synergistically with mitomycin C (MMC), the following randomized phase II study using a "pick the winner" design was undertaken.

Methods: 68 patients with ACC cancer who, had received prior palliative 5-FU/leucovorin-based chemotherapy were randomized to either CPT-11 120 mg/m^2 on days 1 + 15 plus MMC 8 mg/m^2 on day 1 (arm A) or oxaliplatin 85 mg/m^2 on days 1 + 15 plus MMC 8 mg/m^2 on day 1 (arm B); in both treatment arms, courses were repeated every 4 weeks.

Results: 57 patients are presently evaluable for treatment response and toxicity. The objective response rate in arm A is 7/30 (23.3%; 95% confidence interval [CI], 9.9 to 42.3%) as compared to 5/27 in arm B (18.5%; 95% CI, 6.3 to 38.1%). Median time to progression and overall survival have not been reached yet. The regimens were not equitoxic as indicated by the incidence of severe adverse reactions requiring dose reductions (40% vs. 11%), treatment delays (25 vs. 10 courses), and early discontinuations (27% vs. 11%) in arm A and arm B, respectively. The most common toxicities in arm A were granulocytopenia (83%), thrombocytopenia (47%), diarrhea (53%), emesis (53%) and alopecia (97%). In arm B, common toxicities included granulocytopenia (56%), thrombocytopenia (74%), emesis (59%) and peripheral neuropathy (41%).

Conclusion: Both combination regimens seem to be effective in 5-FU/LV pretreated patients with ACC, though the observed response activities do not seem to exceed the single agent activity previously reported for CPT-11 and oxaliplatin alone.

226 POSTER

Preoperative chemoradiation plus intraoperative presacral electrons in T3–4 Nx M0 primary rectal cancer: Early single institution experience

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Purpose: Intense local therapy including intraoperative electron radiotherapy (IOERT) and preoperative chemoradiation has been explored in locally advanced rectal cancer to induce tumor downstaging and promote pelvic disease control.

Materials and Method: From 4/95 to 12/99, 43 T3–4 Nx M0 50 primary rectal cancer patients have been treated with preoperative radiotherapy (45.0 to 50.4 Gy) and simultaneous 5FU (500–1000 mg/m^2 days 1–4 and 22–26) or oral Tegafur (1200 mg/day continous daily through 1 to 28 of radiotherapy). Radical surgery was performed 4 to 6 weeks after the completion of induction tratment and IOERT (10 to 15 Gy) was added to the presacral region. Adjuvant chemotherapy using 5FU and Leucovorin (4 to 6 cycles) was recommended.

Results: Tolerance to treatment was acceptable. Median age was 65 years (range 36–82). There were 34 males and 16 females. Tumor distance from anal verge was less than 5 cm in 15 (30%). Tumor downstaging pathologic findings were: 10 T1, 19 T2, 21 T3–4, 38 N0 and 12 N+, 22 T mic. Sphincter preservation has been achieved in 32 (64%) patients. Median follow-up time is 17 moths. Pelvic tumor control rate is 97%.

Conclusions: Intense local therapy as described is feasible, acceptably tolerated and able to induce significant tumor downstaging effect and encouraging disease control results in primary locally advanced rectal cancer. Up-dated results will be presented.

227 POSTER

A prospective comparison of in-patient versus outpatient DeGramont therapy: Using quality of life, acceptability and response measures: A pilot study

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Purpose: Randomised trial data suggest that the 'DeGramont' regimen (DEG) is now the optimal method of administering 5-Fluorouracil (5FU) and folinic acid (FA) for colorectal cancer. However, the regimen requires hospitalisation for 48 hours, every 2 weeks. As part of a feasibility study for a large UK multicentre trial, we initiated a pilot study to compare cost-evaluation and clinical effectiveness of the inpatient (IP) versus outpatient (OP) DEG.

Method: Central line insertion (CLI) for OPs was a day-case procedure by trained nurses. Compliance, costs, response measures and face-to-face quality of life (QOL) were measured in 26 patients given the choice of 12 courses of either IP or OP DEG.

Results: 13 patients were enrolled into each arm. Failure of compliance for the first 6 cycles occurred in 54% IPs compared with 8% OPs ($p = 0.001$). After 12 cycles of DEG 92% OP and 50% IP had stable disease ($p = 0.01$). OP costs were estimated at 50% of bed costs. Treatment delays were significantly more common in IPs mainly due to bed shortages. QOL was significantly superior in OPs.

Conclusion: Three key requirements to convert IP to OP were identified: CLI, prefilled disposable elastomeric infusors; education of patients and/or carers on changing infusors. Factors determining feasibility of OP DE include availability of CLI, patient and clinical preference. We conclude although OP DEG is practical, cost effective and offers considerable QOL benefits, some patients and hospitals may still need IP delivery.

228 POSTER

Disease oriented treatment of metastatic colorectal cancer (CRC) with dose-dense 5-FU/Folinic acid (FU/FA) combination chemotherapy

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Treatment of metastatic CRC remains a palliative approach, which should emphasize on quality of life and survival prolongation. Continuous infusion of FU in CRC has been found to be equally effective as FU-Bolus but with significantly reduced hematological and peripheral toxicity. FU as weekly 24-hours continuous infusion up to 2600 mg/m" combined with high-dose FA provides a 3-fold increased dose intensity compared to standard bolus FU/FA protocols, an increased frequency of tumor cell targeting, a favorable toxicity profile and activity in FU/FA pretreated patients. This type of short term and high dose administration of FU was chosen for disease oriented treatment: chemotherapy in case of documented progression (UICC-criteria, including tumor related symptoms), no treatment with stable disease, defined as identical results in two consecutive follow-up procedures. A treatment free progression interval (TFPI) of >5–6 months resulted in administration of the previous protocol, otherwise change to a different combination. Protocols: FU/FA: weekly FA 500 mg/m"/2–4 hrs + FU 2.500 mg/m"/24-hrs; LIF: FU/FA + alpha-Interferon 9 mio I.E. day 1 before FU; MFL: FU/FA + Mitomycin 5–6 mg/m"/24-hrs on day 2. Time schedule: 6 wkly treatments > restaging > continuation for additional 6 wks if no progression of disease > restaging. Patients profile: 115 pts.; median age: 63.4 (37–76); m/w: 74/41; ECOG-Status: 0: 38, 1: 67, 2: 10. Immediate response to treatment (after 12 wkly treatments): CR: 12.6%, PR: 32.2%, NC: 39.1%, PD: 11.5, ND (disease not measurable): 4.6%; response after one TFPI: CR: 4.6%, PR: 13.6%, NC: 43.7%, PD: 29.9%, ND: 8.0%. Median duration of TFPI: 5.0 months (range: 3–27). Median survival in months: all pts: 23.4; no TFPI: 11.0; 1 to n TFPI,s of >3 months: 31.0. Toxicities: no grade III/IV hematologic toxicity, 6/115 with grade III diarrhea, 22/115 with a reversible hand-foot-syndrom and LIF.

Conclusions: disease oriented chemotherapy improves the prognosis for the majority of pts. with metastatic CRC. This strategy focuses for the first time on the patient,s individual tumor biology. Short duration, high dose intensity and frequency of FU administration seems to be essential. Implementation of new drugs (CPT-11, Oxaliplatin) will have additional benefit.

229 POSTER

Prevention and treatment of carcinomatosis from colorectal malignancy

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Background: At the time of surgical exploration of the abdomen, approximately 10% of colon cancer patients will be found to have peritoneal seeding. Also, approximately 30% of patients will have disease recurrence within the resection site or on peritoneal surfaces. Phase II studies of peritonectomy procedures and intraperitoneal chemotherapy using mitomycin-C and 5-fluorouracil were employed in an attempt to change the outcome of this clinical situation from a terminal event to long-term survival.

Methods: Patients with primary or recurrent colorectal cancer with peritoneal seeding were evaluated using the Peritoneal Cancer Index (PCI). This is a quantitative prognostic indicator that uses nodule size and distribution to arrive at a numerical score. Also, a Completeness of Cytoreduction Score (CC) based on the extent of cancer following an aggressive cytoreduction was utilized. Other parameters were statistically evaluated.

Results: The PCI was shown to be a prognostic indicator capable of accurately predicting the results of these aggressive treatments ($p < 0.0001$). Also, the CC score had predictive value ($p < 0.0001$). Patients who had carcinomatosis treated in conjunction with a resection of their primary colon cancer showed statistically improved survival over those treated m the setting of recurrent colorectal cancer ($p = 0.02$).

Conclusions: These studies show that peritoneal carcinomatosis can be treated with curative intent. Selection of patients is of utmost importance in these patients requiring aggressive and expensive interventions. Treating carcinomatosis concomitantly with the primary cancer showed benefit with minimal additional morbidity and mortality.

230 PUBLICATION

The prognostic significance of elevated serum CA19-9 level in patients with metastatic colorectal cancer

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Purpose: This study was undertaken to evaluate the prognostic influence of serum CA19-9 level on the survival of patients with metastatic colorectal cancer.

Methods: Serum tumour markers CA19-9, CEA and five other major clinical parameter were prospectively collected for 238 patients at time of diagnosis of unresectable metastatic colorectal cancer. The Cox Proportional Hazard Model was used for multivariate analysis to evaluate the prognostic significance of CA19-9, CEA, LDH, alkaline phosphates, tumour differentiation, ECOG performance status, chemotherapy treatment (leucovorin/5FU) on survival time of patients.

Results: In multivariate analysis, an elevated CA19-9, poorly differentiated tumour histology, poor ECOG performance and absence of chemotherapy treatment were independently adverse prognostic indicators for survival For 101 patients with CA19-9 less than 35 at diagnosis of unresectable metastases, the median survival was 23 months as compared to a median survival of 9 months for another 137 patients with CA19-9 greater than 35 ($p = 0.0011$).

Conclusion: Clinical trials in metastatic colorectal cancer should include CA19-9 as one of the pre-treatment prognostic factors.

231 PUBLICATION

Screening for HNPCC-focussing on families

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HNPCC accounts for about 5% of all colorectal cancers (CRC). HNPCC families are characterised by an increased incidence of extraintestinal cancers as well. Conventional screening stategies focus on patients with CRC. We tried to establish a screening program focussing on families.

Methods: Standardized interview including familial pedigree of patients undergoing colonoscopy in a medical referral center. Malignancies within the families were documented and criteria associated with an increase of familal clusters (>3, Clu+) of HNPCC like tumors (tC) were looked for. (fisher's test).

Results: 463 screened, 1/463 fulfilled Amsterdam criteria, 6/463 Bethesda criteria, 71 showed clusters. The presence of one person within a family diagnosed with cancer at an age < 55 yrs (age+) was closely associated with Clu+: 86/463 age+, 39 (8.4%) of whom cluster + ($p = >0.0001$, fisher's test).

Conclusion: 1) Standard criteria fail to identify families with clusters of tC. 2) Diagnosis of a tC at an age < 55 yrs is strongly associated with Clusters of tC within a family suggesting screening for HNPCC.

232 PUBLICATION

'Tomudex' (raltitrexed) plus 5FU combination treatment for patients with advanced colorectal cancer: A Phase I study

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Objectives: 'Tomudex' (raltitrexed) and 5FU both have clinical activity as single agents in the treatment of advanced colorectal cancer, and preclinical studies have demonstrated a schedule-dependent synergism between these agents, with high antitumour activity when 'Tomudex' is administered prior to 5FU. Therefore, a Phase I trial of 'Tomudex' combined with 5FU was initiated in patients with metastatic colorectal cancer.

Methods: 5FU (24-h infusion) was administered weekly at the following dose levels (mg/m[2]): 1200 (level 1), 1600 (level 2), 2000 (level 3), 2400 (levels 4 and 5), 2800 (level 6) and 2600 (level 7). 'Tomudex' (15-min infusion) was administered on days 8 and 29, 15-min prior to 5FU, at a dose of 2.6 mg/m[2] (levels 1–4 and 7), or 3.0 mg/m[2] (levels 5 and 6). Each cycle consisted of 5 weeks' treatment followed by 1 weeks' rest. Pharmacokinetics of 5FU were obtained at week 1 (without 'Tomudex') and week 2 (after 'Tomudex') in cycle 1.

Results: To date, 35 patients have been entered and have received a total of 82 cycles of treatment. No DLT occurred at dose levels 1–4. At dose level 5 ('Tomudex' 3.0 mg/m[2]; 5FU 2400 mg/m[2]), 2/3 female patients had DLT (grade III diarrhoea and thrombocytopenia, and grade, IV leucopenia and thrombocytopenia; the latter died of lethal septicaemia in week 6), whereas, the 3 male patients had no DLT. No DLTs were experienced by the 6 male patients entered at dose level 6, although 4 withdrew due to nonDLT events. 6 patients (5 F/1 M) entered at dose level 7 are not yet evaluable. Coadministration of 'Tomudex' resulted in a significantly increased 5FU C[max] and AUC in week 2 compared with week 1 ($p = 0.007$ and 0.03 respectively; 2–6 patient samples analysed per dose level). Of 16 patients on dose levels 3–6 evaluable for response, 9 (56%) have achieved a partial response.

Conclusions: The likely recommended dose is 2.6 mg/m[2] for 'Tomudex' and 2600 mg/m[2] for 5FU. This regimen of 'Tomudex' and 5FU demonstrated promising activity and manageable toxicity and will be evaluated in a Phase II trial.

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233 PUBLICATION

'Tomudex' (raltitrexed) plus 5-fluorouracil: A promising option for the treatment of patients with metastatic colorectal cancer

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Objectives: 'Tomudex' (raltitrexed) is a specific inhibitor of thymidylate synthase with activity in advanced colorectal cancer. Synergy has been demonstrated in cancer cell lines when 'Tomudex' is followed 24 h later by 5FU. Therefore, in this Phase I dose-escalation study, patients with metastatic disease, who had failed 5FU or CPT-11, were administered 'Tomudex' followed 24 h later by 5FU (bolus injection), once every 3 weeks.

'Tomudex'/5FU dose (mg/m^2)	OR n	SD n	PD n	DLT n	Mean 5FU AUC (SD) (μM/min)
0.5/900	1PR[a] 1	1	0	10498 (1119)	
1.0/900	0	2	1	0	9176 (611)
1.5/900	0	2	1	0	5362 (2591)
2.0/900	1PR[a]	1	1	0	6794 (1167)
2.5/900	0	3	0	0	19593 (6074)
3.0/900	1CR	0	2	0	16360 (1452)
3.0/1050	0	1	2	0	20979 (6046)
3.0/1200	1MR[a]	1	2	0	20770 (5178)
3.0/1350	1PR[a]	2.	1	3 – nadir fever	20377 (1063)
3.5/1200	0	1	2	0	22801 (8269)
4.0/1200	0	2	3	1 – nadir fever	16880 (3628)
4.5/1200	0	2	1	0	20748 (7539)
5.0/1200[b]	0	2	1	1 – neutropenic fever	NA
Total	5	20	18		

[a]pt previously failed 5FU therapy; [b] 3 pts not yet evaluable for response

Methods/Results: No pt had a DLT at doses ≤3.0/900 mg/m^2; therefore the 5FU dose was increased. At 3.0/1350 mg/m^2, 3/4 pts experienced DLT; the 5FU dose was therefore maintained at 1200 mg/m^2 while the 'Tomudex' dose was escalated. The combination had a manageable toxicity profile, the most common toxicity being short-lived, non-dose-limiting neutropenia (without fever). 5/43 (12%) pts had an OR and 20/43 (47%) had SD. The median survival was 14.3 months (95% CI 11.7, 21.9). 'Tomudex' increased the AUC of 5FU at doses >2.5 mg/m^2.

Conclusions: The median survival in this preliminary study compares favorably with other second-line regimens, including CPT-11 (9.5 months) and oxaliplatin/5FU (7–17 months). These results suggest that this 'Tomudex'/5FU combination has a manageable toxicity profile, and is a potential attractive option for improving palliation and survival in heavily pre-treated pts.

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