combination of CAP and irinotecan (CPT). Based on these data a phase I study of CAP combined with weekly CPT was conducted in patients (pts) with measurable metastatic CRC as first-line chemotherapy.

Methods: CAP (bid) d 1-14 and d 22-35, CPT 30 min. inf. weekly x 6 followed by a one week rest (one cycle). Dose level [DL]1: CAP 1000 mg/m2 bid and CPT 70 mg/m2; DL2: CAP 1250 mg/m2 bid and CPT 70 mg/m2; DL3: CAP 1250 mg/m2 bid and CPT 80 mg/m2.

Results: 37 patients (pts) were entered on 3 DL and 89 cycles have been administered. Pts characteristics: Male/female 26/11 pts; PS 0 (0-2); median age 60 years (32-71); prior adjuvant CTx or/and RTx 14 pts. In the first 17 pts treated at DL1-3 the MTD has been reached at DL3 with diarrhea and neutropenia being dose-limiting. In order to confirm the recommended dose (RD), this DL2 was extended to 15 pts, demonstrating an incidence of DLTs in 5 (33%) out of 15 pts (diarrhea, neutropenia, one toxic death). Because the incidence of DLTs was considered to be too high, DL1 was extended to a total of 16 pts. DLTs were observed in 3 (19%) out of 16 pts. The main toxicity observed was diarrhea. So far, 13 out of 29 response evaluable pts (DL 1-3) (45%; 95%CI: 26-63%) and 6 out of 13 pts (46%; 95% CI 19-75%) at the RD (DL1) achieved an objective response.

Discussion: DL1 is the recommended dose for further studies. The combination of CAP and CPT is feasible and showed promising efficacy as first-line chemotherapy in advanced colorectal cancer.

1074 POSTER

Preoperative chemoradiation with raltitrexed ('Tomudex') alone or in combination with oxaliplatin in T3 rectal carcinoma: review of four phase I-II studies

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Aims: Preoperative radiation plus 5-fluorouracil (5-FU) increases the likelihood of sphincter preservation during surgery for rectal cancer. Tumour downstaging following chemoradiation also correlates with improved prognosis. Hence, there is a demand for more potent downstaging drugs to replace 5-FU in chemoradiation. The efficacy of raltitrexed ('Tomudex'), alone or combined with oxaliplatin, in preoperative chemoradiation was studied in patients with T3 rectal carcinoma.

Methods: Since 1998, 62 patients (pts) with stage II-III extraperitoneal rectal carcinoma have been studied in 4 trials. Radiation plus raltitrexed (2 trials): (1) Phase I study to determine the recommended dose (RD) of raltitrexed (2.0, 2.5, 3.0 mg/m2) concurrent to radiation; (2) Phase II study of raltitrexed (3.0 mg/m2)/radiation. Radiation plus raltitrexed and oxaliplatin (2 trials): (1) Phase I study to determine the RD of oxaliplatin (65, 85, 110, 130 mg/m2)concurrent to radiation plus raltitrexed (3.0 mg/m2); (2) Phase II study of oxaliplatin (130 mg/m2)/raltitrexed (3.0 mg/m2)/radiation. Pts received 45 Gy pelvic radiation (1.8 Gy/day, 5 days/week) with 5.4 Gy boost on the tumour bed. Raltitrexed, with or without oxaliplatin, was administered on Days 1, 19 and 38.

Results: Radiation plus raltitrexed: in Phase I (n=15) the RD was determined as 3.0 mg/m2, and 40% and 66% of pts had downstaging (pT0-1) and sphincter-saving surgery, respectively; only 1 pt had >G2 toxicity (G3 leucopenia, recovery in 3 days). Similar results were observed in Phase II (n=20): 50%, 80% and 15% of pts had downstaging, sphincter-saving surgery and G3 toxicity, respectively. Radiation plus raltitrexed and oxaliplatin: in Phase I (n=18) the RD was determined as oxaliplatin 130 mg/m2 combined with raltitrexed 3.0 mg/m2 and radiation. Overall, 66% and 72% of pts had downstaging and sphincter-saving surgery, respectively. Two pts had >G2 toxicity (G3 leucopenia and G3 proctitis). The Phase II study (n=9) confirmed these results: 55%, 89% and 11% of pts had downstaging, sphincter-saving surgery and G3 toxicity, respectively.

Conclusion: The high rates of tumour response and sphincter-sparing surgery plus low levels of toxicity suggest that raltitrexed is effective with an acceptable toxicity profile, both alone and combined with oxaliplatin, when given concurrently to pelvic radiation preoperatively.

'Tomudex' is a trade mark of the AstraZeneca group of companies

1075 POSTER

Weekly combination of oxaliplatin (OX) and irinotecan (IRI) in 5-FU resistant colorectal cancer (CRC)

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Purpose: OX and IRI are active agents in CRC. The combination of both drugs could enhance the efficacy of a salvage regimen in patients (pts) in whom progression (PD) occurs while they receive a 5-FU based chemotherapy (CT): 5-FU resistant 2nd-line population (FRP). In a recently published trial with OX-IRI only 14/36 pts were FRP and 31/36 received G-CSF to ameliorate risk of neutropenic fever (J Clin ONCOL 17:902).

Methods: We performed a prospective multicenter phase II trial with OX 60 mg/sqm/1h and IRI 80 mg/sqm/1h both on days 1, 8, 15 q 28d, without any use of G-CSF. Instead individual dose optimisation (IDO)was performed in case of toxicity (TOX) by dose modification and omitting scheduled days according to predifined guidelines.

Results: 68 pts received 1 to 9 cycles and are evaluable for TOX: In 27 pts CT was stoped due to objective or subjective TOX before PD occurred and 9 pts had to be admitted to the hospital mainly due to diarrhea. CTC ° III/IV TOX by pts: Diarrhea 26/3, Neutropenia 6/1, no case of neutropenic fever and no toxic death occurred. CTC ° II/III TOX by pts: Nausea 19/1, Emesis 15/1, Asthenia 16/3, Alopecia 8/0, Neurotox 9/5. In 25/225 and 65/225 cycles of CT scheduled day 8 resp. day 15 was omitted due to persisting diarrhea. IRI was increased to 100 mg/sqm in 5 pts (no TOX cycle 1) and reduced to 60 mg/sqm in 20 pts and to 50mg/sqm in 5 pts in forthcoming cycles due to diarrhea or neutropenia. EFFICACY: FRP = 49 pts with median TTP 5 months, median survival from start of 2nd-line 16 month. Response was evaluable in 44 FRP cases. Best response: 5 CR, 10 PR, 15 confirmed NC, 5 not confirmed NC, 9 PD: ORR 34%. In 3rd-line and pts pretreated with OX or IRI actvity was poor.

Conclusion: Weekly OX-IRI showes a remarkable activity in 5-FU resistant CRC compared to IRI alone or OX combined with 5-FU but despite IDO the objective and subjective TOX of the reported schedule is substantial and a starting dose of 60 mg/sqm of both drugs should be tested to define a safer protocol. Neutropenia, Nausea and alopecia seem to be less pronaunced than in other pubished OX-IRI combinations.

1076 POSTER

Integrated analysis of overall survival from two multicenter randomized trials of 5-fluorouracil (5-FU) and leucovorin (LV) with or without trimetrexate (TMTX) in patients with advanced colorectal cancer (ACC)

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Purpose: TMTX is a biomodulator of 5-FU cytotoxicity, especially in combination with LV. Favorable results are seen in Phase II studies of TMTX/5-FU/LV in ACC. Two Phase III, multicenter, randomized trials, one in the United States (TMTX-0034) and one in Europe (TMTX-0509), are designed to compare the efficacy and safety of TMTX/5-FU/LV with 5-FU/LV in first-line treatment of ACC. Survival data from these two studies will be integrated to increase statistical power to detect clinically relevant survival differences between the two treatment arms.

Methods: TMTX-0034 is a double-blind, placebo-controlled trial in 384 patients with ACC, and TMTX-0509 is an open-label trial in 365 patients with ACC. Both studies are similar in design, have identical objectives, include patient populations with similar baseline demographics, and are conducted in parallel. In TMTX-0034, patients receive TMTX 110 mg/m2 (Arm I) or placebo (Arm II) as 60-minute infusions followed 24 hours later by LV 200 mg/m2 as a 60-minute infusion, 5-FU 500 mg/m2 as a bolus infusion, and LV 15 mg orally q6 hours for 7 doses starting 6 hours after 5-FU. The same schedule was used in TMTX-0509, but without the placebo control and with 5-FU at 600 mg/m2 in the control arm. In both studies, each cycle of treatment consists of 6 weeks chemotherapy followed by 2 weeks

rest. Patients are treated until unacceptable toxicity or disease progression. Statistical tests to assess survival include Wilcoxon supported by Log Rank and a nonparametric analysis of covariance (Tangen and Koch, 1999 and 2000).

Results: Patient accrual of the integrated cohort was completed in March 1999. Median follow-up time is 36 months by February 2001. Analysis of the data will occur following the unblinding of TMTX-0034.

Conclusion: TMTX-0034 and TMTX-509 are two definitive Phase III trials in first-line ACC. Final results will be available at the time of the presentation.

1077 POSTER

Comparison of 5 classifications of colorectal carcinoma

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Purpose: The New Classification has been shown to be superior to Dukes, Astler-Coller and TNM as a predictor of individual prognosis in Israeli and American CRC pts after surgery with curative intent (Cancer 86: 782–792, 1999). This study compares five classifications of CRC in a cohort of Japanese pts, after surgery with curative intent.

Methods: Retrospective study of 504 Japanese CRC pts. Minimal follow-up: 5 years after surgery with curative intent. Sources of data: Japanese cancer registry forms, inpatient and outpatient files, and departmental follow-up registers. Tumors were staged according to Dukes, TNM, Astler-Coller, Japanese Society of Colorectal Cancer (JSCCR), and the New Classification. Kaplan-Meier survival curves (disease-free, observed, and adjusted for CRC deaths only) were calculated for each classification. Statistical significance of differences among the various survival curves was assessed by Log Rank. The 5 classifications were compared by multivariate regression analysis (Cox).

Results: All 5 classifications yielded disease-free, observed, and CRC-related survival curves that were highly significant ($p < 0.0001$). JSCCR stages 3a, 3b (in which JSCCR differs from TNM) did not differ significantly in any survival parameter ($p = 0.0756$, $p = 0.1644$, $p = 0.1791$ respectively). Multivariate regression analysis identified the New Classification as the most predictive of recurrence and survival ($p < 0.0001$).

Conclusions: 1. The New Classification is a superior predictor of individual prognosis following curative resection of CRC in Japanese pts as well. 2. The JSCCR classification of stage III CRC is not superior to TNM.

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1078 POSTER

Venous invasion (V.I.) as a prognostic indicator in TNM-II colorectal carcinoma (CRC)

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Purpose: In Israeli CRC pts after surgery with curative intent, V.I. +/− has been shown to define two subsets in each Dukes and Astler-Coller stage, that differ significantly in recurrence and survival (Europ J Cancer, vol 29A, Suppl 6, p S99, 1993). This study assesses if V.I. defines two prognostically ditinct subsets among Japanese TNM-II CRC pts as well.

Methods: Retrospective study of 504 Japanese CRC pts. Minimal follow-up: 5 years after surgery with curative intent. Sources of data: Japanese cancer registry forms, inpatient and outpatient files, and departmental follow-up registers. 151 pts (30%) had TNM-II tumors; V.I. was identified in 56 (37.1%) of them. Disease-free, observed, and CRC-related survival curves (Kaplan-Meier) were calculated for TNM-II V.I.(+) and for TNM-II V.I.(−) pts, and compared for statistical significance (Breslow).

Results: V.I.(+) was associated with an increase in local/regional as well as in distant recurrence in TNM-II CRC following surgery with curative intent. Disease-free, observed, and CRC-related survival of TNM-II V.I.(+) pts were significantly worse than those of TNM-II V.I.(−) pts ($p = 0.0129$, $p = 0.0077$, $p = 0.0141$ respectively). DFS at 5 years was 93% for TNM-II V.I.(−), and 78% for TNM-II V.I.(+).

Conclusions: 1. As in Israeli pts, substaging Japanese TNM-II CRC pts by V.I. defines two patient subsets that differ significantly in recurrence and survival. 2. Consequently, it is suggested that selection of TNM-II CRC pts for adjuvant treatment could be based on the presence of V.I. 3. This method requires no sophisticated or expensive equipment or tests, and it is immediately applicable in any health-care system worldwide.

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Comparison of five methods for substaging node-positive colorectal carcinoma

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Purpose: Future developments in adjuvant modalities may require substaging of node-positive CRC that is accurately indicative of individual prognosis, and upon which choice of agents, dosage and intensity of adjuvant treatment may be based. Venous invasion (V.I.) has been shown to be a superior definer of subsets of Israeli and American node-positive CRC pts, that differ significantly in recurrence and survival (Ann Surg Oncol 6: 161–165, 1999). This study compares 5 methods for substaging node-positive CRC in a cohort of Japanese pts following surgery with curative intent.

Methods: Retrospective study of 504 Japanese CRC pts. Minimal follow-up: 5 years after surgery with curative intent. Sources of data: Japanese cancer registry forms, inpatient and outpatient files, and departmental follow-up registers. 148 pts (29.4%) had node-positive disease [epicolic/paracolic LNs (N1 by the Japanese (JSCCR) classification) in 103 pts; intermediate LNs (N2) in 41 pts; main LNs (N3) in 4 pts]. These 148 pts were substaged according to 5 methods: 1–3 versus 4 or more (TNM N1/N2); 1–4 versus 5 or more (GITSG C1/C2); Astler-Coller C1/C2; JSCCR N1/N2+3; and by V.I.+/−. Disease-free, observed, and CRC-related survival curves (Kaplan-Meier) were calculated for each method, and compared for statistical significance (Breslow).

Results: Substaging by TNM N1/N2, GITSG C1/C2, and V.I.+/− defined subsets that differed significantly in disease-free, observed, and CRC-related survival. Substaging by Astler-Coller C1/C2, and JSCCR N1/N2+3 was not statistically significant ($p = 0.6079$, $p = 0.1171$, $p = 0.0996$; and $p = 0.0845$, $p = 0.2000$, $p = 0.2513$ respectively).

Conclusions: 1. Substaging node-positive CRC by V.I. was the only method that defined subsets that differed significantly in disease-free, observed, and CRC-related survival in Israeli, American and Japanese CRC pts alike. 2. This method has obvious biologic and oncologic significance, for it separates pts that have only lymphatic spread from pts that display microscopic hematogenous spread as well. 3. Consequently, we believe that V.I. is the method of choice for substaging node-positive CRC.

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1080 POSTER

Preoperative chemoradiotherapy (CHT-RDT) in locally advanced rectal cancer (RC). Preliminary results

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Objective: To assess the efficacy and toxicity of neoadjuvant ChT-RDT with 5-fluorouracil(5-FU) continuous infusion (CI) in locally advanced RC.

Materials and methods: From 4/96 to 3/2000, 90 patients (pts) with locally advanced RC (stage II y III) have been treated in a single centre with 5 days CI of 5-FU 300 mg/m2/day every week (w) concurrently with external beam RDT 45 Gy (1.8 Gy/session/5 session/w). Between the sixth and the eigth w after preoperative treatment, radical surgery was planned followed by postoperative ChT with 5-FU-Folinic Acid bolus, if there wasn't any evidence of progression disease (PD).

Results: 90 pts, 62 men and 28 women, with a median age of 62 years (20-76) were included. There were 78 resectable and 12 unresectable tumors. Stages: III, 72 pts (80%); II, 14 (15.6%); T3-T4 Nx 4 (4.4%). One evaluable patient didn't finish ChT because of an anginous pain. Grade III-IV gastrointestinal toxicity was observed in 1 pt. In 3 pts (3.3%), systemic PD was detected at the end of preoperative ChT-RDT. Surgery was performed in 89 pts: radical in 85 (96%) and palliative in 4 (4%). Surgical procedures included: anterior resection in 51 (57.3%), abdominoperineal resection in 36 (40.4%) and other procedures in 2. In 25 pts (41%) anal sphincter was spared. Pathological response rate was 70%: 14 complete response