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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.

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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.

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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 >