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Phase II study of cetuximab combined with FOLFIRI (bi-weekly irinotecan plus infusional 5-FU and folinic acid (FA)) in patients (pts) with metastatic, Epidermal Growth Factor Receptor (EGFR)- expressing colorectal cancer (CRC)

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Cetuximab (Erbitux) is a chimeric monoclonal antibody targeted against the EGFR with activity in CRC.

Objectives: This phase II trial evaluates the safety and the efficacy of cetuximab combined with a FOLFIRI regimen as first-line treatment for pts with metastatic EGFR-expressing CRC.

Methods: The initial dose of cetuximab was 400 mg/m^2, then 250 mg/m^2 i.v. weekly thereafter. FOLFIRI was administered every 2 weeks: Irinotecan 180 mg/m^2, FA 400 mg/m^2 and 5-FU 300 mg/m^2 bolus plus infusion 2,000 mg/m^2/46h in the low dose (LD) group or 400 mg/m^2 bolus plus infusion 2,400 mg/m^2/46h in the high dose (HD) group. Dose limiting toxicity (DLT) was defined as neutropenia/leukopenia, thrombopenia, alk. phosphatase, bilirubin, ASAT, ALAT or skin toxicity > grade 3; neutropenia with fever/infection, anemia, diarrhea, mucositis, creatinine, or any treatment-related organ toxicity > grade 2 during the first 3 cycles.

Results: 28/33 pts screened (85%) had EGFR expressing tumors. Of these 28 pts, 23 (15 males, 8 females) were enrolled, 10 in the LD group and 13 in the HD group. Median age was 65.4 years (35.9-75.5) and Karnofsky performance status 90 (70-100). All pts were evaluable for DLT. The LD group experienced no DLT, while 3 DLTs occurred in the HD group (diarrhea grade 3, allergy grade 3, neutropenia grade 4). Chemotherapy dose modifications were required in 1/13 pts in the HD group. Almost every pt experienced typical cetuximab-related skin toxicity, mostly of grade 1/2. At abstract submission, 21 pts on 22 were evaluable for efficacy: confirmed PR 9 (43%, C.I., 24-63%), SD 11 (52%), PD 1 (5%). Median TTP was 183 days. 7 out of these 23 patients have been discontinued from the trial for surgery of remaining metastases.

Conclusion: The combination of cetuximab with FOLFIRI is safe, feasible and easy to administer to pts with EGFR-expressing metastatic CRC and is clearly active. Additional patients are currently under recruitment (19 new patients have already been recruited) and will be treated in the HD group before considering a phase-III trial.

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Nordic 5-fluorouracil/folinic acid bolus schedule combined with oxaliplatin (FLOX) as first-line treatment to metastatic colorectal cancer.

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Background: This Nordic multicentre phase II study evaluated the efficacy and safety of oxaliplatin combined with the Nordic bolus schedule of 5-fluorouracil (5-FU) and folinic acid (FA) (FLOX) as first-line treatment in metastatic colorectal cancer. Few studies have reported the use of a pure bolus schedule of 5FU and FA combined with oxaliplatin.

Material and methods: Eighty-five patients had measurable metastatic disease and a WHO performance status of 0-2 (58% WHO 1-2). They were treated with oxaliplatin 85 mg/m^2 as a 2-hour infusion day 1, followed by a 5-min bolus infusion with 5FU 500 mg/m^2 and 30 min later a 5-min bolus infusion with FA 60 mg/m^2. The same dose 5FU and FA were given day 1 and 2, every 2 weeks. Evaluation was done after every 4th course. The primary endpoint was the objective response rate.

Results: Fifty-one out of 79 eligible patients achieved a complete (n= 5) or partial (n= 47) response, leading to an overall response rate of 65% (95% CI 53-73%). Nineteen patients showed stable disease and 9 patients had progressive disease. The estimated median time to progression and survival were 6.9 months and 16.1 months in the intention to treat population. Nine patients (11%) received secondary surgery or radiofrequency ablation with a curative intent. A total of 762 cycles of chemotherapy were given. Neutropenia was the main adverse avent with grade 3-4 toxicity in 45% of patients. Febrile neutropenia developed in only 7 patients. No treatment related deaths were seen. Non-haematological toxicity consisted mainly of neuropathy: grade III was seen in 11 patients, grade II in 27 patients.

Conclusion: Oxaliplatin combined with the bolus Nordic schedule of 5FU/FA (FLOX) is a well-tolerated, effective and feasible bolus schedule as first-line treatment of metastatic colorectal cancer with similar response rate and survival as obtained by more complex schedules.

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Prospective multi-centre audit of acute complications following short course preoperative radiotherapy

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Introduction: Retrospective data has suggested that the risk of early complications following short course preoperative radiotherapy (SCPRT) and total mesorectal excision (TME) for operable rectal adenocarcinoma is related to patient age, radiotherapy field length and time from the first day of radiotherapy to surgery (overall treatment time (OTT)). The aim of this study was to examine these relationships in a prospective multi-centre audit.

Method: Data including patient age, radiotherapy field length, overall treatment time, surgical outcomes and complications occurring within 3 months of the 1st day of radiotherapy were collected on 107 patients treated at four radiotherapy centres between 1st October 2001 and 31st September 2002. These were compared and combined with the previously studied cohort of 176 patients treated at one centre between 1st January 1998 and 31st December 1999.

Results: In the prospective cohort (n=107) only age (p=0.001) was significantly associated with acute complications. However, both the OTT (median 9.0 vs 11.0 days p<0.0001) and field length (median 16.6 vs 17.0 cm p=0.03) were significantly shorter in this cohort. In patients from both studies (n=283) increasing age (p=0.001) and field length (independent of operation type) (p=0.02) were associated with an increased risk of acute complications.

Conclusions: Patient selection and radiotherapy technique remain important in minimising acute complications following SCPRT. Data from the Dutch TME trial suggesting an increase in 180-day mortality with increasing OTT in addition to retrospective data may be responsible for the shorter interval between radiotherapy and surgery seen in this prospective study.

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Tegafox, a new combination of UFT/LV and oxaliplatin as first line treatment for patients (pts) with non resectable metastatic colorectal cancer (CRC): results of a completed multicenter phase II.

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Rationale design: The phase I dose escalation study of UFT®/LV in combination with oxaliplatin [ASCO 2001, Abstract no. 572] established UFT® 300 mg/m2/day d1-14, LV 90 mg/day d1-14 and oxaliplatin 130 mg/m2/day d1 every 3 weeks as the recommended phase II doses in first line non operable metastatic CRC pts. Between February 2002 and July 2002, 64 pts with bidimensionally measurable non operable metastatic CRC were enrolled in this phase II study testing this regimen as first line treatment.

Objectives: To evaluate the efficacy (Objective Response Rate) and the safety of this regimen.