). Thus, EGFR expression has historically been a defining criterion for treatment with an EGFR inhibitor. However, growing clinical evidence suggest that this marker correlates poorly with response, with objective responses observed in pts with no or all levels of EGFR expression.
Material and Methods: Pts with histologically confirmed mCRC receive panitumumab (6 mg/kg) and FOLFIRI every 2 weeks. This Amgen-sponsored study (20060314) is ongoing to evaluate the primary endpoint