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COST OF CARING PATIENTS WITH COLORECTAL CANCER WITH CAPECITABINE VS 5-FU BASED REGIMENS: PRELIMINARY RESULTS OF A NATURALISTIC STUDY

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Introduction and aim: Colorectal cancer (CRC), the third most prevalent cancer worldwide, imposes a significant economic and humanistic burden on patients and society. The aim of this analysis was to evaluate the cost of capecitabine vs conventional strategies (5-FU) for the treatment of metastatic CRC in Italy.

Methods: The study was a naturalistic, multicentre, retrospective longitudinal cost of care (COC) analysis. The study included subjects enrolled from 3 centres. Direct healthcare resources attributable to CRC treatment (drugs, ambulatory care, hospitalisations, diagnostics and laboratory exams) were quantified using prices or tariffs expressed in Euro 2005, as appropriate. The analysis was conducted from the National Health Service (NHS) perspective with a 6 month time horizon. Difference in the COC between capecitabine and 5-FU based regimens was tested using Mann–Whitney *U* test.

Results: A total of 197 (5-FU 99, Capecitabine 98) patients affected by CRC (55.3% male; mean age 63.9 ± 10.1 y.o.) were studied. Total direct cost per patients per month in Capecitabine and 5-FU group were 982 (±419) and 3,265 (±1,025) Euro respectively ($P < 0.0001$).

Discussion: CRC imposes significant burden to the NHS and total direct cost of Capecitabine is significantly lower compared to 5-FU.

SAFETY AND CONVENIENCE OF CETUXIMAB (CET) AND IRINOTECAN (IRI) BOTH GIVEN EVERY TWO WEEKS IN METASTATIC COLORECTAL CANCER (MCRC) PATIENTS (PTS). PRELIMINARY REPORT

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The anti-EGFR monoclonal antibody CET is active in IRI-treated mCRC pts, in combination with IRI in a standard weekly timing of administration. Searching for a more practical schedule and following previous reports [1], we decided to test the safety of a more convenient every 2 weeks (q2w) schedule of combination of CET and IRI.

Pts and methods: From 09/2006 to 02/2007 we have treated 14 pts with histologically confirmed, EGFR-expressing, mCRC with ≥1 bi-dimensionally measurable lesion, ECOG PS ≤2, adequate bone marrow, renal, and hepatic functionality; PS 0–1, M/F: 8/6, median age 54 yrs (range 48–71). All pts were previously treated at least with IRI (FOLFIRI or IRI monotherapy) for metastatic disease. Prevalent sites of disease were liver (10 pts) and lung; median number of previous treatment was 2.5 (range 2–4). CET was given q2w at the dose of 400 mg/m^2 and IRI q2w at dose of 180 mg/m^2; instrumental evaluation was done every two months. A total of 41 cycles (cy) were administered (range 3–10, median 5/pts). The most frequent non haematological toxicity was the skin reaction, globally mild: G1–2: 56% of cy, 6 pts; G3: 12%, 2 pts; none G4. Diarrhoea (G3: 22% cy), vomiting (G3: 17% cy), alopecia (G3: 33%) were superimposable to that of traditional weekly schedule of CET + IRI. Haematological toxicity was also moderate: neutropenia G3 in 25% of cy, anaemia in 18%, PLT-penia in 7%. Globally the compliance of this treatment schedule resulted very high: only 8 cy (17%) were delayed due to gastrointestinal symptoms (5 cy) or neutropenia (3). In summary, CET given q2w in combination with q2w IRI may be a feasible and more convenient schedule of administration. Further experiences will elucidate the possible role of higher doses of CET and the response rate of this modified schedule.

ANALYSIS OF KI-RAS MUTATIONS IN STAGE I RECTAL CARCINOMAS AND RESPECTIVE REGIONAL LYMPH NODES

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Introduction: Many evidences show that there is a significant different distribution into age, gender, tumor progression and response to adjuvant treatment in patients with colon and rectal cancers, which have genetic differences between themselves. For example, it is demonstrated that Ki-RAS mutations are more commonly detected in colon than in rectal cancers.

Methods: To verify Ki-RAS mutations in rectal cancer, a series of 42 alcohol fixed-paraffin embedded stage I (No) primary rectal cancer and respective regional multiple lymph nodes were deparaffined, stained with hematoxylin–eosin and microdissected through LPC. Then they were analyzed through PCR, SSCP and direct sequencing of Ki-RAS mutations.

Results: Six of 42 (14%) of primary tumors analyzed showed a Ki-RAS missense mutation in codon 12 or 13 in exon 2. In 50% (3/6), the mutation was GGT→GAT (Gly→Asp) in codon 12, and the other 50% (3/6) was a GGC→GCC (Gly→Ala) in codon 13. In all cases, the same mutations were confirmed in the respective lymph nodes.

Conclusion: In this work we show that the percentage of Ki-RAS mutations in codons 12 and 13 in rectal cancer are sensibly lower than in colon cancer, providing further evidence that these two kinds of tumors should be considered two different entities. Moreover, we show that the detection in regional lymph nodes of the same mutation of primary tumor might represent an indicator of lymph nodes metastasis in rectal carcinoma not detected in routine histologic examination.

BEVACIZUMAB + FOLFIRI AS FIRST-LINE THERAPY IN ADVANCED COLORECTAL CANCER: A MULTICENTER PHASE II STUDY OF THE GRUPPO ONCOLOGICO DELL' ITALIA MERIDIONALE (PROT. GOIM 2601)

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Background: In a randomised phase III trial, the addition of Bevacizumab (Bev) to Irinotecan (Cpt-11) plus bolus Fluorouracil (FU) and Folinic Acid (FA) (IFL regimen) demonstrated to be more active than chemotherapy alone in untreated advanced colorectal cancer (ACC) patients [1]. The bolus administration of FU-FA is considered inferior to infusional regimen in terms of activity and toxicity. So we started a multicenter phase II study to evaluate the activity and safety of the combination of Bev plus FOLFIRI regimen as first line therapy in ACC patients.

Methods: Untreated patients with histologically/citologically confirmed diagnosis of colorectal cancer entered into the trial if they satisfied the following main inclusion criteria: presence of measurable disease, age ≥18 yrs, performance status ≤2 (ECOG scale), adequate bone marrow reserve and renal and hepatic function, informed written consent. Clinically significant cardiovascular disease and thromboembolic disorders were considered exclusion criteria. The enrolled patients received: Cpt-11 at 180 mg/m^2 on day 1, FA at 100 mg/m^2 as 2 h infusion on days 1–2, FU at 400 mg/m^2 as bolus on days 1–2 plus FU at 600 mg/m^2 as 22 h infusion on days 1–2 (FOLFIRI) plus Bev administered at the dosage of 5 mg/kg. The cycles were repeated every 2 weeks. The first evaluation of activity (RECIST criteria) was performed after 4 cycles.

Results: Up to now 38 patients have been enrolled and 31 are evaluable for activity and toxicity. The main characteristics of the evaluable patients are: M/F 16/15; median PS: 1; primary site (C/R) 20/11; sites of disease: liver 19, lung 11, lymph nodes 8, others 5; single/multiple sites 18/13 (58%/42%). Sixteen PR (52%), 10 SD (32%) and 4 PRO (16%) were observed for an ORR of 52% and a TGCR of 84%. The only grade 3–4 (NCI criteria) toxicities were: neutropenia 16% and thrombocytopenia 3%; five patients (16%) had hypertension but only one was uncontrolled by medical therapy and interrupted the study. One patient (3%) had epistaxis.

Conclusions: Our preliminary results indicate that the addition of Bev to FOLFIRI regimen is an active and well tolerated first-line treatment of ACC patients. The study is ongoing.

BONE MARROW INVOLVEMENT IN ADVANCED COLORECTAL CANCER: A CASE REPORT

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Introduction: The haematopoietic dysfunction in cancer patients represents a widely disparate group of clinical conditions. A diffuse marrow involvement usually occurs at the terminal stage of cancer and is extremely rare as an initial presentation in patients with cancer. Recently, a survey [1] reported in 46 adult age cases, bone marrow metastasis. Primary tumours of this series were as follows: prostate 22 cases, breast 13, lung 5, colon 4.

Materials and methods: A 64 year old man with no previous significant medical problems presented to our Institution with one month long history of low back and left hip pain, and intermittent mild abdominal pain. Remarkable laboratory findings were platelets = 24.000 μl and D-Dimers = 7000 mg. We suspected a metastatic bone marrow involvement and therefore a bone marrow aspiration and biopsy were performed. We documented an extensive marrow infiltration by poorly differentiated adenocarcinoma (positive immunochemistry for CK 20 and negative for CK 7, TTF 1 and PSA). Chest X rays and abdominal CT scan revealed no abnormality. Colonfiberscopy found a colon cancer at 10 cm from anal ridge, poorly differentiated adenocarcinoma with mucus-secreting component in histopathology. Whole body bone scan revealed increased uptake in multiple sites. Whole spine MRI revealed an increase of water content due to watery changes of the bone marrow and replacement of the fat by serous materials.

Results: The patient received combination chemotherapy with oxaliplatin and 5-FU/LV (FOLFOX 4). Before cytotoxic chemotherapy transfused platelets. Recovery of blood counts was evident after 1 cycle. A bone marrow aspiration and biopsy performed after 4 cycles were carried out and revealed normocellular marrow with focal bone sclerosis without neoplastic involvement. At the time of this report, 6 months from the diagnosis, the patient is alive with a good performance status and haematologic findings are stable.

Conclusions: When the physician is confronted by a patient with clinical findings of thrombocytopenia and increased D-Dimers (referred to a disseminated intravascular coagulation) which often occurs in bone marrow metastasis, he must remain vigilant for an additional diagnosis such as prostate, breast, lung or gastro-intestinal cancer. Platelets transfusions coupled with specific treatment of the underlying disease remain the mainstay of therapy for such extensive marrow infiltrative conditions.

CAPECITABINE IN COMBINATION WITH OXALIPLATIN OR WITH IRINOTECAN IN ELDERLY PATIENTS WITH ADVANCED COLORECTAL CANCER: PRELIMINARY RESULTS OF A RANDOMIZED PHASE II STUDY

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Background: Elderly patients (pts) are a special population due to the comorbidities, the altered drug metabolism and the loss of functional capacity, which are associated to an increased drug toxicity. Single-agent therapy is a common practice in elderly pts with advanced colorectal cancer (ACC) and there are not conclusive data in literature on the combination regimens used in these cases. Capecitabine has demonstrated comparable efficacy to bolus 5-FU/FA regimens with clinically safety advantages. The aim of this trial is to evaluate it when combined to oxaliplatin (CAPOX) or irinotecan (CAPIRI) in elderly pts with ACC.

Patients and methods: Pts ≥70 years (yrs) old with histologically confirmed ACC, measurable disease, PS 0–2, and adequate renal, hepatic and bone marrow function were included. Previous chemotherapy for advanced disease, CNS involvement or >3 geriatric syndromes was not allowed. Pts were randomized to receive CAPOX (oxaliplatin 65 mg/m^2 i.v. d1, 8 and capecitabine 1000 mg/m^2 orally bid d1–14; q21) or CAPIRI (irinotecan 80 mg/m^2 i.v. d1, 8 and capecitabine 1000 mg/m^2 orally bid d1–14; q21) until progressive disease, unacceptable toxicity or consent withdrawal. Patients were followed by a geriatric and a quality of life (QoL) assessment with specific scales and EORTC-QLQ-C30 questionnaire.

Results: Sixty-eight pts (of target 94) were analyzed (37 received CAPOX and 31 CAPIRI). Characteristics: CAPOX: median age 75 yrs (range 70–85); PS: 0/1/2 = 21/15/1; prior adjuvant therapy: 28.5%; CAPIRI: median age 74 yrs (range 70–85); PS: 0/1/2 = 18/13/0; prior adjuvant therapy: 22.5%. Safety analysis was performed in all analyzed pts. The most frequent grade 3–4 adverse events were diarrhea (CAPIRI: 19.3%; CAPOX: 14.2%) and neutropenia (CAPIRI: 22.5%; CAPOX 2.8%). No treatment related death occurred. Among evaluable pts (26 in CAPIRI and 31 in CAPOX), one complete response and 9 partial responses were reported in CAPIRI arm (RR: 38.4%); ten partial responses in CAPOX arm (RR: 32.2%). The median response duration was 8.2 months (range 5–11) for CAPIRI and 6 months (range 4–8.4) for CAPOX. Median time to progression and overall survival have not been reached.

Conclusions: The employment of capecitabine given in doublet combination is feasible in the elderly population with ACC. The safety profile of two regimens allows an evaluation with biological agents. Both combinations are active. Final results will be presented at the meeting.

PHASE II TRIAL OF A BIWEEKLY REGIMEN OF FLUOROURACIL AND LEUCOVORIN PLUS IRINOTECAN IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED GASTRIC CANCER

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Introduction: To investigate the therapeutic value and safety of the biweekly regimen comprehensive of 5-fluorouracil (5-FU) and leucovorin (LV) plus irinotecan (CPT-11) in patients with previously untreated advanced gastric cancer (AGC).

Patients and methods: A total of 50 patients (M/F 35/15; median age = 65) with AGC, neither of whom had received chemotherapy for advanced disease, were accrued in this trial. Fifteen patients (30%) were 70 years old or older. At the time of their accrual, cytotoxic chemotherapy, consisting of intravenous LV 100 mg/m^2 (2-hour infusion) followed by 5-FU 400 mg/m^2 (bolus) and 5-FU 600 mg/m^2 (22-hour continuous infusion) on therapeutic days 1 and 2 plus CPT-11 180 mg/m^2 (1-hour infusion) on day 1, was initiated. Treatment courses were repeated every 2 weeks until evidence of progressive disease, unacceptable toxicity or withdrawal of consent.

Results: All the patients were assessable for toxicity and 48 out of 50 for response evaluation, having completed at least four courses of chemotherapy. Complete response was achieved in 2 patients (4%, intent to treat) and partial response in 16 (32%) [overall response rate, 36%; 95% confidence interval (CI): 22%–50%]. Twenty-four patients (48%) had a stable disease and 6 patients (16%) progressed. The median time to progression was 8 months (95% CI: 6–10 months) and median overall survival 14 months (95% CI: 6–22 months). Between the subgroups of patients <70 years old and 70 or older, there were no significant differences in efficacy. One toxic death occurred. Treatment tolerance was generally mild to moderate and easy to treat. The main grade 3/4 toxicities were neutropenia (32%), diarrhea (16%), and anemia (8%). Grade 3–4 neutropenia was the only treatment-related serious adverse event significantly more common in patients older than those aged ≤70 (53.3% vs 22.8%, respectively; $P = 0.03$).

Conclusions: Our data suggest that the biweekly regimen of LV and 5-FU plus CPT-11 in untreated patients with AGC is active with acceptable safety profile. Further evaluation of this regimen seems to be warranted in a phase III trial.

ANALYSIS OF TP53, KI-RAS, AND P16^{INK4A} PROMOTER METHYLATION AS POTENTIAL PROGNOSTIC FACTORS IN PATIENTS WITH COLORECTAL CANCER

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Background: Colorectal Carcinoma (CRC) is one of the most common solid tumor in the western world. Despite the improvement in detection and surgical therapy during last years, the outcome of patients affected by CRC remains limited by metastatic relapse. A large number of studies conducted on the plasma and serum of patients with CRC have shown that such subjects have higher levels of circulating DNA fragments than healthy subjects. The aim of this study was to evaluate the presence of free tumor DNA in the plasma of CRC patients in order to understand its possible prognostic role.

Material and methods: Ki-Ras, TP53 mutations and P16^{INK4A} methylation status were analyzed in tumor tissues and plasma of 66 CRC patients. Besides twenty blood sample of healthy subjects and seven non-neoplastic intestinal tissues were analyzed for the same alterations as control. The analysis was performed using PCR SSCP techniques for K-Ras and TP53 and by Methylation Specific PCR (MSP) for the methylation status of the P16^{INK4A} gene promoter.

Results: In 50/66 primitive tumors (76%) at least one significant alteration was identified in Ki-Ras and/or TP53 and/or P16^{INK4A} genes. Eighteen of 50 patients presented the same alteration both in the plasma and in the tumor tissue. No one of these alterations has been found in the control group. At univariate analysis, Ki-Ras mutations are related to quicker relapse ($P < 0.01$), whereas only a trend towards statistical significance ($P = 0.083$) was observed for the TP53 mutations.

Conclusion: These data suggest that the detection of circulating tumor DNA using the analysis of Ki-Ras and TP53 mutational status is a potential tool for early detection of postoperative CRC recurrence.

MOLECULAR ANALYSIS OF TP53, KI-RAS2 AND P16 METHYLATION STATUS IN TISSUE AND PLASMA OF SUBJECTS AFFECTED BY GASTROINTESTINAL CANCER (GIC)

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Introduction: Gastrointestinal Cancer (GIC) is one of the most common leading cause of cancer-related death in Western society. Despite the advances in the last

years have resulted in improved outcomes for patients, prognosis remain poor and limited by metastating relapse. The aim of this study was to evaluate the existence of circulating cancer cells in patients with GIC to detect the presence of the same genetic alterations in TP53, Ki-Ras2 and P16 in tissue and plasma.

Material and Methods: The analyses were performed on matched tumor tissue and plasma obtained preoperative from 57 patients affected by CRC and 8 affected by Gastric cancer who underwent resective surgery, and plasma obtained from 52 patients during the post-operative period. Besides the same analyses were conducted on a third group of 37 healthy subjects as control. The analysis of Ki-Ras2 and TP53 was performed using the PCR, SSCP techniques and sequencing, P16 methylation status was evaluated using MSP technique (Methylation Specific PCR).

Results: TP53 mutations were found both in the plasma and in the tissue in 9/65 (14%), in 13/65 (20%) only in the tissue and no mutations in both were found in 43/65 (48%). Ki-Ras2 gene was mutated, in 5/65 (8%), both in plasma and in tissue, in 22/65 (34%) subjects were not detected mutations in plasma but only in tissue and in 38/45 (58%) none of them. Methylation status of P16 was analyzed in 36 cases: in 9/36 (25%) P16 was methylated in the tissue, between them 4/9 were methylated also in the plasma (44%). No alterations in TP53, Ki-Ras2 and P16 were found in the control group.

Conclusion: The analyses of genetic alterations of the primary tumors can be an useful tool to understand the possibility to have a metastating relapse and to obtain informations suitable for a better treatment.