Methods: We retrospectively analyzed 331 patients with MCRC who underwent first-line oxaliplatin based chemotherapy. Treatment outcome was compared patients who initiated chemotherapy during April 2005 and March 2007 (cohort A; n = 157) and that of patients during April 2007 and March 2009 (cohort B; n = 174). To evaluate the impact of exposure to each agent in any lines of chemotherapy, we applied time-varying covariates analysis to avoid possible lead-time bias.
Results: Median overall survival (OS) of cohort A and cohort B was 21.3 and 28.6 months, respectively, with significantly better OS in cohort B (HR 0.66, 95% CI 0.50–0.87, P = 0.003). Exposure to bevacizumab (25% vs. 76%), anti-EGFR (18% vs. 33%) or curative surgery after chemotherapy (4% vs. 10%) was significantly higher in cohort B. According to a multivariate Cox model with exposure to each agent class as a time-varying covariate, the hazard ratios (HR) of death were 0.31 (95% CI, 0.18–0.46; p < 0.001) for irinotecan, 0.71 (95% CI, 0.51–0.96; p = 0.03) for bevacizumab, 0.62 (95% CI, 0.40–0.89; p = 0.01) for anti-EGFR, 0.22 (95% CI, 0.06–0.57; p = 0.004) for surgery.
Conclusions: Increased exposure to molecular targeting agents or curative surgery after chemotherapy appears to contribute to improvement of OS in recent patients with MCRC who underwent oxaliplatin based chemotherapy.

6101 POSTER

Promising Results After Radionuclide Therapy With 177Lu-DOTA-octreotate in Patients With Disseminated Neuroendocrine Hindgut Tumours

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Background: Peptide receptor radiotherapy was introduced as a therapeutic option for neuroendocrine tumours more than a decade ago. Hindgut carcinoids have historically had only limited treatment options when metastasized. This report focuses on the outcome of this patient group after therapy with 177Lu-DOTA-octreotate.
Material and Methods: Since December 2005, 16 patients (8 M/8 F) with hindgut carcinoids have received 2−8 courses of 7.4 GBq 177Lu-DOTA-octreotate until a maximum of 23 Gy absorbed dose to the kidneys as dose limiting organs. Median age was 53years (25−75). All patients were in TNM stage IV. Ki-67 was available for 15 patients, one patient <2% (G1), 13 patients ⩽20% (G2), one patient =30% (G3). Eight out of 14 patients with liver metastases showed an involvement of more than 50% of the liver volume. Mean time from primary diagnosis to start of 177Lu-DOTA-octreotate was 39 months (2−99 months). Twelve patients had undergone resection of the primary tumour at diagnosis and one had received external radiotherapy. Six patients had been objected to chemotherapy and had progressed or suffered from intolerable side effects, eight received 177Lu-DOTA-octreotate as first line systemic treatment. Radiological evaluation was performed according to RECIST criteria.
Results: From time of diagnosis, mean-follow-up was 70 months, median 57 (range 14–139 m). Mean follow-up after start of therapy was 33.4 months, median 39 (range 11−63m). Two patients died 14 and 48 months after start of therapy, corresponding to 48/67 months after diagnosis. One patient was lost to follow-up 11 months after start of treatment, 13 are alive. Best response this far: 0% CR, PR 9 patients (56%), SD 7 patients (44%). 0% PD. Decrease of tumour burden was observed up to 57 months after start of therapy. Four patients could undergo subsequent tumour reductive surgery. Six patients progressed after initial response. Side effects: 12/16 patients showed transient thrombocytopenia, 10 grade 1&2, one grade 3, one grade 4; 9/16 showed transient neutropenia (7 grade 2, 2 grade 3, none grade 4); slightly elevated S-creatinine occurred in 4/16 patients; all grade 1.
Conclusion: Patients with advanced hindgut tumours demonstrate a high response rate and mild side effects on radionuclide therapy. 177Lu-DOTA-octreotate treatment should be considered as first line in this patient category.

6102 POSTER

Stage II Colon Cancer in Brazil − a Single Institution Experience

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Background: As stage II colon cancer patients may have a good outcome and adjuvant chemotherapy in this setting is controversial, the aim of the present study was to determine the clinical outcome of patients treated in a public institution from Brazil.
Patients and Methods: The tumour registry at National Institute of Cancer from Brazil was searched to identify patients with stage II colon cancer who underwent resection between January 2000 and December 2005. Data from 162 consecutive patients were collected using a standardized procedure. The Pearson Chi-square test and the Kaplan–Meier method were used.
Results: The median age at diagnosis was 62 (24−90); 45% were man; 35% reported a family history of colorectal cancer; 26% had a preoperative CEA >10 ng/mL. The mean time between diagnosis and surgery was 85 days. Intestinal obstruction and perforation were reported in 11.8% and 3.8% of patients, respectively. The pathological staging (AJCC 6º ed) was IIB (T4) in 79.6% and among these, invasion of other organs or structures was reported in 16% (22 patients). In 6.3% the tumour grade was poorly differentiated; 24% and 11% had vascular and perineural invasion, respectively. The mean number of lymph nodes examined in each specimen was 24. Adjuvant chemotherapy was indicated for 58 patients (35.8%). The mean time between surgery and initiation of adjuvant chemotherapy was 60 days. The regimen of treatment was bolus fluorouracil plus leucovorin, either a monthly 5-day course or a weekly 1-day course. Age less than 75 years (p < 0.002) and tumour invasion or adherence to other organs or structures (p < 0.001), but not histological grade, perforation or less than 12 nodes sampled, were significantly associated with the administration of adjuvant chemotherapy. With a median follow up of 67 months, the progression free survival at 3 and 5 years was 96.7% and 95.2%, respectively. Five years overall survival was 90.9%.
Conclusions: Most patients in this Brazilian cohort did not receive adjuvant chemotherapy, with age at diagnosis and tumour invasion the most frequent determinants. Efforts should be done to reduce the interval between diagnosis and surgery and the time to initiation of adjuvant treatment. Progression free and overall survivals were comparable with reported literature data.

6103 POSTER

Oxaliplatin and Capecitabine (CAPOX) in Non Selected Patients With Metastatic Colorectal Cancer (MCRC) After First-line Irinotecan Based Regimen

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Background: It has not yet been established the best second line chemotherapy for MCRC although some studies suggest a better role for oxaliplatin after irinotecan than for irinotecan after oxaliplatin. We analysed if our data could be comparable to those of Tournigand, et al (JCO2004; 22:229).
Patients and Methods: This is a unicentric retrospective study including patients with MCRC who received CAPOX after progression to front-line treatment which initially was irinotecan, fluorouracil and leucovorin (IFL) and since 2005 with low dose capecitabine, irinotecan (CAPIRI) and bevacizumab in patients without contraindications to receive the targeted agent. The primary endpoint was overall survival (OS) and the second ones were response rate (RR), progression-free survival (PFS) and the safety profile.
Results: Between February 2002 and September 2010, 138 evaluable patients from a Spanish Medical Oncology Department were enrolled. Patients and treatment's characteristics are displayed in table 1.
The median OS was 7.85 months (95% CI, 6.73–8.97). The RR, the tumour growth control rate and the progression rate was 16%, 51% and 49%, respectively. The median PFS were 3.5 months. The median number of cycles received were 5 (limits: 1−24). Most frequent treatment-related grade 3−4 toxicities were diarrhea (9%), vomiting (6%) and asthenia (4%). 7% of

patients stopped oxaliplatin due to peripheral neuropathy. There was no toxicity related death.
Conclusion: These data suggest good tolerability and efficacy for second-line CAPOX in non selected (31% ECOG2 and 26% ⩾70 years old) patients with MCRC pretreated with irinotecan based regimen. Our results in clinical practice setting are similar to those published in trials using FOLFOX indicating the promise of this regimen as an effective second-line therapy.

Table 1

Patients' and treatment's characteristics (N = 138)	N° (%)
Median age (years)	65
Range	37–80
Performance Status (ECOG)	
2	43 (31.2)
1	43 (31.2)
0	24 (17.4)
K-RAS gene status: wild type/mutated/unknown	42(30.4)/24(17.4)/72(52.2)
Primary tumour location	
Colon except sigma	79 (57.3)
Sigma	14 (10.1)
Rectum	45 (32.6)
Metastatic disease location	
Liver	113 (81.9)
Nodes	97 (70.3)
Lung	63 (45.7)
Peritoneum	51 (36.4)
Others	12 (8.7)
Number of metastatic sites	
1	29 (21)
>1	109 (79)
Median CEA (ng/ml)	58
Range	0.9–11500
Front-line chemotherapy	
IFL	43 (31.2)
CAPIRI (contraindication of Bevacizumab)	17 (12.3)
CAPIRI + Bevacizumab	78 (56.5)
Chemotherapy dose (cycle repeat every 21 days)	
Capecitabine (mg/m^2/day × 14 days)	
2000	48 (34.8)
1700	60 (43.5)
<1700	30 (21.7)
Oxaliplatin (mg/m^2 day 1)	
130	23 (16.7)
100	94 (68.1)
<100	21 (15.2)
Other chemotherapy lines	
0	54 (39.1)
3	43 (31.2)
>3	41 (29.7)

6104 POSTER

A Phase II Randomized Study of Two Doses of Vorinostat in Combination With 5-FU/LV in Patients With Refractory Colorectal Cancer (CRC)

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Background: Data from a phase I clinical trial confirmed the feasibility of combining vorinostat doses 600- 1700 mg/day x 3 days with standard doses 5-FU/LV in patients (pts) with refractory CRC. Activity was noted at vorinostat dose-levels (DL) of ⩾ 800 mg/day. We conducted a phase II clinical trial to better define the activity of this combination in 5-FU-refractory CRC at the vorinostat DL of 800 and 1400 mg/day (registered on cancer.gov as NCT00942266 and supported by a grant from MERCK).
Methods: Pts with metastatic CRC who failed standard chemotherapy and progressed within 4 weeks from a fluoropyrimidine-based treatment were enrolled. Pts were randomized to receive low dose (LD) 800 mg/day or high dose (HD) 1400 mg/day vorinostat for 3 days. LV 400 mg/m^2 followed by 5-FU 400 mg/m^2 bolus and 2400 mg/m^2 × 46 hrs were administered on days 2−3 of a 14-day cycle. Randomization was stratified by performance status (0−1 vs. 2) and LDH (normal vs. elevated). A 2-stage design was performed: if ⩽ 8/15 pts had disease control at two months, that treatment arm was terminated; if ⩾ 9/15 pts have disease control, a total of 43 pts on that arm were enrolled. 43 pts have an 80% power to detect an improvement in 2-month disease control rate (DCR) by 20% (assuming 50% DCR for 5-FU/LV).
Results: 15 pts (6 male, median-age 62, 7 elevated LDH, 2 ECOG 2) were enrolled at the HD and 43 pts (21 male, median-age 60, 27 elevated LDH, 5 ECOG 2) at the LD levels. Common grade 3/4 toxicities were: grade (G) 3 fatigue in 3 LD pts and 5 HD patients, G3 nausea in 4 LD patients and 2 HD patients, G3 diarrhea in 2 LD and 2 HD patients, G3 hand-foot in 3 LD and 3 HD pts. No differences were noted in the pharmacokinetics cohorts of vorinostat between the LD (10 pts) and HD (10 pts) in terms of C_{max}, C_{ss}, and AUC, suggesting bioavailability saturation at doses ⩾ 800 mg. No G3 QTc was noted on the HD arm in 10 pts with intense EKG monitoring. 8/15 pts had disease control (SD) on the HD arm, which was closed to accrual. 9/15 (1 PR, 8 SD) had disease control on LD, which was expanded. On the LD arm, 1/43 pts had a PR and 22/43 had SD for a 2-month DCR of 53.5%. The median PFS on the LD arm was 2.43 months (KRAS Mt = 2.53 vs. KRAS Wt = 2.04, p = 0.32) and the median OS was 6.74 months (KRAS Mt = 6.74 vs. KRAS Wt = 5.85, p = 0.56). All LD patients deriving disease control ⩾ 6 months were KRAS Mt (4/29) with lung pre-dominant metastases.
Conclusions: The addition of the histone deacetylase inhibitor vorinostat does not enhance 5-FU/LV activity sufficiently to warrant further investigation in unselected 5-FU-refractory CRC patients.

6105 POSTER

Phase II Trial of Temsirolimus Alone and in Combination With Irinotecan for KRas Mutant Chemotherapy Resistant Metastatic Colorectal Cancer and the Importance of KRas Mutations in the Plasma

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Background: Metastatic colorectal cancer (mCRC) with *KRAS* mutation represents a major therapeutic challenge. The present study evaluated the safety and efficacy of the mTOR inhibitor temsirolimus alone and in combination with irinotecan in chemotherapy refractory mCRC with *KRAS* mutations. Furthermore, the importance of quantitative measurement of *KRAS* mutations in plasma was investigated.
Methods: The study was planned as two phase II trials in the same study. Patients received a weekly dose of temsirolimus 25 mg IV followed by response evaluation every 6 weeks. Monotherapy was continued until progression, and followed by combination therapy consisting of biweekly irinotecan 180 mg/m^2 IV and temsirolimus. Eligibility criteria included; histopathologically verified chemotherapy resistant mCRC, *KRAS* mutation, adequate PS and organ function. A quantitative PCR method was used to asses the number of *KRAS* mutated alleles in plasma prior to each cycle.
Results: Sixty-four patients were included. There were no grade 4 adverse events, but 30% experienced grade 3 toxicity, primarily infections or laboratory changes. The median number of monotherapy cycles was 3 (range 0−17) and that of combination therapy 3 (0−19). None of the patients achieved an objective response according to RECIST but 38% (24/64) had stable disease on monotherapy and 63% (22/35) on combination therapy. 12 cases of tumour shrinkage were detected. The median time to progression (TTP) was 45 days and 84 days, respectively. The median overall survival was 160 days in the total cohort.
The concordance between *KRAS* status in tumour and plasma (*pKRAS*) was 82%. Patients with high *pKRAS* (>75% quartile) had a 77% risk of early progression on monotherapy compared to 43% in patients with lower levels (p = 0.036). All patients with tumour reduction during treatment had low *pKRAS*. Survival analysis also showed that *pKRAS* was a strong prognostic factor.
Conclusion: Temsirolimus has limited efficacy in metastatic colorectal cancer, but quantitative measurement of *KRAS* in plasma may serve as predictor for outcome and a tool for monitoring patients with *KRAS* mutant colorectal cancer.