confirms that infusional 5-FU/FA plus IRI should be considered as a reference treatment in metastatic CRC.

1089 ORAL

Improved safety of capecitabine vs bolus 5-FU/leucovorin (LV) as adjuvant therapy for colon cancer (the X-ACT phase III study)

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Background: tumor-activated capecitabine (X) produced significantly superior response rates and equivalent progression-free and overall survival compared to bolus 5-FU/LV (Mayo clinic regimen, M), with an improved safety profile and fewer hospitalizations in 1st-line metastatic colorectal cancer (n=1207 patients). This high activity, improved safety and patient preference for oral chemotherapy led us to move X forward into the adjuvant setting and compare it to the current global standard, M.

Materials and methods: patients with fully resected Dukes' C colon carcinoma were assigned to oral X (8 cycles of 1250 mg/m^2 twice daily days 1-14, every 3 weeks) or i.v. M (6 cycles of LV 20 mg/m^2 + 5-FU 425 mg/m^2 days I-5, every 4 weeks) for 24 weeks.

Results: a total of 1987 patients from 162 centers in 25 countries were randomised between 11/98 and 11/01. The arms were well balanced for median age (years) [range]: X 60.4 [25-80], M 61.0 [22-82]; ECOG score (% 0/1): X 86/14, M 86/14; sex (% Male/Female): X 54/46, M 54/46; and nodal status (% N1/N2): X 69/30, M 71/29. Overall, 81% of X patients received all 8 cycles and 87% of M patients received all 6 cycles. The most common, related, clinical adverse events (AEs, ≥15% all grades) are presented in the table. X consistently caused less all grade nausea/vomiting, diarrhea, stomatitis and neutropenia, across all age groups (<60, 60-70, >70). X caused less grade 3-4 stomatitis (X 2%, M 15%) and neutropenia (X 2%, M 26%) but more grade 3 hand-foot syndrome (X 18%, M <1%). Grade 3-4 diarrhea (X 12%, M 13%), nausea/vomiting (X 3%, M 3%) and fatigue (X <1%, M 1%) were comparable. Dose reductions for AEs were similar in incidence (X 40%, M 44%) with second dose reduction less common with X (13%), than with M (26%). All-cause, 60-day mortality was X 5 (0.5%) and M 4 (0.4%). Treatment-related deaths were X 3 (0.3%) and M 4 (0.4%).

	Capecitabine (Xeloda®) n=996 All grades (%)	Mayo n=973 All grades (%)	P value
Diarrhea	46	64	<0.001
Nausea/ Vomiting	36	51	<0.001
Stomatitis	22	61	<0.001
Neutropenia	32	63	<0.001
Fatigue/ Asthenia	23	23	0.98
Alopecia	6	22	<0.001
Hand-foot syndrome	61	10	<0.001

Conclusion: in the adjuvant setting oral X has an improved safety profile vs i.v. M, with less diarrhea, nausea/vomiting, stomatitis and alopecia, as seen in metastatic disease. Efficacy data are expected in 2004 after 632 events and if positive would suggest an important role for capecitabine in adjuvant therapy, given these encouraging results and the known patient preference for oral chemotherapy.

1090 ORAL

Continuation of irinotecan (CPT-11) beyond 8 cycles does not improve outcome in patients with advanced colorectal cancer resistant to fluoropyrimidines: results of a phase III multi-centre randomised trial

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Background: Irinotecan (CPT-11) given until disease progression (PD) is an accepted standard therapy for advanced colorectal cancer (CRC) resistant to fluoropyrimidines.

Purpose: To determine whether continuation of CPT-11 beyond 8 cycles improves outcome.

Patients and Methods: Patients (pts) with locally advanced or metastatic CRC and radiological evidence of PD within 24 weeks of completion of fluoropyrimidines were eligible. Pts may have received previous adjuvant chemotherapy and a maximum of 3 lines of palliative chemotherapy. All pts were treated with CPT-11 350 mg/m2 IV over 30 minutes, 3 weekly for 8 cycles, and those with disease response or stabilisation were then randomised to continuation until PD or best supportive care (BSC).

Results: Between 11/97 and 12/02, 333 pts were recruited, of whom 55 pts (16.5%) achieved disease response or stabilisation and underwent randomisation. 230 pts (69%) developed PD, 30 pts withdrew with toxicity, 2 pts refused randomisation and continued CPT-11, and 2 pts were withdrawn. The mean age of randomised pts was 62.4 years (range 42-78). Patient demographics between the 2 arms were well matched. 25 pts, including 6 responders, continued CPT-11 and a total of 277 further cycles were delivered; the median number of cycles delivered was 12 (range 9-20). No further responses were observed after randomisation. The only grade 3/4 toxicity observed was diarrhoea (8%). 30 pts, including 8 responders, were randomised to BSC with 1 remaining in CR. 16 pts with PD received further chemotherapy, of whom 8 received further CPT-11. No difference in progression-free survival (PFS) was observed at 6 months (36.4% for the CPT-11 continuation arm, 95% CI 17.4-55.7 vs 25% for the BSC arm, 95% CI 34.2-71.4; p=0.999). There was no difference in overall survival at 1 year (46.3% for the CPT-11 continuation arm, 95% CI 25.1-65.1 vs 54.8% for the BSC arm, 95% CI 34.2-71.4; p=0.11). No differences in mean global quality of life scores 12 weeks after randomisation were seen (p=0.446).

Conclusion: Continuation of CPT-11 beyond 8 cycles in the small group of patients with disease response or stabilisation does not improve PFS nor OS, nor does it result in significant additional toxicity, or further deterioration in quality of life.

1091 ORAL

How to explain the improvement in survival for colorectal cancer? A French population-based study

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Population-based statistics indicate that colorectal cancer survival has improved over the past 20 years. Little is known about the reasons of this trend. We have previously reported the important role of operative mortality reduction (Mitry et al. Br J Surg 2002; 89:1557-62). The purpose of this work was to study trends in colorectal survival over a 24-year period and to understand the reasons of the improvement in survival beyond the reduction of operative mortality.

Patients et methods: A series of 5,874 cases of colorectal cancers diagnosed between 1976 and 1999 in a well-defined French population were included. Trends in relative survival were estimated.

Results: The dramatic decrease in operative mortality after surgery for cure did not explain all the improvement in survival: after exclusion of operative mortality, the 5-year relative survival rate increased from 49.2 to 56.3 per cent between the 1976-87 and 1988-99 periods (50.3 and 58.0 (p<0.001) in patients under 75 and 47.1 and 53.6 per cent (p<0.001) in patients 75 and over, respectively). Trends were different between age groups. In patients 75 and over there was an increase in the proportion of patients resected for cure from 57.5% (1976-87) to 77.9% (1988-99) associated with an overall improvement in stage at diagnosis. Survival after surgery for cure as well as stage specific survival remained stable indicating that the improvement in survival was in relation with the increase proportion of patients resected for cure. In patients under 75, the increase of patients resected for cure was not the only explanation since there was also an improvement in survival after surgery for cure (from 64.9% to 72.7%, p=0.003) mainly because of the improvement in prognosis of stage III tumours (from 35.7% to 48.6%, p = 0.001). Five-year relative survival did not significantly change for advanced tumours but a significant improvement was observed for 1- and 2-year relative survival in patients under 75.

Conclusion: Trends in survival are very different between age groups. The improvement seen in overall survival for older patients can be attributed to the increase in the proportion of patients resected for cure. For younger patients, there was an increase in the proportion of patients operated for cure but also an improvement in stage-specific survival for stage III tumours suggesting a role for adjuvant chemotherapy. Progress in palliative

chemotherapy efficacy probably explains the improvement in 1- and 2-year relative survival in patients under 75 with advanced tumours.

Genitourinary cancer

1092 ORAL

PSA doubling time (PSADT) is quite variable in untreated, clinically localized, low to intermediate grade, prostate adenocarcinoma (CA)

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Introduction and Objectives: PSADT may allow for a clinician to formulate an individualized management according to the biological behavior of malignancy, as it reflects tumor kinetics. PSADT of untreated, low to intermediate grade, clinically localized prostate CA is analyzed and correlated with clinical parameters.

Methods: A prospective single-arm cohort study has been in progress since November 1995 to assess the feasibility of a watchful observation protocol with selective delayed intervention using clinical, histologic, or rapid PSA progression as treatment indication in clinically localized, low to intermediate grade, prostate CA. Study patients were initially managed with watchful observation alone. Eligible subjects had clinical stage $T_{1b\text{-}2b}N_0M_0$!, Gleason score (GS) $\leq$ 7, and PSA $\leq$ 15 ng/ml. Patients were followed every 3 months for the first 2 years and then every 6 months. At each visit, PSA, medical history and physical examination were obtained. PSADT was estimated from a linear regression of ln(PSA) on time, assuming a simple exponential growth model. Associations of PSADT with baseline clinical parameters were evaluated with correlation analysis.

Results: The study was closed in September 2001 and accrued 244 eligible patients. Of these, 231 patients had at least 3 PSA measurements and a minimum of 6 months follow-up as of March 2003, and were the basis for the analysis of PSADT. Median age was 71 years (range: 49-84). The distribution of clinical stage, PSA at entry and GS were as followed: T1: T2 = 154:77, initial PSA < 5: 5-9.9:10-14.9 = 68:123:40, GS 3-5:6:7:Gx = 49:130:50:2. Median PSA at entry was 6.5 (range: 0.3-14.6). In this cohort, median follow-up was 45 months (range: 6-85) and median frequency of PSA measurement was 8 times (range: 3-21). The distribution of PSADT was as followed: <2 years: 26, 2-3 years: 26, 3-4 years: 26, 4-5 years: 13, 5-10 years: 42, 10-20 years: 26, 20-50 years: 16, >50 years: 56. The median PSADT was 7.0 years. 98 patients (42%) had PSADT > 10 years. PSADT was correlated with clinical T stage (p=0.044), but not with age, GS, or initial PSA level.

Conclusions: PSADT of untreated, low to intermediate grade, clinically localized prostate CA varied widely. 42% of the cohort had PSADT >10 years. PSADT was correlated with clinical T stage.

1093 ORAL

Local dose escalation using temporary interstitial source brachytherapy (high-dose-rate) for clinically localized prostate cancer: Long-term outcome in hormone naïve men

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Purpose: To report the long-term outcome of patients treated with high local doses to the prostate in hormone naïve men.

Materials & Methods: A total of 579 men were consecutively treated with EBRT and dose-escalating high-dose-rate brachytherapy (HDR-BT) boost since 1986 in two prospective trials. There were 378 patients treated at William Beaumont Hospital and 201 patients at Kiel University. A short course of neo-adjuvant/concurrent androgen deprivation therapy (ADT) was given to 222 patients. All hormone naïve patients with a follow-up longer than 18 months were selected for this analysis. This cohort of 324 patients was analyzed according to biochemical control (BC), cancer-specific survival (CSS), overall survival (OS), and clinical local recurrence (c-LR) rates. The ASTRO definition for biochemical failure was used.

Results: Mean follow-up for all patients was 5.3 years (1.5-13.9). For all 324 hormone naïve patients, the 5 yr biochemical control (BC) rate was 79%. Cancer-specific survival (CSS) was 98%, and overall survival (OS) was 90%, respectively. The 5 yr clinical local recurrence (c-LR) rate was 7.6%. For patients with one of following poor prognostic factors, $\geq$ T2b, GS $\geq$ 7, initial PSA $\geq$10 ng/ml, the BC, CSS, OS and c-LR 5 yr rates were 81%, 97%, 90% and 4.9%, respectively. For patients with two poor prognostic factors the BC, CSS, OS and c-LR 5 yr rates were 85%, 100%, 91% and 5.2%, respectively. For very high risk patients with all three poor prognostic factors the BC, CSS, OS and c-LR 5 yr rates were 69%, 96%, 87% and 13.8%, respectively.

Conclusions: The results prove that our technique of TRUS guided interstitial conformal HDR-BT is a very successful method to deliver high doses to the prostate. Long-term survival outcomes are excellent in all patients with prostate cancer even for those at highest risk.

1094 ORAL

High dose radiation therapy with intensity modulated radiation therapy (IMRT) improves outcomes in localized prostate cancer. A large single institution experience

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Purpose: To compare the outcomes of high dose radiation therapy using IMRT with standard doses using 3D conformal technique in localized prostate cancer at the Cleveland Clinic Foundation.

Materials and Method: A total of 731 patients with localized prostate cancer were treated with conformal external beam radiation therapy between 1992 and 2001. All cases had available pretreatment PSA (iPSA) and biopsy Gleason scores (bGS), no nodal metastasis, a minimum 2 year follow-up, and >5 follow-up PSA levels. AD for $\leq$6 months (AD) was utilized in 47% (8% had AD for >6 months but < 12 months). The frequency by T-stage was: T1-T2A in 75%, T2B-T2C in 17%, and T3 in 8%. The frequency by iPSA was: $\leq$10 in 57% and >10 - 20 in 27%and >20 in 16%. The frequency by bGS was: $\leq$6 in 52%, and > or =7 in 48%. The age range for the patients was from 47 to 85 years (median 68 years). The median follow-up was 45 months (range: 24-103 months). Three-dimensional conformal radiation therapy (3DCRT) was utilized in 453 (62%) patients and IMRT in 278 (38%) patients. The median doses delivered with 3DCRT was 78Gy (range 66 to 78) and IMRT 83Gy (delivered at 2.5Gy per fraction to 70 Gy; this being equivalent to 83 Gy at standard fractionation of 1.8 Gy using an alpha/beta of 2). The ASTRO definition for biochemical failure was used. Toxicity was assessed using Radiation Therapy Oncology Group (RTOG)criteria.

Results: The biochemical relapse free survival (bRFS) for the entire cohort at three years was 85%. The 3-year bRFS for patients treated with 3DCRT was 81% vs. 91% for IMRT (p= 0.0012). A multivariate analysis of factors affecting bRFS was performed for using the following: race, iPSA (continuous), bGS (<or= 6 vs >or= 7), stage (T1-T2A vs T2B-C vs T3), treatment modality (3DCRT vs IMRT), use of AD, and total dose (continuous). T stage (p<0.0001), iPSA levels (p<0.0010), bGS(p=0.0020), and dose (p=0.0508) were independent predictors of outcome. Any (grade 1 or higher) **acute** genito-urinary (GU) side effects for patients receiving 3DCRT and IMRT were 80% and 79% respectively. Grade 2 or higher acute GU toxicity was seen in 20% and 18% of 3DCRT and IMRT patients, respectively. Any (grade 1 or higher) acute gastro-intestinal (GI) side effects for patients receiving 3DCRT and IMRT were 76% and 65% respectively. Grade 2 or higher acute GI toxicity was seen in 19% and 11% of 3DCRT and IMRT patients, respectively. Any (grade 1 or higher) *late* GU side effects for patients receiving 3DCRT and IMRT were 6% and 3% respectively. Grade 2 or higher late GU toxicity was seen in 4% and 1.5% of 3DCRT and IMRT patients, respectively. Any (grade 1 or higher) late GI side effects for patients receiving 3DCRT and IMRT were 15% and 13% respectively. Grade 2 or higher late GI toxicity was seen in 8% and 5% of 3DCRT and IMRT patients, respectively.

Conclusions: Higher doses of radiation delivered by IMRT resulted in better bRFS outcomes in patients with localized prostate cancer receiving external beam radiation therapy using conformal techniques. IMRT can be effectively used to safely increase dose delivery without compromising on quality of life. Hypofractionation is an effective method to dose escalate in localized prostate cancer. Longer follow-up is needed to further substantiate these results.