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