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Mature results from the 'Tomudex' (raltitrexed) comparative study in advanced colorectal cancer (ACC)

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Purpose: To compare 'Tomudex' (raltitrexed) a new direct, specific thymidylate synthase (TS) inhibitor with 5 Fluorouracil (5FU) plus high dose Leucovorin (LV) as first line treatment for Advanced Colorectal Cancer (ACC).

Methods: 495 patients with ACC were randomised to receive either raltitrexed 3 mg/m^2 once every 3 weeks or 5FU 400 mg/m^2 plus LV 200 mg/m^2 daily x 5 every 4 weeks.

Results: Following a mean treatment duration of 16 weeks for raltitrexed and 19 weeks for 5FU/LV, no statistically significant differences were seen in objective tumour response rates (19% raltitrexed v 18% 5FU/LV) or survival (median 10.7 mths raltitrexed v 11.8 mths 5FU/LV, hazard ratio = 1.13; 95% CI 0.87 to 1.45 $p = 0.36$) at 9 months follow up (approximately 50% patient deaths). Patients in the raltitrexed group had significantly less WHO grade 3 or 4 mucositis (2% v 16%), less leucopenia (6% v 13%) and diarrhoea (10% v 19%). Transaminases were elevated in 13% of raltitrexed patients. These rises have been observed in previous studies and do not result in any clinical sequelae. Both treatment arms demonstrated palliative benefits including improved performance status and disease related symptoms.

Conclusion: Raltitrexed is a new, effective single agent in the first line treatment of ACC, demonstrating comparable survival and response rates to 5FU plus high dose LV. Raltitrexed also shows an improved toxicity profile, similar palliative benefits and a more convenient 3 weekly dosing regimen than 5FU based regimens.

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Quality of life advantages demonstrated for patients receiving Tomudex compared with those receiving 5-fluorouracil plus leucovorin (5 FU+LV) in the treatment of advanced colorectal cancer (ACC)

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Purpose: Quality of Life (QoL) is a major component of palliative care and an important factor demonstrating the impact of treatment. Recent reports have indicated that, compared with best supportive care alone, 5FU-based therapy can improve the QoL of ACC patients. This study compared the impact of 'Tomudex' (raltitrexed) and 5FU+LV on the QoL of patients with ACC.

Methods: In this large international Phase III trial, 246 patients with ACC were randomised to 'Tomudex' 3 mg/m^2/IV/3 weeks and 249 patients to 5FU+LV 400 mg/m^2 bolus IV and 200 mg/m^2 IV daily 5/4 weeks (Machover regimen). QoL was assessed prior to treatment, then at weeks 2, 5, 10 and 15 using the RSCL and EQ5D instruments. In addition, patients were evaluated for toxicity. Patients were followed up for 9 months minimum.

Results: Instrument completion rates were between 90% at baseline to 64% up to week 20. Actual numbers after that timepoint were lower and are not included in this comparison. At week 2 ie during the first cycle of treatment, significant differences were seen in favour of 'Tomudex' in 3 of the 4 dimensions of the RSCL (physical symptoms $p < 0.001$, activity levels $p = 0.011$ and overall quality of life $p < 0.001$) and indicated differences in psychological symptoms ($p = 0.0503$), and in 5 of the 8 dimensions of the EQ5D (mobility $p = 0.019$, usual activities $p = 0.002$, general health state $p = 0.003$, mean health state VAS score $p < 0.001$ and mean index value $p = 0.046$.) There were no other significant differences between the 2 arms up to week 20. Earlier analysis of predefined RSCL toxicity symptoms showed significant advantage for 'Tomudex' at weeks 2, 5 and 10 ($p < 0.001$, $p = 0.046$, $p = 0.487$ respectively) and this was supported by the difference in the incidence of WHO grade 3/4 toxicities during cycles 1, 2 and 3 and fewer 'Tomudex' patients requiring dose reduction or delay (25.3% 'Tomudex' vs 43% 5FU+LV).

Conclusion: 'Tomudex' maintained QoL significantly better than did the Machover regimen during cycle 1 of therapy, coinciding with the advantageous toxicity profile of 'Tomudex' compared with 5FU+LV at that time. 'Tomudex', therefore can provide benefits in terms of improvements in QoL in the treatment of ACC and in addition has a more convenient dosing schedule.

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Adjuvant chemo-radiotherapy of rectum carcinoma: Comparison of 12 months vs. 6 months chemotherapy

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Purpose: Postoperative chemo-radiotherapy has been established as standard treatment for stage B and C rectum carcinoma. However, it is not yet established for what time period chemotherapy should be continued.

Patients and Method: From 1993 until 1996 188 patients with surgically resected rectum carcinoma Dukes B2–3 and C received local radiotherapy (45 Gy) and were randomly assigned to therapy with folinic acid 100 mg/m^2 plus 5-fluorouracil 450 mg/m^2, day 1–5 every 4 weeks for 12 cycles and 6 cycles, respectively.

Results: After a median follow-up time of 3 years and 2 months no significant difference concerning disease-free survival ($p = 0.6$) and survival ($p = 0.9$) was observed.

Conclusion: Although the early interim analysis does not allow definite conclusion the preliminary data suggest that adjuvant chemotherapy for 12 months is not superior to 6 months.

1101 ORAL

Radiochemotherapy for carcinoma of the anal canal

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Purpose: This prospective study was set up in 1985 to evaluate treatment of anal cancer by combined radiation and chemotherapy (RCT). We now can report our results achieved with a single protocol which has been unchanged for over 10 years.

Methods: Between 1985 and 1996, 62 patients with epidermoid carcinoma of the anal canal were treated by a protocol of RCT with 5-FU and MMC. No patient had surgery as primary treatment. Only biopsies were taken for histological examination. RT was delivered with 10 MV-photons in single fractions of 1.8–2.0 Gy/day for 5 days a week over 5 weeks up to a median dose of 50 Gy. 5-FU was administered on day 1–4 in a dose of 1000 mg/m^2/24 h and on day 29–32, the second course being adjusted to the extent of treatment toxicity. MMC was given on day 1 as a bolus of 10 mg/m^2 and on day 29 in accordance to treatment toxicity.

Results: The tumour specific survival, NED-survival and local tumour control rate were 78%, 76% and 85% after 5 years. Significant prognostic factors for all 3 endpoints were the T-category (T1/2 vs T3/4) and the lymph node status (N0 vs. N1–3). The total 5-FU dose had a significant influence on tumour specific survival (>6 g: 70% vs. < = 6 g: 46%, $p = 0.02$). An APR for local failure was carried out in 7 patients. No patient had an APR for toxicity reasons. Severe acute toxicity was observed in some patients (enteritis WHO-grade 3 in 39% and grade 4 in 2% as well as leukopenia grade 3 in 24% and grade 4 in 2% of our patients). A late toxicity grade 3 (acc. to Eschwege) was noted only in 3% of the patients.

Conclusion: RCT is an effective treatment for all stages of anal carcinoma. Quality of life can be maintained in most cases by preservation of anorectal function.

1102 ORAL

Interim report on toxicity and compliance of the FOGT-1 and FOGT-2 trials for adjuvant postoperative therapy in colon- and rectal cancer

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Purpose: FOGT has initiated two prospective controlled randomized trials to improve adjuvant therapy of colon cancer stage UICC II/T4NOM0 and III (FOGT-1) and rectal cancer stage UICC II and III (FOGT-2). This interim report analyses toxicity and acceptance of the three treatment arms.

Methods: "Standard group" (ArmA) consists of 5-FU+levamisole, (LEV, Ergamisol^R). In ArmB 5-FU is modulated by Folinic Acid (FA, Rescuvolin^R) (5-FU+FA+LEV), in ArmC with Interferon alpha (IFNa, Roferon^R) (5-FU+IFNa+LEV). Rectal cancers, in addition, were irradiated with 54 Gy. Chemotherapy doses are adjusted to toxicity, if toxic events >

WHO 2 occur. Until 10/96, 56 hospitals have recruited a total of 946 pts. (FOGT 1 521 pts., FOGT 2 425 pts.). Toxicity and discontinuance rates were noted.

Results: Among the 839 pts. evaluable according to "intention to treat" (FOGT-1: 464, FOGT-2: 375), a toxic event > WHO2 occurred in 139 (17%), and treatment was stopped in 177 (21%). Toxicities > WHO2 in FOGT-1 A, B, C were 5%, 7%, 21%, in FOGT-2 20%, 16%, 38%, respectively. Discontinuance rates in Arms A, B, and C of FOGT-1 were 23%, 17%, 25%, and 20%, 20%, 23% in FOGT-2, respectively. Treatment was stopped in Arms A, B, C because of toxicity or patient's demand in 11%, 8%, 16% in FOGT-1 or 7%, 13%, 10% in FOGT-2, respectively. The overall discontinuance rate due to toxicity or patients' demand was 11%. Toxicity in ArmC seemed to be higher, and was mainly due to leukopenia and diarrhea.

Conclusion: The rate of discontinuance is within those of other trials, e.g. the Intergroup Studies (Laurie 1990, Moertel 1990), so that FOGT-1 and FOGT-2 trials are safe and acceptable concerning toxicity and patient compatibility.

1103 ORAL

Adjuvant chemotherapy in Dukes' B and C colorectal cancer. A cost-effectiveness analysis

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Purpose: Adjuvant chemotherapy (ACT) is now standard practice in the treatment of Duke's C colorectal carcinoma (CRC) and this has increased the financial burden on health care systems world-wide. This study was initiated to clarify the cost-effectiveness of this therapy.

Methods: Between 1993 and 1996, 95 patients (Dukes' B and C) in northern Norway were included in a national randomised CRC study, and assigned to surgery plus adjuvant chemotherapy or surgery alone. In April 1996, 94 patients were evaluable and 82 still alive. The total treatment costs were calculated and a questionnaire for assessment of the quality of life (QoL) was mailed to all survivors. 62 responded.

Results: ACT raised the total treatment costs by £3,360. The median QoL was 0.83 (0–1 scale) in both arms. Employing a 5% discount rate and an improved survival of ACT ranging from 5–15%, we calculated the cost of one quality adjusted life year (QALY) to be between £4,800 and £16,800.

Conclusion: Using a cut-off point level of £20,000 per QALY, ACT in CRC appears to be cost-effective only when the improvement in 5-year survival is ≥5%. ACT does not affect short-term QoL.

Clinical pharmacology and phase I studies

1104 ORAL

A phase I study with S-1, an oral 5-FU formulation, in patients with solid tumors

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S-1 is an oral formulation of Tegafur (FT), a prodrug of 5-FU, combined with a dihydropyrimidine-dehydrogenase (DPD) inhibitor and oxonic acid (molar ratio 1: 0.4: 1), which inhibits 5-FU phosphoribosylation in the GI-tract. We determined the maximum tolerated dose (MTD), side-effects and pharmacokinetics (PK) of S-1. 23 patients (pts) with solid tumors (including 6 colorectal and 4 gastric), mean age 53 yr., median PS 1, received cycles consisting of S-1 administration during 4 weeks followed by 1 week rest. Doses of 25, 45, 35 and 40 mg/m^2 b.i.d. were successively studied in 6, 5, 6 and 6 pts resp., receiving 23, 5, 12 and 6 cycles evaluable for toxicity. The side effects were mild at 25 mg/m^2. At 45 mg/m^2 diarrhea (grade (G) 3 in 1 pt, G4 in 2 pts), anorexia (G3 in 1 pt, G4 in 1 pt) and fatigue (G3 in 2 pts) were dose limiting toxicities (DLTs). No severe toxicity was observed at 35 mg/m^2. At 40 mg/m^2 diarrhea was the DLT (G3/nausea G3 in 1 pt, G4/vomiting G4 in 1 pt). One tumor regression was observed in a pt with gastric cancer, while 13 pts are still on study. 5-FU levels reached a plateau of 0.3–2 μM after 1–2 hr; uracil levels, indicative for DPD inhibition, increased from 0.1 to 1–10 μM. In conclusion, 40 mg/m^2 b.i.d. is the MTD of S-1 with diarrhea as the most important DLT. Effective DPD inhibition results in cytotoxic 5-FU plasma levels. Phase II studies with S-1 will be performed in colorectal and gastric cancer.

1105 ORAL

A comparison of clinical pharmacodynamics of different administration schedules of oral topotecan (TPT, Hycamtin®)

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Purpose: In vitro and in vivo experiments indicated that prolonged exposure to TPT yielded the best anti-tumour efficacy. An oral formulation was developed to conveniently enable treatment schedules aiming at prolonged exposure. Bioavailability in man is 32–44%.

Methods: We performed phase I studies with once daily (OD) × 5 (29 patients (pts)), OD × 10 (19 pts), twice daily (BID) × 10 (20 pts), and BID × 21 (131 pts) schedules. Pharmacokinetic studies were performed in 55 pts.

Results: Dose limiting toxicities were observed at total daily doses of 2.7 mg/m^2, 1.6 mg/m^2, 1.6 mg/m$_2$, and 1.2 mg/m^2 respectively, and consisted of myelosuppression with OD × 5, myelosuppression and diarrhea in both 10 day schedules, and diarrhea in the 21 day schedule. AUC(t) lactone TPT was consistently higher on day 4 (OD × 5) and day 8 (10 and 21 days schedule), respectively. Intrapatient variation was (59.5 ± 51.0%) with the BID × 21 schedule (N = 13) (96.5 ± 70.1%) with BID × 10 (n = 10), (34.5 ± 25.0%) with OD × 10 and (25.4 ± 31.0%) with the OD × 5 schedule (n = 22).

The correlation between the AUC(t) day 1 TPT and the percentage of decrease of leucocytes is significant in 3 schedules of administration with correlation coefficients of R = 0.76 (p = 0.001) (OD × 5), R = 0.69 (p = 0.03) (BID × 10), and R = 0.66 (p = 0.03) (BID × 21). A similar trend was found in OD × 10 schedule with R = 0.61 (p = 0.06). The correlation with the percentage decrease of platelets was R = 0.78 (p = 0.03) (BID × 10), R = 0.83 (p = 0.01) (OD × 10), and R = 0.60 (p = 0.004) (OD × 5).

AUC per course was calculated by multiplying AUC observed after a single dose by the number of doses given per course. At MTD the resulting AUC per course did not show significant differences between schedules, being: 107.4 ± 33.7 (OD × 5), 145.3 ± 23.8 (OD × 10), 100.0 ± 41.5 (BID × 10), and 164.9 ± 92.2 (BID × 21), respectively. For all schedules a significant correlation between the AUC(t) per course of the lactone form of TPT and parameters of myelotoxicity was found, with comparable sigmoidal relationships versus percentage decrease of WBC.

Conclusion: Schedule rather than AUC per course appears to be related to the type of toxicity of oral TPT. Toxicity shifts from diarrhea with BID × 21, through a combination of myelotoxicity and diarrhea with 10 day schedules, to granulocytopenia in OD × 5. Balancing no difference in total exposure on one hand, and toxicity on the other, the once daily ×5 oral administration of TPT should get priority in further development.

1106 ORAL

Clinical and pharmacokinetic evaluation of the new bisnaphtalamide LU 79553 administered every 21 days in patients with solid tumors: An EORTC/ECSG study

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Purpose: LU 79553 (L) is a new bisnaphtalamide intercalating agent with profound activity in in vitro and in vivo preclinical models. We are performing a clinical Phase I study in patients (pts) with advanced solid malignancies.

Methods: L was administered as iv infusion q 21 d with a starting dose of 10 mg/m^2, escalated to 160 mg/m^2. Infusion time was adapted to local toxicity.

Results: 37 pts have received a total of 96 courses and are evaluable for toxicity (CTC) and response (WHO). Hematologic toxicity (HT) by pts were: 3/3 pts grade (g) 3 leukopenia (WBC) at 90 mg/m^2; 1/6 pts g 3 anemia, 2/6 pts g 3 WBC, 1/6 pts g 3 thrombocytopenia, 1/6 pts g 3 and 1/6 pts g 4 neutropenia (ANC) at 120 mg/m^2; 1/3 pts g 3 and 1/3 pts g 4 ANC at 160 mg/m^2. Significant non-HT by pts were: g 2 thrombophlebitis at infusion site 1/5 pts at 50 mg/m^2, 3/6 pts at 70 mg/m^2 and 2/6 pts at 120 mg/m^2.