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Once weekly radiotherapy for patients with locally advanced or recurrent rectal cancer

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Purpose: To asses the effectiveness, in terms of symptomatic response (Bowel pain, rectal bleeding, discharge and tenesmus) and tolerability of a 6 Gy weekly regime of palliative pelvic radiotherapy in patients with symptomatic locally advanced, inoperable or recurrent cancer of the rectum.

Methods: 30 patients, 14 women and 16 men, median age 75 years (Range 45–92 years) were treated with 6 Gy weekly fractions of pelvic radiotherapy, delivered by 3 field conformal techniques, up to a dose of 36 Gy. Patients were assessed prior to radiotherapy, weekly during and one month following radiotherapy, using the RTOG and LENT SOMA scoring systems. Quality of life using the EORTC system was also assessed.

Results: Of the 30 patients evaluated 13% (4 patients) had a complete symptomatic response, 70% (21 patients) had a partial symptomatic response and 17% (5 patients) had no symptomatic response. The overall symptomatic response rate therefore was 83% (65–95%, CI = 95%). Toxicity was minimal. Severe toxicities were considered to be grade 3–4. No patients had grade 3–4 bowel toxicity and 7% (2 patients) had grade 3–4 bladder toxicity.

Conclusion: In selected patients, 6 Gy weekly radiotherapy provides good palliation, is well tolerated and is highly acceptable to patients.

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Adjuvant combined radiochemotherapy in rectal cancer

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Purpose: Assessment of the influence of combined radiochemotherapy on local tumour control, disease free survival and side effects.

Methods: 67 patients (44 male, 23 female median age 59 yrs) received postoperative adjuvant radiochemotherapy (5-FU, Levamizole, Interferon). A total dose of 50.4 Gy (single dose 1.8 Gy) was delivered. Tumour stage showed the following distribution T 1 n = 1, T 2 n = 6, T 3 n = 53, T 4 n = 7; N0 n = 31, N1 n = 29, N2 n = 7. UICC stage I n = 1, II n = 30, III n = 36. Abdominoperineal resectio (APR) was performed in 24 pat. and deep anterior resection (AR) in 43 pat.

Results: The 2 yr- and 5 yr-survival rate (yr-sr) was 90% and 66% for all patients. Median follow up was 31.6 months 53 patients are alive, 5 patients developed local recurrence, 19 pat. distant metastases. Significant better survival was observed in patients with AR compared to APR with 95% and 78% vs. 80.5% and 39% 2 yr. and 5 yr-sr ($p = 0.024$). Patients with histological risks (lymphangiosis, angioinvasion, R1 resection) did show significant worse survival with 71% and 0% vs. 92% and 71% (without) $p < 0.005$. Severe side effects RTOG > grade 2, ARO grade 2 did not occur.

Conclusion: Adjuvant combined radiochemotherapy in rectal cancer shows a high local control (92.5%), with high survival rate in disease free patients. Over all survival was worse in patients with APR due to deep tumour site and with histological risks.

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CPT-11 and L-OHP combination versus alternated combination of LV5FU2 + CPT-11/LV5FU2 + L-OHP in 5-FU resistant advanced colorectal cancer (CRC): Preliminary results

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This randomized phase II study was performed to evaluate the activity of 2 schedules including CPT-11/L-OHP associated or not with 5-FU in 5-FU resistant advanced CRC. Eligibility: CRC with mesurable disease; documented progression during 5-FU or within 6 months of 5-FU treatment; ≤1 prior 5-FU palliative regimen; Performance status ≤2. Since July 97, 62 of 72 planned pts (PS 0/1/2:31/29/2, median age:A:64/B:62 (43–75) were enrolled and received 203 cycles (cy) Treatment was randomly assigned between arm A: CPT-11 (180 mg/m^2) day 1 (d1)/LV5FU2 (De Gramont Regimen) d1d2 alternated with L-OHP (85 mg/m^2) d15/LV5FU2 (same schedule) d15d16 (d1 = d29) and arm B L-OHP (85 mg/m^2)/CPT-11 (200 mg/m^2) d1 every 3 weeks.

	ARM A	ARM B
Efficacy: Evaluable pts	22	19
PR/SD/PD	3 (14%)/14 (64%)/5 (23%)	4 (21%)/9 (47%)/6 (32%)
Median TTP (months)	7.0 (1.5–10.5)	4.8 (1.3–8.6)
G3-4 Toxicity (pt/cy)	30 pts/96 cy	20 pts/107 cy
Neutropenia	10 (33%)/25 (26%)	6 (30%)/9 (8%)
Febrile neutropenia	2 (7%)/2 (2%)	–/–
Diarrhea	4 (13%)/4 (4%)	1 (5%)/1 (1%)
Nausea/vomiting	1 (3%)/1 (1%)	2 (10%)/3 (3%)
G1-2 neurotoxicity*	13 (43%)/33 (34%)	15 (75%)/43 (40%)

*specific scale, Levi et al

In conclusion, both arms are active and safe in 5-FU resistant colorectal cancer.

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Folinic acid (FA) and 5-fluorouracil (FU) alone or with irinotecan (CPT-11) for advanced colorectal cancer (ACC): Preliminary results of a randomized phase II trial

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Purpose: In order to verify the effectiveness and feasibility of the addition of CPT-11 to the "de Gramont" schedule, the GOIM initiated a randomized multicenter trial in patients with naive ACC.

Methods: Patients with measurable ACC were randomly assigned (random ratio arm A vs arm B = 1:2) to arm A: FA (levo-isomer form) 100 mg/m^2 administered as a 2-hour infusion, followed by FU 400 mg/m^2 bolus and FU 600 mg/m^2 given as a 22-hour infusion, for two consecutive days; or arm B: CPT-11 180 mg/m^2 infused intravenously over 90 minutes on day 1, followed by the same schedule of arm A. Both treatments were repeated at 2-weeks interval.

Results: A total of 102 pts were enrolled (arm A: 34 arm B: 68); at present 70 (arm A: 25; arm B: 45) are evaluable for response and toxicity. Five objective responses (OR = CR + PR) were seen in arm A and 19 in arm B, with an overall response rate of 20% and 42%, respectively. Median response durations were 5+ months in arm A and 6+ months 9 in arm B. Toxicities were graded according to the NCI criteria and the observed toxic effetcs (% grade 3–4) were as follows (A/B): anemia 0/2, leukopenia 8/4, thrombocytopenia 2/0, nausea and vomiting 0/7, diarrhea 2/9.

Conclusion: The preliminary results of this trial indicate the effectiveness of the addition of CPT-11 at the above mentioned doses in the treatment of ACC.

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Chronomodulated (chrono) infusion of 5-fluorouracil (5-FU) and 1-folinic acid (FA) in 91 patients (pts) with metastatic colorectal cancer: The Regina Elena Cancer Institute experience

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Introduction: Chronotherapy consists in the administration of drugs at specific timing to optimize therapeutic index; consequently antineoplastic agents are better tollerated by host tissues and higher dose-intensities can be administerd. We have previously demonstrated in a phase I study an increase of 5-FU and 1-FA doses to 900 mg/m^2 and 150 mg/m^2 respectively (EJC '97).

Purpose: The aim of this study was to evaluate the efficacy of chrono 5-FU and FA in 91 patients with advanced colorectal cancer.

Methods: These drugs were delivered from 10.00 p.m. to 10.00 a.m. with peak flow at 4.00 a.m. for 5 consecutive days every 3 weeks by means of an ambulatory pump. Two groups were considered: group A, untreated measurable metastatic pts and group B, pts with at least one of these characteristics: IInd or IIIrd line therapy (26 pts), IInd tumor (8 pts), PS 3 (3 pts), unmeasurable disease (4 pts), age > 70 years (6 pts).

Results: Patient data: group A (48 pts)/B (43 pts): M 27/27, F 21/16, median age 60/66 (31–70/36–78), WHO PS 0 23/21, 1 17/10, 2 8/9, 3 0/3;

primary tumor was rectum in 12/10 pts; synchronous metastases, 34/25, liver metastases 42/28, >50% involvment 14/8; "2 metastastatic sites 27/23; symptomatic pts A/B 28/25, previous adjuvant chemotherapy 8/8; previous radiotherapy 18/14. Treatment was administred until disease progression, unacceptable toxicity or refusal. We observed 22/91 RC + RP (20%), 15 (31%) in A pts and 7 (16%); SD 15/14, PD 12/13; TTP: A/B 6/5.8; TTF: A/B: 5.2/3.4 mths; median overall survival was 13.8 mths with no difference in the 2 groups A/B 13.8/12.6 mths; median 2-yr OS was 26.6% (A/B; 27.6/25.4). Median OS in CR + PR pts was 25 months with a 2-yr OS of 59% while it was 13 mths in SD pts and (12% at 2 yrs) and 8 in PD pts (22%) ($p < 0.0001$). Multivariate analysis identified RC + RP > PS > liver involvment as independent prognostic factors for survival.

Conclusions: Chrono FUFA is an active regimen in untreated measurable patients and also in those generally excluded from clinical trials. This experience further identifies the emerging role of tumor shrinkage as an indicator of better survival.

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Qualitative and chronological assessment of toxicities during treatment with raltitrexed ('Tomudex') in 861 patients: Implications for patient management

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Introduction: Effective management of drug-related toxicity necessitates a knowledge of the nature and time of emergence of adverse events. Further analysis of the toxicity profile of raltitrexed ('Tomudex') was undertaken to evaluate the incidence, severity and sequence of toxicities in a Phase II and 3 Phase III clinical trials. Patients with aCRC received raltitrexed 3 mg/m^2 by 15-min infusion q21 days. The most frequent toxicities (>5% pts) occurring during the first 10 cycles (6 months) were analysed.

Results: WHO graded toxicities:

	Incidence GI-IV (% pts)	Incidence GIII-IV (% pts)	Early incidence GIII-IV (% pts)		↑Incidence[a] GI-IV (cycle day)
			Cycle 1	Cycle 2	
Non-haematological (n = 861)					
Asthenia[b]	51.1	9.3[c]	3.0[c]	2.4[c]	1–4, 8
Diarrhoea	39.3	11.1	2.6	2.4	1–6
Fever	30.8	1.5	0.6	0.6	2–6
Mucositis	11.3	1.4	0.6	0	None
Nausea/vomiting	65.8	8.1	3.1	1.6	1–9
Pain	44.3	6.2	1.6	1.6	1, 8
Haematological/biochemical (n = 616)					
Anaemia	20.4	6.3	1.1	1.2	5–11, 12–18[d]
AST/ALT ↑	17.9	8.9	2.6	3.6	<5, 12–18[d]
Neutropenia	16.7	11.2	1.8	2.2	5–11, 12–18[d]

[a]Toxicity incidence ≥1%/cycle day or period. [b]Mild, moderate or severe. [c]Severe resulting in withdrawal. [d]Within period specified, dependent on blood sampling time.

Death thought to be causally related to drag treatment occurred in 3.8% of 684 patients receiving raltitrexed in Phase III studies. However, two-thirds of these deaths occurred in the absence of dose reductions specified in the protocols or current dose recommendations.

Conclusions: Toxicities, including diarrhoea and neutropenia, may emerge early during treatment with raltitrexed, and in the 3-week interim period before the following dose is administered. Adequate monitoring should occur and patient vigilance encouraged to ensure early detection of gastrointestinal and haematological toxicities. Patients experiencing these toxicities should be carefully supported with appropriate therapy and either (1) withdrawn from treatment (grade IV or grade III gastrointestinal with grade IV haematological toxicity) or (2) continued on treatment at an appropriate reduced dose following complete toxicity resolution.

'Tomudex' is a trade mark, the property of Zeneca Ltd.

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'Tomudex' (raltitrexed) plus radiotherapy as post-operative treatment or palliative treatment for patients with rectal cancer: Phase I studies

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Objectives: Optimal treatment regimens for radiotherapy plus chemotherapy have not been determined in rectal cancer. 'Tomudex' is an alternative to 5FU in patients with advanced colorectal cancer and its radiosensitising effects, acceptable toxicity profile and convenient administration schedule make it an attractive combination candidate for further investigation. Two Phase I dose-escalation studies were initiated to determine the optimal dose of 'Tomudex' in combination with radiotherapy as post-operative adjuvant treatment for patients with operable rectal cancer (adjuvant study) or as palliative treatment for inoperable/recurrent rectal cancer (inoperable study).

Methods: Radiotherapy (50.4 Gy total) was delivered in 1.8 Gy daily fractions 5 times per week for 5–6 weeks in the adjuvant study, and in 2.0 Gy daily fractions 5 times per week for 5 weeks in the inoperable investigation. In both studies, a single dose of 'Tomudex' was administered at least 1 h prior to radiotherapy on days 1 and 22. The planned dose levels of 'Tomudex' were 2.0, 2.6 and 3.0 mg/m[2]. At least 3 patients were to be entered at each dose level. The recommended dose was defined as 1 level below the maximum tolerated dose. Once the recommended dose was defined, at least 6 additional patients were to be entered at this dose level. Toxicity was assessed by monitoring clinical/laboratory findings and adverse events.

Results: The adjuvant study is now complete and, among the 22 patients evaluated for toxicity, DLT was seen for 2/8 patients at dose level 1, 2/11 at dose level 2 and for all 3 patients at dose level 3. Of 19 patients entered in the inoperable study, 2 had a DLT at dose level 2 but the 6 patients entered at dose level 3 have not yet experienced a DLT. This latter study is ongoing and further data will be presented at this meeting.

Conclusions: The recommended dose of 'Tomudex' when combined with post-operative radiotherapy is 2.6 mg/m[2]. The combination of 'Tomudex' plus radiotherapy is feasible, convenient and appears promising for both operable and inoperable/recurrent rectal cancer. 'Tomudex' is a trade mark, the property of Zeneca Ltd.

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Characterization of genetic subtypes of colorectal cancers

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Purpose: The aims of this study is to identify the subgroups of sporadic colorectal cancers with APC or hMLH1, hMSH2 mutations and the further characterization of these subtypes of colon cancers on the basis of the mutation frequencies and expression of p53, TGFBR II, E2F1, E2F4, Cadherin E. Catenin B, p16, Cyclin D genes.

Methods: The mutation and expression of the above mentioned genes have been evaluated in 134 sporadic colorectal cancer and in their normal mucosa by immunohistochemistry, Western blot and PCR-SSCP analysis. The DNA methylation assay of the promoter regions of hMLH1, p16 genes has also been performed by Hpa II, Msp I digested PCR technique.

Results: APC mutations (cd 1450) have been detected in 20% of the tumors. Mutation frequency of hMLH1 and hMH2 was found to be 30% and 20%, respectively. The mt APC tumors contain high level of Cyclin D, E2F1 and low level of p16. P53 mutation could be detected in 45% of mt APC colon cancers. The p53 mutation is infrequent (5%) in the mt hMLH1 tumors. TGFBR II and E2F4 mutations were found in 25% and 40% of mt hMLH1 cases. The hypermethylations of the promoter regions of p16 gene is more frequent in mt APC tumors (30%) than that of the mutant hMLH1 colon cancers.

Conclusions: Our studies might suggest two alternative genetic pathways for sporadic colorectal tumorigenesis initiated by the mutation of APC or DNA mismatch repair genes. The two pathways of colon carcinogenesis could be characterized by different prognostic factors. APC mutated pathway is involved in the upregulation of Catenin B, Cyclin D frequent mutation of p53 and down regulation of Cadherin E. hMLH1 mutated pathway is accompanied by high level of Cadherin E, frequent mutation of TGFBR II, E2F4 gene and low level of Cyclin D and p53, resulting in a favourable clinical outcome of these tumours.

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Randomized phase II study of CPT-11 plus mitomycin C versus oxaliplatin plus mitomycin C in previously treated patients with advanced colorectal cancer (ACC)

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Purpose: CPT-11 and oxaliplatin are two new agents with promising activity in ACC. Based on preclinical suggestive evidence that both drugs might act