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Could delayed coloanal anastomosis (DCA) without derivative stoma improve morbi-mortality after total mesorectal excision (TME) for mid and low rectal carcinoma: a feasibility study

S. Evrard, T. Razafindratsira, F. Leblanc, M. Fonck, R. Brunet, Y. Bécouarn, S. Mathoulin-Pélissier. *Institut Bergonié, Digestive Tumours Unit, Bordeaux, France*

Background: Anastomotic leakage varies between 3 and 25% after TME. Coloanal fistula may lead to the constitution of a pelvic abscess, the loss of the sphincter in case of preoperative radiotherapy. It is the main cause of postoperative mortality and should impair long term results of survival in rectal cancer. A derivative stoma is usually realised after a preoperative radiotherapy which may also bring some complications, a loss of quality of life for the patient and a financial burden for society. Hypothesis: DCA could diminish the rate of fistula without stoma.
Method: Laparoscopy was performed by default. After complete mobilisation of the left colon, a TME was realised. The rectum was cut by endoanal route. Rectum and sigmoid colon were pulled through the anus and resected at the level of the inferior mesenteric artery. 10 cm of colon were exteriorised. 6 days later, the patient was reoperated on. The exteriorised colon was cut and a direct colonanal anastomosis was performed without derivative stoma.
Results: 23 patients were enrolled in this feasibility study. Mean distance between the tumour and the anal verge was 6 cm [3– 10]. 18 (78%) patients had neoadjuvant radiochemotherapy. Laparotomy was chosen in 3 patients respectively for, a T4 tumour, a parietal dehiscence, hepatic lesions. Using laparoscopy (20), conversion rate was 10% (for bleeding). Resection was classified as R0 in 22 cases (95%), R1 in 1 case.
The two main complications were ischemic necrosis of the left colon from both part of the anus. For these two patients, a new mobilisation of the colon was followed by a new DCA with favourable outcome. One had an ischemy of the sole exteriorised colon resolved by the second step of the procedure. A bleeding of the posterior part of the prostate required haemostasis, a slippage of the small bowel behind the descending colon needed repositioning and closure of the mesenteric window; lastly a perimarginal abscess of the buttock was drained during the second step. 4 patients (17%) needed to be reoperated on for complications.
No anastomotic leakage appeared in any patient. No derivative stoma was required even in the cases needing a reoperation for complications. No patient needed a readmission to hospital after the initial discharge.
Conclusion: DCA may lead to a dramatic decrease in morbi-mortality after surgical treatment of mid and low rectal cancers without derivative stoma even after preop chemoradiotherapy. A drastic reduction of the cost may also be expected.

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Capecitabine (C), in combination with irinotecan (I) and oxaliplatin (O) (XELOXIRI) as first-line treatment of metastatic colorectal cancer (MCRC): results of a pilot study by the Gruppo Oncologico Nord-Ovest (G.O.N.O.)

S. Bursi[1], G. Masi[1], F. Loupakis[1], A. Antonuzzo[2], S. Chiara[3], E. Pfanner[4], I. Petrini[4], M.T. Barletta[1], G.G. Baldi[1], A. Falcone[5]. *[1]Az USL 6, Division of Medical Oncology, Livorno, Italy; [2]Az USL 6, Day Hospital of Medical Oncology, Piombino, Italy; [3]IST, Division of Medical Oncology, Genova, Italy; [4]S. Chiara Hospital, Division of Medical Oncology, Pisa, Italy; [5]University of Pisa, Department of Oncology, Pisa, Italy*

Background: The triple drug regimen FOLFOXIRI demonstrated improved Response Rate (RR), secondary R0-surgery on mts, PFS and OS compared to FOLFIRI in a phase III trial by the G.O.N.O. group in MCRC patients (pts). Oral C has similar efficacy compared to 5-FU and therefore it could substitute 5-FU in the FOLFOXIRI regimen thus avoiding a central venous catheter.
Methods: The G.O.N.O. started a pilot study to evaluate escalating doses of C in combination with fixed doses of I, O (XELOXIRI) in metastatic and not resectable CRC pts. The objectives of the study are the determination of the recommended dose (RD) of C in combination with I and O, safety and activity of the combination and analysis of plasma pharmacokinetics. The planned treatment in the first 3 patients was: I 165 mg/sqm over 1-h on day 1, O 85 mg/sqm over 2-h on day 1 and C 2500 mg/sqm/die from day 1 to 7, repeated every 2 weeks. C dose was increased to 3000 mg/sqm/die or decreased to 2000 mg/sqm/die in subsequent groups of 3 to 6 pts on the basis of the observed dose limiting toxicities (DLT).
Results: Up today 40 patients have been enrolled. Main patients characteristic are: gender (M/F) = 28/12, PS (0/1/2) = 34/5/1, age (median/range) = 64/42−76, sites of disease (single/multiple) = 21/19. The DLT was G3−4 diarrhea that was observed in 2 out 6 patients receiving C at 2500 mg/sqm, in 2 out 3 patients receiving C at 3000 mg/sqm and in 1 out 6 patients receiving C at 2000 mg/sqm. This last dose was defined the RD. Among the 30 patients treated at the RD main G3−4 toxicities were: diarrhea 23%, neutropenia 27%, febrile neutropenia 8%, thrombocytopenia 7%, neurotoxicity 3%. One toxic death for diarrhea and sepsis occurred. Up today 26 out of the 30 patients (4 patients too early) treated at the RD are assessable for response (ITT analysis). We observed 18 RP, 5 SD and 3 treatment failures with a response rate of 70% (95% CI: 48−86%). The median follow-up is 10.5 months and median PFS is 9.2+ months, while median OS isn't yet reached.
Conclusions: XELOXIRI is a feasible triple drug regimen with diarrhea being the DLT. The recommended dose of C is 2000 mg/sqm and at this dose-level the observed toxicities are manageable. Preliminary results on activity of XELOXIRI at the RD are promising. The study is still accruing patients and updated results will be presented. Partially supported by Fondazione ARCO.

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Neoadjuvant bevacizumab plus XELOX is feasible in patients with potentially curable metastatic colorectal cancer receiving synchronous resection

B. Gruenberger[1], W. Scheithauer[1], D. Tamandl[2], C. Zielinski[1], J. Schueller[1], T. Gruenberger[2]. *[1]Medical University Vienna, Dept. Oncology, Vienna, Austria; [2]Medical University Vienna, Dept. General Surgery, Vienna, Austria*

Background: Bevacizumab (Avastin®) in combination with standard first-line chemotherapy regimens has become the standard of care in patients (pts) with metastatic colorectal cancer (mCRC). The side effect profile of bevacizumab in pts with metastatic CRC is well established; however, there are limited data on the effect on surgical wound-healing and hepatic regeneration following liver resection.
Methods: Pts with mCRC and liver metastases potentially curable by resection were eligible for this single-centre, non-randomised phase II trial. Eligibility criteria: pts at high risk of early recurrence; synchronous liver metastases; primary non-optimally resectable disease, multiple liver metastases; lymph node-positive primary CRC. Pts received six cycles (3 months) of neoadjuvant XELOX (capecitabine 3500 mg/m^2/day days 1–7 plus oxaliplatin 85 mg/m^2 day 1) plus bevacizumab 5 mg/kg every 2 weeks. The sixth cycle did not include bevacizumab resulting in a gap of 5 weeks between last bevacizumab dose and surgery. The same regimen was reinitiated 5 week after surgery for additional 3 months.
Results: In total, 56 pts have been enrolled and are evaluable having received 6 cycles of therapy and undergone surgery. Ten evaluable pts (4 male, 6 female) with a median age 55 (49–67) years and ECOG PS 0/1 (100%/0%) received synchronous resection of their primary (2 rectum, 8 colon) and the liver metastases. Assessments following neoadjuvant therapy found that all pts with synchronous resection responded, with 4 (40%) complete responses and 6 (60%) partial responses in the liver. All pts underwent potentially curative resection; one pt required a second liver resection due to recurrence. Peri- and post-operative complications are consistent with pts with liver resection only. No pts experienced wound-healing or bleeding complications and no pts required perioperative blood transfusion; median length of hospitalisation was 8 (7–18) days. Only three pts experienced postoperative complications: wound infection, sepsis and anastomotic leak (all n = 1). Eight pts have received adjuvant bevacizumab plus XELOX as scheduled.
Conclusions: These data provide further evidence that bevacizumab in the neoadjuvant setting can be safely administered in pts with metastatic CRC, including those with synchronous bowel and liver resection, without increasing the rate of surgical or wound healing complications or severity of bleeding.

3065 POSTER

Safety and efficacy of sunitinib and FOLFIRI in combination in treatment-naive metastatic colorectal cancer (mCRC): a phase I study

F. Vazquez[1], A. Carrato[1], N. Starling[2], I. Chau[2], P. Hill[3], M.J. Lechuga[4], J. Tursi[4], R. Chao[5], D. Cunningham[6]. *[1]Elche University Hospital, Medical Oncology Service, Alicante, Spain; [2]Royal Marsden Hospital, Cancer Therapeutics, Sutton, United Kingdom; [3]Pfizer Ltd, Sandwich, Sandwich, United Kingdom; [4]Pfizer Italia Srl, Clinical Research Oncology, Milan, Italy; [5]Pfizer Inc., Global Research and Development, La Jolla, USA; [6]Royal Marsden Hospital, Gastrointestinal Unit, Sutton, United Kingdom*

Background: Sunitinib malate (SUTENT®; SU), an oral, multitargeted inhibitor of VEGFRs and other tyrosine kinases, is approved for the treatment of advanced RCC and imatinib-resistant or -intolerant GIST. Inhibition of VEGF in combination with chemotherapy has been shown to improve survival of patients (pts) with mCRC. Thus, the antiangiogenic

activity of SU may augment the antitumour activity of FOLFIRI. In this phase I, dose-finding study, SU in combination with FOLFIRI was investigated in pts with mCRC.
Patients and Methods: Successive cohorts of 3–6 treatment-naive mCRC pts received FOLFIRI (irinotecan 180 mg/m^2, l-leucovorin 200 mg/m^2 and 5-FU 400 mg/m^2 on day 1, followed by 5-FU 2,400 mg/m^2 46-hr infusion) every 2 wks in combination with escalating doses of SU. 2 SU doses (37.5 and 50 mg/d) were investigated with 2 dosing schedules: 4/2 (4 wks on, 2 wks off) and continuous dosing. The primary endpoint was the maximum tolerated dose (MTD), the dose at which $\leqslant$1 in 6 pts experienced dose-limiting toxicities (DLTs), and overall safety of SU in combination with FOLFIRI. Preliminary antitumour activity of the combination regimen was also assessed (RECIST criteria). Data for patients on the 4/2 dosing schedule are reported here.
Results: 13 patients on the 4/2 schedule (7 at 37.5 and 6 at 50 mg/d) were evaluable for safety. No DLTs or grade 3/4 AEs were observed in the first 3 pts in the 37.5 mg/d cohort. 2 of 6 pts in the 50 mg/d cohort experienced DLTs (1 grade 4 neutropenia; 1 grade 4 febrile neutropenia who later developed grade 4 diarrhoea and grade 5 C. difficile infection). Another pt had grade 3 diarrhoea. The 37.5 mg/d cohort was expanded and no DLTs occurred among the 4 additional evaluable pts. The MTD for SU on the 4/2 schedule with FOLFIRI was determined to be 37.5 mg/d. Dose delays in the 37.5 mg/d group were required in 3 pts for a total of 6 cycles delayed by 1 wk. Updated tolerability results will be presented. Initial efficacy data of the two dose groups are shown in the Table.

Response outcomes	37.5 mg/d (n = 7)	50 mg/d (n = 6)
Confirmed PR	4[a]	0
SD	3	6
PD	0	0

[a]1 PR maintained for >6 months.

Conclusions: As of March 2007, data show that SU 37.5 mg/d on a 4/2 schedule in combination with FOLFIRI is tolerable, and shows promising antitumour activity in treatment-naive mCRC pts. Enrolment on the continuous dosing schedule of SU in this combination regimen is ongoing.

3066 POSTER

Exploring first line chemotherapy options in metastatic colorectal cancer (mCRC): nationwide heterogeneity in patient management

K. Field[1], S. Kosmider[1], M. Jefford[2], R. Jennens[2], M. Green[1], P. Gibbs[1]. *[1]Western Hospital, Department of Medical Oncology, Melbourne, Australia; [2]Peter MacCallum Cancer Centre, Department of Medical Oncology, Melbourne, Australia*

Background: In an increasing number of clinical scenarios, numerous chemotherapy (CT) options appear to offer similar outcomes, but there remains an absence of direct comparative trials or adequate phase III data. Potential influences on physician decision making in these contexts include expert opinion, personal experience and marketing influence; treatment practices may carry significant cost impacts. mCRC is such a circumstance; where oxaliplatin- or irinotecan-based CT provides similar efficacy and rates of severe toxicity, but there are a range of regimens, doses and adjunctive treatments. We sought to document the range of decisions made by Australian oncologists in this setting.
Methods: A questionnaire was mailed to all members of the Medical Oncology Group of Australia assessing preference for 1st line CT in pts with mCRC, regimens, doses and adjunctive treatments.
Results: Evaluable responses were obtained from 188 (60%) oncologists and fellows, of whom 162 (51%) managed patients with mCRC. Oxaliplatin-based treatment was the preferred 1st line CT for 150 of the 162 (93%) respondents. 107 (67%) stated preference was based on efficacy; 27 (17%) perceived favourable toxicity profile. A FOLFOX6-like regimen (bolus 5-FU day 1 only) was preferred by 96 (59%), FOLFOX4 by 41 (25%) and XELOX by 14 (9%). Leucovorin doses of 200 mg/m^2 were used by 53 (33%), 20 mg/m^2 by 54 (33%) and 41 (25%) used a fixed 50 mg dose. When using oxaliplatin, 66 (41%) never used calcium and magnesium prophylaxis, 56 (35%) used it in all patients, and 35 (22%) only when neurotoxicity developed.
Conclusions: Substantial heterogeneity exists in the 1st line treatment of pts with mCRC in Australia, with oxaliplatin having a dominant role. While high dose leucovorin is not superior to low dose in phase III studies, many oncologists continue to use high doses. Without the assistance of phase III evidence for calcium and magnesium use, a wide variety of approaches are seen. These data provide a strong rationale for further study in this area and the provision of tools to assist with decision making, including guidelines to allow more uniform management nationwide.

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Irinotecan Metronomic Chemotherapy (MC) in patients with diagnosis of metastatic colorectal cancer (MCRC): clinical, pharmacodynamic (PD) and pharmacokinetic (PK) evaluation

G. Baldi[1], G. Bocci[2], M.T. Barletta[1], A. Fioravanti[2], F. Loupakis[1], P. Orlandi[2], G. Allegrini[1], R. Danesi[2], M. Del Tacca[2], A. Falcone[1]. *[1]Ospedale Civile ASL 6, Oncology, Livorno, Italy; [2]Division of Pharmacology and Chemotherapy University of Pisa, Internal Medicine, Pisa, Italy*

Background: Long-term, regular frequency, low-dose chemotherapy (metronomic/antiangiogenic chemotherapy) has been recently developed. The antitumor effect of the MC with Cyclophosphamide is due to an increase of thrombospondin-1 (TSP-1) plasma level.
Methods: An exploratory study was conducted to assess the feasibility, the activity and the optimal metronomic dose of CPT-11 when administered as protracted continuous infusion (c.i.) in pretreated MCRC. A PD evaluation of anti- and pro-angiogenic factors, such as the TSP-1 and the vascular endothelial growth factor (VEGF) and a PK analysis of the CPT-11 and its metabolites were performed. Three different CPT-11 dose levels have been evaluated: 1.4, 2.8 and 4.2 mg/sqm/day; 25%, 50% and 75% of the maximum CPT-11 tolerated dose in c.i. (5.6 mg/sqm/day), respectively.
Results: Twenty patients entered the study. Patients characteristics were: M/F = 11/9, median age = 71 years (range 51−79); PS 0/1/2 = 8/11/1; median of previous lines of chemotherapy: 3 (range 2−5). No toxicities of grade >1 NCI scale have been observed. Four patients (20%) obtained a stable disease with a median duration of 14 weeks (range 11−20). The antiangiogenic effect of metronomic CPT-11 seems to be suggested by the TSP-1 plasma concentrations that were increased at the CPT-11 1.4 and 2.8 mg/m^2/day schedules (e.g. at day 49, 153.4$\pm$30.1% and 130.4$\pm$9.2% vs. 100% of baseline values before treatment, respectively) and by the initial, but variable, increase in plasma VEGF (e.g. at day 21, 124.4$\pm$41.7% and 132.3$\pm$46.8%, respectively) probably due to the induced hypoxic conditions of tumour. The low, but measurable, levels of plasma CPT-11 and SN-38 reached the Cmax of 277.6$\pm$125.3 ng/ml and 1.62$\pm$0.45 ng/ml (mean$\pm$SD), respectively, at the lowest CPT-11 dose. Interestingly, the SN-38 plasma concentrations were statistically related to TSP-1 plasma levels in the 4 patients with stable disease (P = 0.0062, r = 0.3995).
Conclusions: Plasma SN-38 concentrations were measurable and related to the increase of the antiangiogenic factor TSP-1 that markedly increased during metronomic CPT-11 administration, suggesting a modulation of the angiogenic process MCRC patients. Supported by A.I.R.C and ARCO foundation.

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Capecitabine + irinotecan + bevacizumab as first-line therapy for patients (pts) with metastatic colorectal cancer (MCRC): preliminary phase II study results

S. Beslija[1], M. Banjin[2], S. Jungic[3], N. Obralic[2], G. Kecman-Malcic[3], I. Rakita[3], B. Salkic[2], A. Pasic[2], L. Tinjic[4], E. Ajanovic[5]. *[1]Clinical Center Sarajevo, Institute for Oncology, Sarajevo, Bosnia-Herzegovina; [2]Clinical Center Sarajevo, Oncology, Sarajevo, Bosnia-Herzegovina; [3]Clinical Center Banja Luka, Oncology, Banja Luka, Bosnia-Herzegovina; [4]Hoffmann-La Roche, Business Unit Oncology, Sarajevo, Bosnia-Herzegovina; [5]Hoffmann-La Roche, Medical Department, Sarajevo, Bosnia-Herzegovina*

Background: The oral fluoropyrimidine capecitabine (Xeloda) has improved efficacy, safety and convenience vs. 5-FU/LV in MCRC [Van Cutsem et al. Br J Cancer 2004] and early-stage colon cancer [Twelves et al. NEJM 2005]. A recent study showed that irinotecan + capecitabine q2w is active and well tolerated [Garcia-Alfonso et al. ESMO 2006]. The humanised monoclonal antibody bevacizumab (Avastin) targets VEGF and limits tumour angiogenesis. The addition of bevacizumab to 5-FU/LV/irinotecan (IFL) results in significant improvements in survival among pts with MCRC [Hurwitz et al. NEJM 2004]. Replacing 5-FU/LV with capecitabine in this combination is a logical step forward. Here we report data from an open-label phase II trial of capecitabine + irinotecan + bevacizumab in MCRC.
Materials and Methods: Pts with untreated, histologically confirmed MCRC received irinotecan 175 mg/m^2 i.v. on day 1, capecitabine 1000 mg/m^2 orally bid on days 2–8, and bevacizumab 5 mg/m^2 on day 1 q2w for 12 cycles in the absence of disease progression or unacceptable toxicity. Pts without progressive disease after 12 cycles of capecitabine + irinotecan + bevacizumab continued on the same dose of bevacizumab + capecitabine 1500 mg/m^2 bid on days 2–8, q2w. The primary endpoint was progression-free survival (PFS); secondary endpoints were response rate (RECIST), overall survival (OS), safety and quality of life.
Results: 28 out of 32 pts have been enrolled. Baseline characteristics: male/female 46%/54%; median age 53 years (range 30–70); disease stage