activity of SU may augment the antitumour activity of FOLFIRI. In this phase I, dose-finding study, SU in combination with FOLFIRI was investigated in pts with mCRC.
Patients and Methods: Successive cohorts of 3–6 treatment-naive mCRC pts received FOLFIRI (irinotecan 180 mg/m^2, l-leucovorin 200 mg/m^2 and 5-FU 400 mg/m^2 on day 1, followed by 5-FU 2,400 mg/m^2 46-hr infusion) every 2 wks in combination with escalating doses of SU. 2 SU doses (37.5 and 50 mg/d) were investigated with 2 dosing schedules: 4/2 (4 wks on, 2 wks off) and continuous dosing. The primary endpoint was the maximum tolerated dose (MTD), the dose at which $\leqslant$1 in 6 pts experienced dose-limiting toxicities (DLTs), and overall safety of SU in combination with FOLFIRI. Preliminary antitumour activity of the combination regimen was also assessed (RECIST criteria). Data for patients on the 4/2 dosing schedule are reported here.
Results: 13 patients on the 4/2 schedule (7 at 37.5 and 6 at 50 mg/d) were evaluable for safety. No DLTs or grade 3/4 AEs were observed in the first 3 pts in the 37.5 mg/d cohort. 2 of 6 pts in the 50 mg/d cohort experienced DLTs (1 grade 4 neutropenia; 1 grade 4 febrile neutropenia who later developed grade 4 diarrhoea and grade 5 C. difficile infection). Another pt had grade 3 diarrhoea. The 37.5 mg/d cohort was expanded and no DLTs occurred among the 4 additional evaluable pts. The MTD for SU on the 4/2 schedule with FOLFIRI was determined to be 37.5 mg/d. Dose delays in the 37.5 mg/d group were required in 3 pts for a total of 6 cycles delayed by 1 wk. Updated tolerability results will be presented. Initial efficacy data of the two dose groups are shown in the Table.

Response outcomes	37.5 mg/d (n = 7)	50 mg/d (n = 6)
Confirmed PR	4[a]	0
SD	3	6
PD	0	0

[a]1 PR maintained for >6 months.

Conclusions: As of March 2007, data show that SU 37.5 mg/d on a 4/2 schedule in combination with FOLFIRI is tolerable, and shows promising antitumour activity in treatment-naive mCRC pts. Enrolment on the continuous dosing schedule of SU in this combination regimen is ongoing.

3066 POSTER

Exploring first line chemotherapy options in metastatic colorectal cancer (mCRC): nationwide heterogeneity in patient management

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Background: In an increasing number of clinical scenarios, numerous chemotherapy (CT) options appear to offer similar outcomes, but there remains an absence of direct comparative trials or adequate phase III data. Potential influences on physician decision making in these contexts include expert opinion, personal experience and marketing influence; treatment practices may carry significant cost impacts. mCRC is such a circumstance; where oxaliplatin- or irinotecan-based CT provides similar efficacy and rates of severe toxicity, but there are a range of regimens, doses and adjunctive treatments. We sought to document the range of decisions made by Australian oncologists in this setting.
Methods: A questionnaire was mailed to all members of the Medical Oncology Group of Australia assessing preference for 1st line CT in pts with mCRC, regimens, doses and adjunctive treatments.
Results: Evaluable responses were obtained from 188 (60%) oncologists and fellows, of whom 162 (51%) managed patients with mCRC. Oxaliplatin-based treatment was the preferred 1st line CT for 150 of the 162 (93%) respondents. 107 (67%) stated preference was based on efficacy; 27 (17%) perceived favourable toxicity profile. A FOLFOX6-like regimen (bolus 5-FU day 1 only) was preferred by 96 (59%), FOLFOX4 by 41 (25%) and XELOX by 14 (9%). Leucovorin doses of 200 mg/m^2 were used by 53 (33%), 20 mg/m^2 by 54 (33%) and 41 (25%) used a fixed 50 mg dose. When using oxaliplatin, 66 (41%) never used calcium and magnesium prophylaxis, 56 (35%) used it in all patients, and 35 (22%) only when neurotoxicity developed.
Conclusions: Substantial heterogeneity exists in the 1st line treatment of pts with mCRC in Australia, with oxaliplatin having a dominant role. While high dose leucovorin is not superior to low dose in phase III studies, many oncologists continue to use high doses. Without the assistance of phase III evidence for calcium and magnesium use, a wide variety of approaches are seen. These data provide a strong rationale for further study in this area and the provision of tools to assist with decision making, including guidelines to allow more uniform management nationwide.

3067 POSTER

Irinotecan Metronomic Chemotherapy (MC) in patients with diagnosis of metastatic colorectal cancer (MCRC): clinical, pharmacodynamic (PD) and pharmacokinetic (PK) evaluation

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Background: Long-term, regular frequency, low-dose chemotherapy (metronomic/antiangiogenic chemotherapy) has been recently developed. The antitumor effect of the MC with Cyclophosphamide is due to an increase of thrombospondin-1 (TSP-1) plasma level.
Methods: An exploratory study was conducted to assess the feasibility, the activity and the optimal metronomic dose of CPT-11 when administered as protracted continuous infusion (c.i.) in pretreated MCRC. A PD evaluation of anti- and pro-angiogenic factors, such as the TSP-1 and the vascular endothelial growth factor (VEGF) and a PK analysis of the CPT-11 and its metabolites were performed. Three different CPT-11 dose levels have been evaluated: 1.4, 2.8 and 4.2 mg/sqm/day; 25%, 50% and 75% of the maximum CPT-11 tolerated dose in c.i. (5.6 mg/sqm/day), respectively.
Results: Twenty patients entered the study. Patients characteristics were: M/F = 11/9, median age = 71 years (range 51−79); PS 0/1/2 = 8/11/1; median of previous lines of chemotherapy: 3 (range 2−5). No toxicities of grade >1 NCI scale have been observed. Four patients (20%) obtained a stable disease with a median duration of 14 weeks (range 11−20). The antiangiogenic effect of metronomic CPT-11 seems to be suggested by the TSP-1 plasma concentrations that were increased at the CPT-11 1.4 and 2.8 mg/m^2/day schedules (e.g. at day 49, 153.4$\pm$30.1% and 130.4$\pm$9.2% vs. 100% of baseline values before treatment, respectively) and by the initial, but variable, increase in plasma VEGF (e.g. at day 21, 124.4$\pm$41.7% and 132.3$\pm$46.8%, respectively) probably due to the induced hypoxic conditions of tumour. The low, but measurable, levels of plasma CPT-11 and SN-38 reached the Cmax of 277.6$\pm$125.3 ng/ml and 1.62$\pm$0.45 ng/ml (mean$\pm$SD), respectively, at the lowest CPT-11 dose. Interestingly, the SN-38 plasma concentrations were statistically related to TSP-1 plasma levels in the 4 patients with stable disease (P = 0.0062, r = 0.3995).
Conclusions: Plasma SN-38 concentrations were measurable and related to the increase of the antiangiogenic factor TSP-1 that markedly increased during metronomic CPT-11 administration, suggesting a modulation of the angiogenic process MCRC patients. Supported by A.I.R.C and ARCO foundation.

3068 POSTER

Capecitabine + irinotecan + bevacizumab as first-line therapy for patients (pts) with metastatic colorectal cancer (MCRC): preliminary phase II study results

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Background: The oral fluoropyrimidine capecitabine (Xeloda) has improved efficacy, safety and convenience vs. 5-FU/LV in MCRC [Van Cutsem et al. Br J Cancer 2004] and early-stage colon cancer [Twelves et al. NEJM 2005]. A recent study showed that irinotecan + capecitabine q2w is active and well tolerated [Garcia-Alfonso et al. ESMO 2006]. The humanised monoclonal antibody bevacizumab (Avastin) targets VEGF and limits tumour angiogenesis. The addition of bevacizumab to 5-FU/LV/irinotecan (IFL) results in significant improvements in survival among pts with MCRC [Hurwitz et al. NEJM 2004]. Replacing 5-FU/LV with capecitabine in this combination is a logical step forward. Here we report data from an open-label phase II trial of capecitabine + irinotecan + bevacizumab in MCRC.
Materials and Methods: Pts with untreated, histologically confirmed MCRC received irinotecan 175 mg/m^2 i.v. on day 1, capecitabine 1000 mg/m^2 orally bid on days 2–8, and bevacizumab 5 mg/m^2 on day 1 q2w for 12 cycles in the absence of disease progression or unacceptable toxicity. Pts without progressive disease after 12 cycles of capecitabine + irinotecan + bevacizumab continued on the same dose of bevacizumab + capecitabine 1500 mg/m^2 bid on days 2–8, q2w. The primary endpoint was progression-free survival (PFS); secondary endpoints were response rate (RECIST), overall survival (OS), safety and quality of life.
Results: 28 out of 32 pts have been enrolled. Baseline characteristics: male/female 46%/54%; median age 53 years (range 30–70); disease stage

at initial diagnosis II/III/IV 21%/14%/64%; no. of metastatic sites 1/>1 46%/54%; most common metastatic site liver; prior adjuvant therapy 33% (Mayo 5-FU/LV). Pts received a median of 12 cycles (range 1–12) of capecitabine + irinotecan + bevacizumab; capecitabine + bevacizumab range: 0–26. All 28 pts are evaluable for safety and 26 for efficacy. The overall response rate is 69% (3 CR, 15 PR); 2 pts (8%) have stable disease and 6 have progressed. One pt has died. Median PFS and median OS have not yet been reached. The only grade 3 adverse events are diarrhoea (11%), hand–foot syndrome (7%), fatigue (4%), mucositis (4%), enteritis (4%) and ileus (4%); there is one report of grade 4 leukopenia. All other adverse events are mild-to-moderate.
Conclusions: The capecitabine + irinotecan + bevacizumab combination appears to be highly active and well tolerated as first-line treatment for MCRC, providing support for further evaluation of this combination.

3069 POSTER

Study of CPT-11, oxaliplatin, UFT triple therapy (SCOUT) in advanced colorectal cancer (ACRC): an effective and well-tolerated regimen

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Background: Treatment-related toxicity and poor performance status can prevent patients from receiving second-line therapy after failure of first-line treatment. We investigated the feasibility of triple-drug therapy with irinotecan, oxaliplatin, and UFT with leucovorin (LV) in a phase I/II open-label dose-finding trial in patients with ACRC. Of particular interest was whether patients could benefit further from chemotherapy after disease progression.
Methods: Eligible patients aged ⩾18 y had histologically confirmed advanced, inoperable, measurable metastatic disease, no prior chemotherapy other than adjuvant 5-fluorouracil (5-FU) ⩾6 mo previously, and adequate bone marrow, liver, and kidney function. In phase I, patients received irinotecan 180 mg/m^2 on d1, oxaliplatin 85–100 mg/m^2 on d15, and UFT 200–300 mg/m^2/d with LV 90 mg/d on d1–21 of a 28-d cycle. The maximum tolerated dose (MTD) was established at irinotecan 180 mg/m^2, oxaliplatin 100 mg/m^2, UFT 250 mg/m^2/d, and LV 90 mg/d. Patients were treated at the MTD in the phase II study.
Results: Patients (median age 62 [range 24–79] y, ⩾3 marker lesions in 32 patients, disease confined to liver in 12 patients) were recruited, 25 in phase I and 20 added in phase II for a total of 29 at the MTD. Treatment was highly effective, with a response rate of 66% (95% CI 49–80%) in 38 evaluable patients and clinical benefit in 89% (95% CI 75–97%). At a median follow-up of 10.3 mo, median time to progression was 8.5 mo (95% CI −7.6 to 10.4 mo) in 40 evaluable patients; median overall survival (ITT population n = 45) was 16.8 mo (95% CI −11.3 to 28.3 mo). Two patients underwent resection of liver metastases (1 R0, 1 R1). Grade 3 adverse events at the MTD included: diarrhea (n = 3; 10%); neurotoxicity (n = 1; 3%); lethargy (n = 1; 3%). One patient had grade 4 cardiac toxicity. No hand–foot syndrome (HFS) was seen. In 30 patients with confirmed radiologic progression, 21 (70%) had second-line therapy (Table).

Second-line regimen	N
SCOUT retreatment[a]	8
Irinotecan/cetuximab	3
Mitomycin C/capecitabine	4
Oxaliplatin/5-FU	2
Capecitabine	1
Phase I studies	3

[a]Up to four 6-mo cycles.

Conclusions: In the first-line treatment of patients with ACRC, UFT plus LV with alternating irinotecan and oxaliplatin gives a high response rate, with minimal alopecia and neurotoxicity and no HFS, thus permitting administration of repeated treatment courses and resection in suitable patients. The SCOUT regimen is an effective and convenient treatment for patients with ACRC.

3070 POSTER

Bevacizumab in patients with previously treated metastatic colorectal cancer: preliminary results of a phase II study (bevacolor)

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Background: The activity of bevacizumab(Avastin®) as part of second-line therapies in metastatic colorectal cancer (mCRC) is currently under investigation. The aim of this study was to determine the safety and efficacy of adding bevacizumab (BV) to common chemotherapy regimens used in second-line therapy in mCRC.
Methods: A multicentre phase II study was conducted in fifty-three patients with mCRC progressing after first-line oxaliplatin or irinotecan-based chemotherapies. They received bevacizumab (BV) 2.5 mg/kg/week, until disease progression, on day 1 of a chemotherapy regimen chosen by the investigator.
Results: Overall, 35 men and 18 women, performance status 0 to 2, median age 62 (33−80) years, were treated. Ten patients (19%) had liver metastases and 39 patients (74%) had more than one metastatic site. The first-line treatment previously administered to patients was Folfox (53%), Folfiri (22%), Xelox (20%) and other chemotherapies (5%). Second line treatments included Folfiri (57%), Folfox (26%), Irinotecan (15%), Xeliri (2%). Patients received a median of 8 cycles (2−13) of chemotherapy and BV and 43 (81%) received BV at the dose of 5 mg/kg every 2 weeks.
After a follow up of 6 months, best response was assessed: one (2%) patient had a complete response (CR), 16 (30%) had partial response (PR), 29 (55%) had stable disease (SD) and 5 (9%) progressed. The rate of disease control defined as CR +PR +SD was 87% [95% CI, 78%-96%] and objective response rate (CR +PR) was 32% [95% CI, 19%-46%].
A total of 51 (96%) patients had adverse events and thirty-two (60%) had Grade 3/4 CTC AE toxicities including neutropenia in 11 (21%) patients, diarrhea in 7 (13%) and asthenia in 5 (9%). Grade 3/4 targeted toxicities (known to occur with BV) were reported in 6 (11%) patients, they included hypertension in 3 (6%) patients and thromboembolism in 3 (6%). Three deaths occurred mainly due to disease progression, no toxic death was observed.
Conclusions: The administration of BV, associated to chemotherapy is acceptable as 2nd line treatment in patients with mCRC, achieving an objective response rate of 32%. The toxicity profile of Bevacizumab in combination with standard chemotherapies in mCRC was acceptable. More details including progression free survival and overall survival will be given at the congress.

3071 POSTER

Impact of intensity modulated radiation therapy (IMRT) on bone marrow tolerance during combined treatment with chemotherapy for patients with anal canal cancer

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Background: IMRT has been introduced as a mean to improve sparing of normal structures during radiation therapy. Present study is reporting the experience of a single institution with the use of IMRT and conformal external beam radiation combined with chemotherapy for patients with anal canal carcinoma.
Materials and Methods: From 2004–2007, fifty patients with T2−4 squamous cell anal canal carcinoma were treated to doses of 54−59.8 Gy in 30−33 fractions without interruption and concurrently with 2 cycles of chemotherapy during weeks 1 and 6 of radiation using 5-Fluorouracil (5-Fu, 1000 mg/m^2/day, 96 hours continuous infusion) and Mitomycin C (MMC, 10 mg/m^2, bolus on day 1). Radiation was delivered with IMRT in 18 patients and 3D-conformal radiation therapy (3D-CRT) in 32 patients. Dose of 30 Gy in 15 fractions were prescribed to elective iliac and inguinal nodes and 54−59.6 Gy to the tumor bed and involved nodes. A two-phase CT-based planning is done for both techniques. Pelvic bone marrow was defined as the region extending from the iliac crests to the ischial tuberosities. Hematological toxicity was assessed by weekly blood counts