a period of 24-h, and dichotomy index (I < O), quantifying the differences in activity distribution between the rest span and the active phase. Paired rhythm parameters at C0 and C4 were compared by Wilcoxon signed rank test.
Results: Median values and quartile distribution [1st-3rd] of the 3 circadian rest/activity rhythm parameters were not significantly different at baseline (C0) and after 4 courses of CHT (C4) (Table 1). After CHT, however, the number of pts remaining in the same tercile ranged from 44 to 53%, according to the parameter (34 pts for r24, 40 for I < O, and 41 for mAct). Among the remaining pts, after 4 courses of CHT, the rhythm parameters significantly improved or deteriorated in nearly half of the pts each (20 and 23 for r24, 19 and 18 for I < O, 17 and 19 for mAct, respectively).
Conclusions: The main chemotherapy regimen for colorectal cancer modified the rest/activity circadian rhythm in nearly half of the patients in opposite directions. This supports large interpatient variability in response of the circadian timing system to chemotherapy. Understanding the relations between circadian system status and treatment-related toxicity and efficacy will lead to improve the therapeutic index through tailoring delivery schedule to the individual features of the patient.

Table 1

	Range of variation	C0	C4	p
r24	−1.0 to 1.0	0.41 [0.25–0.55]	0.45 [0.25–0.57]	0.34
I < O	0 to 100	97.5 [92.2–99.2]	98.2 [95.6–99.3]	0.15
mAct	0 to ∞	112 [90–127]	112 [86–132]	0.88

Publication
GI – colorectal cancer

663 PUBLICATION

Prognostic index for adjuvant treatment in locally advanced rectal cancer after preoperative chemoradiotherapy and radiotherapy

R. Lohynska, J. Prausova, E. Kubala, B. Malinova, K. Kubackova. *University Hospital Motol, Radiotherapy and Oncology, Prague, Czech Republic*

Background: Preoperative radiotherapy and chemoradiotherapy lower the risk of local recurrence and improve survival in stage II and III rectal cancer. After preoperative treatment is this initially homogeneous group stratified and patients have different relapse rate and survival.
Methods: A total of 174 patients (34% women and 66% men) with locally advanced rectal adenocarcinoma were treated with preoperative radiotherapy or chemoradiotherapy and retrospectively evaluated. The median follow up is 24 months (range 3–74 months). All patients received preoperative external beam radiation (40–50 Gy/20–25 fractions/4–5 weeks) using linear accelerator and 3D planning. Concomitant CHRT with 5-FU was carried out in 25% of patients. The data were analysed with statistical software SPSS version 10.0.
Results: Radical resection underwent 86% of patients, non-radical tumor resection 2% and inoperable tumor persisted in 7% (at the beginning it was 13% of patients). Distant metastases were detected peroperatively in 5%. Statistically significant factors that influence both overall and disease free survival are postradiotherapy stage ($p = 0.005$), postradiotherapy grading ($p < 0.001$), angioinvasion or perineural spread ($p = 0.023$), radicality of surgery ($p < 0.001$) and gender ($p = 0.036$). Local recurrence was associated in preradiotherapy T4 tumors ($p = 0.048$) and angioinvasion or perineural spread (0.049). Two-year OS was 85% and 5-year OS was 60%. Prognostic index is calculated from prognostic factors (stage, radicality of surgical procedure, grade, angionvasion and distance from the anal verge) and overall score devides patients into 4 groups with different relapse risk and OS. Excellent prognosis is achieved in patients of low risk group (radical surgery, pT1-pT2 good differentiated tumors with negative lymphnodes, no angioinvasion, no perineural spread, or complete remision after preoperative treatment), this group counts for 14% of all patients and 2-year DFS and OS and 5-year DFS and OS are 100% (all patients are alive without recurrence). Patients with intermediate risk have a 5-year OS 80%, patients with high risk of relapse have 5-year OS 55% and in group of very high risk no patient survived 5 years.
Conclusion: Patient with low risk relapse have relapse risk less than 5% and in our institution adjuvant chemotherapy in this low risk group after preoperative radiotherapy is omitted.

664 PUBLICATION

Cetuximab in combination with irinotecan/5-fluorouracil (5-FU)/folinic acid (FA) (FOLFIRI) in the first-line treatment of metastatic colorectal cancer (mCRC)

M. Peeters[1], J.-L. Raoul[2], J.-L. van Laethem[3], P. Rougier[4], C. Brezault[5], F. Husseini[6], L. Cals[7], A. Zubel[8], J.-C. Vedovato[9]. [1]*Ghent University Hospital, Dept. Gastroenterology/Hepatology, Gent, Belgium;* [2]*Centre E Marquis, Rennes, France;* [3]*Hôpital Erasme, Brussels, Belgium;* [4]*Hôpital A. Paré, Boulogne, France;* [5]*Hôpital Cochin, Paris, France;* [6]*Hôpital Pasteur, Colmar, France;* [7]*Hôpital Font Pré, Toulon, France;* [8]*Merck KGaA, Darmstadt, Germany;* [9]*Merck Lipha Santé, Paris, France*

Background: FOLFIRI is a standard option in the first-line treatment of mCRC. Cetuximab (Erbitux®) is an IgG1 monoclonal antibody targeting the epidermal growth factor receptor (EGFR), which is commonly expressed in mCRC. Cetuximab is active in mCRC patients failing on irinotecan-based therapy. This phase I/II trial investigated the safety and efficacy of cetuximab+FOLFIRI in the first-line treatment of EGFR-expressing mCRC.
Materials and Methods: Patients with immunohistochemistry-determined EGFR-expressing mCRC, who had not been treated for metastatic disease, received cetuximab (initial dose 400 mg/m^2 followed by 250 mg/m^2/week). FOLFIRI was given every 2 weeks: irinotecan 180 mg/m^2, FA 400 mg/m^2 and 5-FU 300 mg/m^{2}bolus plus 2,000 mg/m^2/46-h infusion (low-dose, LD) or 400 mg/m^{2}bolus plus 2,400 mg/m^2/46-h infusion (high-dose, HD). The use of LD 5-FU was part of the early dose-finding phase of the study.
Results: This analysis was performed on the per-protocol HD population of 42 patients: 64.3%/35.7% male/female, mean age 60.0 years, median KPS 100, 79% colon primary tumour. There were 19 confirmed objective responses (all partial responses [PR]) (45.2%) and 16 patients with stable disease (SD) (38.1%), giving a disease control rate (complete response+PR+SD) of 83.3%. The median response duration was 306 days (10 months), and median survival was 699 days (23 months). 10 patients (23.8%) were able to undergo resection of metastases for curative intent, 9 of whom had liver metastases. There were 8 R0 resections. Treatment was well tolerated. 66.7% of the 42 patients experienced grade 3/4 adverse events, the most frequent of which were leucopenia (16.7%), diarrhoea (14.3%), vomiting and intestinal obstruction (11.9% each), skin rash and abdominal pain (9.5% each), and asthenia and dyspnoea (7.1% each).
Conclusions: Cetuximab+FOLFIRI, incorporating high-dose 5-FU, is a feasible and active combination for the first-line treatment of EGFR-expressing mCRC. 45.2% of patients achieved an objective response. The median survival was 23 months and 23.8% patients were able to undergo resection of initially unresectable metastases. Based on these results, a new phase III trial was started.

665 PUBLICATION

Phase I/II study of 24-hour infusion of irinotecan (CPT-11) in combination with sequential oral leucovorin (LV) and uracil/tegafur (UFT) for patients with metastatic colorectal cancer

S. Sadahiro[1], Y. Maeda[1], T. Suzuki[1], A. Kamijo[1], H. Makuuchi[1], C. Murayama[2]. [1]*Tokai University, Surgery, Isehara, Kanagawa, Japan;* [2]*Tokai University, Radiology, Isehara, Kanagawa, Japan*

Background and Objective: A combined therapy using irinotecan (CPT-11), 5-fluorouracil (5-FU) and leucovorin (LV) is one of the standard chemotherapies (CT) for metastatic colorectal cancer (MCRC). The cytocidal effect of CPT-11 is specific to the S phase of the cell cycle. Therefore, its antineoplastic effect may be greater when administered in small dosages over an extended period, rather than when given at larger dosages for a shorter period. It has been reported that when a combination of 5-FU and CPT-11 is given sequentially it is more effective than when given concurrently. The effects of an oral administration of a combination of uracil/tegafur (UFT) and LV and an intravenous infusion of 5-FU combined with LV are comparable but the former is more convenient. Therefore, for a Phase I/II study, a schedule in which 24-hour continuous infusion of CPT-11 followed by sequential oral administration of UFT/LV was selected.
Methods: The subjects were patients (pts) who had MCRC with measurable lesions. Prior CT or adjuvant CT was allowed when they were interrupted at least 4 weeks before beginning this study. Each course was composed of the following: 24-hour infusion of CPT-11 on days 1 and 15: and oral UFT and LV divided into 3 parts were given on days 3–7, 10–14, 17–21 and 24–28. This regimen was repeated every 4 weeks. The dosages given during the Phase I study are shown in the table below. The maximum tolerated dose (MTD) was based on the dose-limiting toxicity (DLT) of the first course: the dosages one level below the MTD was adopted for the recommended dosage (RD) in the Phase II study.
Results: Three pts each were assigned to levels 1 and 2. No DLT was recognized in any of them. At level 3, 3 of the 6 pts developed a DLT, i.e.,