248 POSTER

Postoperative adjuvant chemotherapy with or without radiotherapy for rectal cancer

K.-R. Park[1], K.-K. Lee[1], I.-J. Lee[1], I.-Y. Kim[2], K.-Y. Sim[3], D.-S. Kim[2], J.-Y. Lee[1]. [1] *Yonsei University Wonju College of Medicine, Department of Radiation Oncology, Wonju, Korea;* [2] *Yonsei University Wonju College of Medicine, Department of General Surgery, Wonju, Korea;* [3] *Yonsei University Wonju College of Medicine, Department of Medical Oncology, Wonju, Korea*

Background: To determine whether the addition of radiotherapy to postoperative adjuvant chemotherapy results in improved disease-free survival and overall survival in AJCC stage II and III rectal cancer

Materials and Methods: From 1989 to1999 144 patients with AJCC stage II and III rectal cancer treated with radical surgery and postoperative CT or CCRT were included in a prospective non-randomized study. Of 144 patients, 72 patients were treated with postoperative CT alone and the other 72 patients with postoperative CCRT. The chemotherapy regimen mainly consisted of oral UFT on a daily basis for 1-12 months (median 12 months) or 5-FU (500mg/m^2 for 5 days) intravenous (IV) chemotherapy with 4 week intervals for 1-18 cycles (median 6 cycles) and leucovorin. Radiotherapy with 4500 cGy was delivered to the surgical bed and regional pelvic lymph nodes area followed by 540-1440 cGy (median 540 cGy) boost to the surgical bed. The follow-up period ranged from 20 to 150 months with a median of 44 months.

Results: The 5-year overall survival (OS) was 60.9% and 68.9% (p=0.0915), and the 5-year disease-free survival (DFS) was 56.1% and 63.8% (p=0.3510) for postoperative CT and postoperative CCRT, respectively. For stage II, the 5-year OS was 71.1% and 92.2%, and the 5-year DFS was 57.3% and 85.4% for postoperative CT and CCRT, respectively. The OS was significantly improved (p=0.0379) and the DFS was slightly improved but didn't show any statistical difference (p=0.1482) for postoperative CCRT compared to postoperative CT alone for stage II. In the patients with stage III, the 5-year OS was 52.0% and 55.0%, and the 5-year DFS was 47.8% and 49.8% for postoperative CT and postoperative CCRT, respectively. There were no statistically significant differences between postoperative CT and CCRT (p=0.4280 and p=0.7891) in OS and DFS for stage III.

Conclusions: This study showed that postoperative CCRT compared with CT alone significantly improved OS in stage II without lymph node metastasis but not in more advanced stage III with lymph node metastasis.

249 POSTER

Continuous infusion of oxaliplatin plus chronomodulated capecitabine in advanced colorectal cancer (CRC): a feasibility study

D. Santini[1], M. Di Seri[2], B. Vincenzi[1], P.P. Petrella[2], A. La Cesa[1], R. Rossi[2], C. Grilli[1], M.L. Colloca[2], G. Tonini[1]. [1] *Campus Bio-Medico University, Oncology, Rome, Italy;* [2] *La Sapienza University, Oncology, Rome, Italy*

Background: the combination of oxaliplatin and capecitabine or XELOX, is an effective and safe approach to the treatment of advanced CRC. Aim of the study was to define the feasibility and toxicity of XELOX administered through a new and original schedule in different lines of chemotherapy. Response rate was evaluated. Chronomodulated capecitabine could be a convenient oral alternative to chronomodulated infusional 5-FU combined with infusional oxaliplatin to further improve therapy in this setting.

Material and methods: between May 2002 and January 2003 26 CRC patients entered the study. Patients characteristics: male/female: 16/11; performance status according to ECOG: 0 (15), 1 (9) and 2 (2); median age: 65 (32-77); 61.5% (16/26) >1 metastatic site; 30.7% (8/26) > 2 metastatic sites; sites of metastases: liver (14), lung (11), peritoneal involvement (4), local (5), nodes (12). Treatment: oxaliplatin 70 mg/mq c.i. for 12 hrs (8.00 a.m. to 8.00 p.m.) d 1,8 plus chronomodulated capecitabine 2000 mg/mq/die os (h 8.00 a.m. 25% of total dose; h 6.00 p.m. 25% of total dose; h 11.00 p.m. 50% of total dose), d 1-14. Every 21 days. 93 cycles infused.

Results: toxicity G3/4: 26 patients evaluable. Most frequent related G3/4 adverse reactions were diarrhoea 8/26, nausea/vomiting 1/26, neuropathy 1/26, asthenia 2/26, hand-foot syndrome 1/26, neutropenia 1/26, transaminitis 1/26. G3/4 anemia and leucopenia have not been observed. Moreover, no G3/4 mucositis has been recorded. No pts withdrew due to adverse events. Response rates: 1° line (10 patients, 9 evaluable for clinical response): 5 PR (55.5%), 1 CR (11%), 3 P (33.5%). Patients treated in following lines (16 patients, 9 evaluable at moment): 3 PR (33.5%), 3 SD (33.5%), 3 P (33.5%). Moreover, we observed 2 PR, 3 SD and 2 P in patients previously progressed with oxaliplatin-based regimens.

Conclusions: this schedule appeared to be highly active and feasible with low incidence of G3-4 toxicities. This study is ongoing until 46 evaluable patients will be enrolled.

250 POSTER

Preoperative chemoradiotherapy in combination with intraoperative radiotherapy for T3-4Nx rectal cancer

S. Sadahiro[1], K. Ishikawa[1], T. Suzuki[1], H. Makuuchi[1], C. Murayama[2]. [1] *Tokai University, Surgery, Japan;* [2] *Tokai University, Radiology, Japan*

Background: Local recurrence was noted in more than 20% of patients (pts) with a circumferential resection margin (CRM) of 1 mm or less. However, securing an adequately long CRM can be difficult in some pts. We have used preoperative chemoradiotherapy in combination with intraoperative electron beam radiation (IORT). We irradiated the electron beam over the entire surface of the resected pelvic wall to create a new tumor-free margin because the absorbed dose of IORT is densely distributed in the shallow area from the irradiated surface. The outcome of pts treated with this approach was retrospectively compared with the pts treated with surgery alone.

Methods: Between 1991 and 2001, 98 pts of adenocarcinoma of the middle or lower-third of the rectum and a preoperative diagnosis of cT3-4NxM0 underwent surgery following the preoperative irradiation(XRT) of 20 Gy in 10 frs. [RT group]. 67 pts between 1991 and 1998 received only preoperative XRT [preRT group], while 32 pts in 1999 and thereafter were given oral Tegafur/Uracil (UFT) concurrently [preCRT group]. Radical surgery was performed approximately 2 weeks after the completion of XRT. 82 pts with resectable adenocarcinoma of the rectum (pT2-4NxM0) treated by surgery alone during the same period were compared as the control. [NoRT group]

Results: No significant difference was observed in pts characteristics and morbidity rate between the RT and the NoRT groups. Local recurrence was observed in 2 pts (2%) in the RT group and in 11 pts (13%) in the NoRT group; the rate in the RT group was significantly lower than that in the NoRT group (p = 0.004). Distant metastasis was seen in approximately 20% in each group. The disease-free survival (DFS) in the RT group was significantly better than that in the NoRT group (p = 0.04). The 5-year DFS was 71% and 59% in the RT group and NoRT group, respectively. The over-all survival (OS) in the RT group was significantly better than that in the NoRT group (p = 0.03). The 5-year OS was 82% and 65% in the RT group and the NoRT group, respectively. A subgroup analysis did not exhibit obvious downstaging in the preCRT group. However, the percent of tumor shrinkage was 22 ± 11% in the preRT group and 35 ± 11% in the preCRT group, with a significantly higher value in the preCRT group (p < 0.001). Sphincter preservation (SP) was possible in 78% of the pts. in the preCRT group, and this was significantly higher than that in the preRT group (41%; p = 0.002).

Conclusions: Combined preoperative and intraoperative radiation therapy against cT3-4Nx rectal cancer significantly reduces the local recurrence and significantly improves prognosis. Preoperative chemoradiotherapy using oral UFT increases SP without increasing adverse reactions.

251 POSTER

Down-regulated expression of thymidyalte synthase protein and messenger rna by oxaliplatin in colon cancer cells

K.H. Yeh[1], S.H. Yeh[2], J.P. Wan[1], J.S. Lin[1], A.L. Cheng[3]. [1] *Far Eastern Memorial Hospital, Departments of Internal Medicine and Medical Resea, Taipei, Taiwan;* [2] *National Taiwan University College of Medicine, Hepatitis Research Center, Taipei, Taiwan;* [3] *National Taiwan University College of Medicine, Cancer Research Center, Taipei, Taiwan*

In the past years, we designed an innovative HDFL24 regimen using high-dose weekly 24-hour infusion of 5-FU (2,600 mg/m^2) and leucovorin (300 mg/m^2) in the treatment of CRC. The overall response rate was 42.9% with surprisingly low myelotoxicity and other treatment-related toxicity (J Clin Oncol 1994;12:875; Anticancer Res 1997;17:3867). For further improve the treatment response, combining HDFL with new effective anti-cancer agents (such as oxaliplatin, irinotecan) are used. In the first-line treatment for metastatic CRC, either Oxaliplatin-HDFL or Irinotecan-HDFL may achieve a response rate of more than 50%. However, in the salvage treatment for metastatic CRC patients who had failed or progressed after 5-FU/LV (especially HDFL), only *Oxaliplatin-HDFL* may achieve a salvage response rate of about 13-25%. Irinotecan-HDFL or oxaliplatin alone had very poor salvage response (response rate of about 5% or less). We hypothesize that oxaliplatin may reverse the HDFL-related drug resistance via pivotal unknown mechanism(s).

After initial studies, we used DLD-1 cells as the *in vitro* model system. First, we revealed that oxaliplatin and 5-FU act synergistically on DLD-1 cells by MTT assay and median effect analysis. Second, we treated the cells with a serial concentration of oxaliplatin, such as 2-10 μ M, and the treatment resulted in down-regulation of TS protein expression by Western blotting. Further, we treated the cells with a serial concentration of oxaliplatin, such as 2 to10 μ M, and the oxaliplatin pre-treatment resulted in down-regulation of TS mRNA level up to 40% (mean ± S.D. of ratio to reference control = 0.60 ± 0.21, range: 0.42 0.84) by real-time PCR assay using the Lightcycler (*Roche Molecular Biochemicals*).

In this study, our data provide important information explaining the reason why combination of oxaliplatin and 5-FU results in better objective response in 5-FU-resistant patients than oxaliplatin alone does. Our data also suggest that TS down-regulation happens at the transcriptional level. TS modulation and down-regulation had shed light on the useful potential strategy to achieve objective response in 5-FU-resistant colorectal cancer patients.

252 POSTER

Preoperative chemoradiation with oral Tegafur for locally advanced rectal cancer: intermediate results.

F.A. Calvo[1], J.A. Diaz-Gonzalez[1], F.J. Serrano[1], M. Gomez-Espi[1], M.D. De la Mata[1], E. Lozano[1], E. Del Valle[2], F. Muñoz-Jimenez[2], R. Herranz[1].
[1] Hospital General Universitario Gregorio Marañon, Oncology, Madrid, Spain; [2] Hospital General Universitario Gregorio Marañon, Surgery, Madrid, Spain

Background: a phase II oriented study has evaluated tolerance and efficacy (downstaging, characteristics of residual tumor and patient outcome) of neoadjuvant chemoradiation using concurrent daily high-dose Tegafur for rectal cancer.

Material and methods: from 5/98 to 5/01 62 consecutive patients with cT_{3-4} and/or cN_+ rectal cancer were treated with 45-50.4 Gy (1.8 Gy/day; 25-28 fractions), and oral Tegafur 1200 mg/day (400 mg every 8 hours, including weekends). Surgery was performed 6 weeks after the completion of chemoradiation. All patients received a presacral boost with intraoperative electron radiation (10-12.5 Gy). Adjuvant chemotherapy was recommended (5FU-LV, 4-6 cycles).

Results: there were 43 males and 19 females, 25 patients (40%) were >70 years old. Severe co-morbidity was present in 43% of patients. In the neoadjuvant treatment segment 13 patients (21%) had grade 3 dermatitis, 16 (26%) grade 3 and 2 (3%) grade 4 diarrhea, and 1 patient had grade 3 anemia. The median dose of radiotherapy was 50.4 Gy. Surgery consisted on anterior resection in 38 patients (61%) and abdomino-perineal amputation in 24 (39%). Adjuvant chemotherapy was given to 67% of patients. Thirty-four patients (55%) had minimal microscopic residual tumor in the surgical specimen (*mic* category). The total T downstaging rate was 58% (N downstaging 31%). With a median follow-up of +29 months, the pelvic control rate was 97%, disease free survival 79% and overall survival 86%.

Conclusions: neoadjuvant chemoradiation with oral Tegafur is feasible, acceptably tolerated and active, with the advantages of oral fluoropirimidin potentiation during protracted preoperative radiation therapy programs.

253 POSTER

The potential role of erbb-2 and cyclooxygenase-2 expression in human colon carcinoma and risk conditions

A.C. Tsamandas[1], V. Zolota[1], P. Ravazoula[1], T. Kourelis[2], C. Kalogeropoulou[3], I. Tsota[3], P. Petsas[3], K. Tepetes[4], D. Bonikos[1], D. Kardamakis[3]. *[1] University of Patras School of Medicine, Department of Pathology, Patras, Greece; [2] University of Patras School of Medicine, Medical Oncology, Patras, Greece; [3] University of Patras School of Medicine, Radiology, Patras, Greece; [4] University of Patras School of Medicine, Surgery, Patras, Greece*

Background: ERBB2/Neu receptor tyrosine kinase and cyclooxygenase-2 (COX-2) represent promising molecular targets for cancer therapy and/or prevention. This study investigates the relation between ERBB2 and MET expression and COX-2 presence in human colon carcinomas.

Design: Immunohistochemistry was performed on paraffin sections from 124 primary human colon carcinomas (CC), 10 cases of ulcerative colitis and 20 villous colonic adenomas (risk conditions for human CC). Membranous stain for ERBB2/MET and cytoplasmic stain for COX-2 were evaluated in neoplastic tissue, non-neoplastic dysplastic tissue (NNDT) surrounding the tumor, and normal mucosa (NM).

Results: The table shows the results. ERBB2, COX-2 and MET expression was higher in well differentiated tumors ($p \leq 0.001$). Strong MET expression was also present in the NNDT. Increased ERBB-2, COX-2 and MET expression was recorded in 7/10 cases of ulcerative colitis and 18/20 adenomas. Linear regression revealed a strong positive correlation between membranous CERBB2 and cytoplasmic COX-2 staining ($r=0.83$, $p \leq 0.0001$) in neoplastic and NNDT epithelial populations. Thus, ERBB2 may play a key role in regulating COX-2 expression in neoplastic and putative precancerous colon epithelial cells.

Table: ERBB2, COX-2 and MET expression

Condition	# cases	ERBB2*	COX-2*	MET*
NM	6	6.9±1.2	2.6±1.2	60.6±7.3
NNDT	62	12.7 ± 2.4^{a}	8.9 ± 1.5^{a}	96.3±11.9
WDCC	40	$97.3\pm18.2^{a,b,c}$	$98.3\pm17.3^{a,b,c}$	$95.1\pm12.8^{a,c}$
MDCC	64	$23.7\pm4.6^{b,d}$	$41.3\pm7.3^{b,d}$	$42.1\pm3.8^{a,b}$
PDCC	20	$8.6\pm2.6^{d,c}$	$9.1\pm3.2^{d,c}$	$19.8\pm3.9^{b,c}$

*M±SM, WD: well differentiated, MD: moderately differentiated, PD: poorly differentiated, $^{a,b,c}p \leq 0.001$, $^{d}p \leq 0.05$

Conclusions: This study shows that overexpression of ERBB2 and COX-2 may represent an early dysfunctional event of human colon carcinogenesis. These markers may be important targets relevant to chemoprevention or adjunct therapy of well-differentiated colon carcinoma. However more direct studies are needed to clearly establish these observations.

254 POSTER

Radiotherapy for rectal cancer causes acute and prolonged impairment of cobalamin status.

M. Guren[1,2], J. Schneede[3], K.M. Tveit[1], P.M. Ueland[3], S. Dueland[2,1].
[1] Ullevaal University Hospital, Dept. of Oncolgy, Oslo, Norway; [2] The Norwegian Radium Hospital, Dept. of Clinical Cancer Research, Oslo, Norway; [3] Haukeland University Hospital, Dept. of Pharmacology, Bergen, Norway

Background: Radiotherapy for rectal cancer may induce acute or late injury to the intestine. The terminal ileum may be prone to damage since it may be included in the radiation volume, and its position is relatively fixed. The terminal ileum is the only site for receptor mediated absorption of vitamin B12. The aim of the study was to investigate whether (neo-)adjuvant radiotherapy for rectal cancer may have negative impact on cobalamin status.

Method: Consecutive patients with rectal cancer receiving pelvic radiotherapy with curative intent (50 Gy in daily fractions of 2 Gy, during 5 weeks) were evaluated prospectively. Serum cobalamin, serum methylmalonic acid (MMA) and serum total homocysteine (tHcy) were measured in 54 patients at start and end of radiotherapy, at follow-up 4-6 weeks after completed radiotherapy, and in 23 patients 1 year after radiotherapy.

Results: Mean serum cobalamin decreased from 306 pmol/L pretreatment to 267 pmol/L ($p<0.0005$) at the end of radiotherapy, and further to 247 pmol/L ($p<0.0005$) at follow-up after 4-6 weeks. Mean serum MMA was 0.16 μmol/L at start of treatment, 0.17 at the end of radiotherapy (n.s.), and had increased to 0.19 ($p=0.007$) 4-6 weeks after radiotherapy. There was also a significant reduction in serum and erythrocyte folate 4-6 weeks after radiotherapy, as compared to baseline. However, there was no change in serum tHcy levels. One year after radiotherapy, mean cobalamin was 249 (lower than baseline, $p=0.023$), and mean MMA was 0.21 (higher than baseline, $p<0.0005$).

Conclusion: Our data show biochemical evidence of early impairment of cobalamin status during and in the weeks after radiotherapy for rectal cancer, as reflected by a reduction of serum cobalamin combined with an increase of serum MMA. At follow-up 1 year after radiotherapy, there was evidence of persistently impaired cobalamin status. This observation may motivate routine monitoring of cobalamin status during follow-up of patients after radiotherapy.