Conclusions: The combination of gefitinib and capecitabine is feasible at doses 250/1250 in advanced colorectal cancer. The combination appears to have a manageable tolerability profile. It is too early to assess efficacy. IRESSA is a trademark of the AstraZeneca group of companies

701 PUBLICATION

Phase II multi center study of combination therapy with irinotecan and S-1 for metastatic colorectal cancer

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Background: The currently first-line chemotherapy for metastatic colorectal cancer is multiple-drug therapy including Irinotecan or Oxaliplatin. On the other hand, the efficacy of oral fluorinated pyrimidine anticancer drugs has recently attracted more attention. The oral fluorinated pyrimidine compound S-1, even when used alone, has been reported to show considerable efficacy, achieving a response rate of 39.5% in patients with colorectal cancer (Shirao K, et al: Cancer). Therefore, we planned to conduct a phase II clinical study of combination therapy with irinotecan and S-1, a new oral anticancer drug of the fluorinated pyrimidine type (Komatsu Y, et al: Jpn J Clin Oncol).
Patients and Methods: The antitumor effect was the primary endpoint, while the safety, progression-free survival time, and median survival time were the secondary endpoints. The subjects were untreated patients with metastatic colorectal cancer aged 20–75 years. Based on the results of our previous phase I/II study in patients with gastric cancer (Komatsu Y, et al: UEGW 2005), the dosage was established in consideration of safety for outpatient therapy. Irinotecan was administered at a dose of 100 mg/m^2 (on days 1 and 15) as an intravenous infusion over 90 minutes, and oral S-1 (40 mg/m^2) was administered after breakfast and dinner and then withdrawn for 2 weeks.
Results: At the time of abstract submission, 30 patients were enrolled in the present study. There were 22 men and 8 women. No other serious adverse reactions occurred (either hematological or non-hematological), and all patients could receive therapy safely on an outpatient basis. Interim analysis suggested excellent results, with a response rate of 60%. Median survival time is not reached yet.
Summary: Combination therapy with Irinotecan and S-1 achieved a high response rate and could be given safely. These findings suggest that the therapy has potential as first-line treatment for metastatic colorectal cancer. And it may be equal to a FOLFIRI treatment for metastatic colorectal cancer. The latest data will be reported at the meeting.

702 PUBLICATION

Cetuximab and irinotecan/5-fluorouracil (5-FU)/folinic acid (FA) (AIO) is active and safe in the first-line treatment of metastatic colorectal cancer (mCRC) expressing the epidermal growth factor receptor (EGFR)

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Background: The AIO schedule of irinotecan/5-FU/FA is highly active in mCRC. Cetuximab (Erbitux®) is an IgG1 monoclonal antibody, specific for the EGFR, which is active in mCRC. This phase I/II study investigated the safety/tolerability, pharmacokinetics (PK) and activity of cetuximab when added to irinotecan/5-FU/FA (AIO) for the first-line treatment of mCRC.
Materials and Methods: 21 patients with previously untreated, EGFR-expressing mCRC received cetuximab (400 mg/m^2 initial dose and 250 mg/m^2/week, thereafter) and infusional 5-FU (24-h) at two dose levels (1,500 mg/m^2 [low-5-FU group, n = 6] or 2,000 mg/m^2 [high-5-FU group, n = 15]), plus FA at 500 mg/m^2 and irinotecan at 80 mg/m^2, weekly x6 q50d. Dose-limiting toxicities (DLTs) were: neutropenia or skin toxicity >grade 3; febrile neutropenia/leucopenia; thrombocytopenia, diarrhoea, mucositis >grade 2; other relevant organ toxicity >grade 2, each in the first cycle of treatment.
Results: 20 patients were assessable for tolerability in the first cycle. There were 3 DLTs (20%) in the high-5-FU group (diarrhoea grade 3 [n = 2] and diarrhoea grade 4 [n = 1]) and none in the low-5-FU group. In the high-5-FU group, 7/14 patients (50%) received ⩽80% of planned dose during the first cycle due to dose reductions, and treatment delays were required in 10/14 patients. In the low-5-FU group, all 6 patients received >80% of the planned dose. 5 patients had a dose delay of cetuximab during the first cycle (3 due to skin toxicity, 2 due to diarrhoea caused by chemotherapy). Throughout the study, common grade 3/4 adverse events were acne-like rash (38%), diarrhoea (29%) and nausea and vomiting (5%). Most were grade 3 events: only two incidents of grade 4 events were reported (1 grade 4 acne-like rash and 1 diarrhoea). Cetuximab PKs were not affected by chemotherapy, and derived PK parameters were similar in the 2 different 5-FU dose groups. 14/21 assessable patients (67%, 95% CI: 47%-87%) had a response (2 complete and 12 partial responses), and 6 (29%) had stable disease. Median survival (OS) was 33 months. 4 patients received secondary surgery of their liver metastases with curative intent. A fifth was eligible for surgery but declined.
Conclusions: Cetuximab plus weekly infusional 5-FU/FA (AIO) and irinotecan is safe and has demonstrated a promising overall response rate of 67% and median OS of 33 months. A 5-FU dose of 1,500 mg/m^2 in this combination is recommended for further studies in this setting.

703 PUBLICATION

Phase II multicenter study of capecitabine plus oxaliplatin (XELOX) sequentially followed by capecitabine and irinotecan (XELIRI) in first-line therapy for metastatic colorectal cancer (MCRC)

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Background: In phase II trials XELOX or XELIRI shown good antitumor efficacy and tolerability in first-line in MCRC. The aim of this study is to explore the efficacy and safety of XELOX sequentially followed by XELIRI as first-line treatment of MCRC. We want to evaluate specifically the impact of sequential scheduling on the dose-limiting neurotoxicity associated with oxaliplatin accumulation.
Material and Methods: Pts with histological or cytological confirmation of MCRC, ECOG PS ⩽2 and adequate bone marrow, renal and hepatic function were included. Prior chemotherapy for MCRC was not allowed. Pts received 4 cycles of XELOX (capecitabine 1000 mg/m^2 orally bid d1–14 + oxaliplatin 130 mg/m^2 i.v. d1, q3w) followed by 4 cycles of XELIRI (capecitabine 1000 mg/m^2 bid d1–14 + irinotecan 240 mg/m^2 i.v. d1, q3w). This sequential schedule was repeated until unacceptable toxicity or disease progression.

	XELOX		XELIRI	
	Grade2	Grade3	Grade2	Grade3
Neutropenia	6	6	8	8
Anemia	13	3	15	0
Diarrhea	13	6	23	8
Intestinal suboclusion	0	3	0	0
Neurosensory	6	6	8	0
Paresthesia	0	3	0	0
Nausea	13	0	15	0
Vomiting	9	3	23	0
Asthenia	16	3	15	8

Results: Up to date, 33 pts have been enrolled: M/F (70%/30%); median age 69 years (range 41–78); ECOG PS 0–1 (94%). Previous treatment included surgery (81%), adjuvant chemotherapy (33%) and radiotherapy (12%). 169 cycles (median 4, range 1–16) have been administered. During the 1st sequential schedule, 32 pts received XELOX (106 cycles, median 4), and 13 pts received XELIRI (47 cycles, median 4). In the 2nd sequential

schedule, 3 pts received XELOX (9 cycles, median 4) and 2 pts received XELIRI (7 cycles, median 3.5). Median relative dose intensity was: 98% for capecitabina and 100% for oxaliplatin, 80% for capecitabina and 92% for irinotecan during 1st XELOX/XELIRI sequence. In 19 evaluable pts for efficacy, the ORR was 47% (95% CI, 25–70%). 13 pts are not evaluable (4 adverse events; 8 on treatment and 1 lost of follow-up). The median TTP was 11.9 months (95% CI, 4.4–19.5). There were no grade 4 adverse events. Main toxicities per patient has shown in the table.
Conclusions: Sequential schedule of XELOX followed by XELIRI has shown a good safety and efficacy, including a promising low rate of grade 3 neurosensory/paresthesia toxicity in the fist-line treatment of MCRC.

704 PUBLICATION

Does radiotherapy technique influence survival in rectal cancer? A multivariate analysis

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Aim: Treatment results of postoperative chemoradiotherapy (CRT) and the effect of radiotherapy techniques on the outcome in local or advanced rectal cancer were investigated.
Patients and Methods: A total of 69 patients (39 male, 30 female) with surgically removed rectal cancer (pT3–4 pN0-any pT pN+) treated with postoperative CRT between July 1999 and December 2004 were analyzed retrospectively. Median age was 58 (24–83) years. Low anterior resection was performed in 39 patients and abdominoperineal resection in 30. The median number of removed and metastatic lymph nodes was 12 and 2 (1–49) respectively. Patients were pathologically staged as follows: IIa 39%, IIb 4.3%, IIIa 5.8%, IIIb 31.9 and IIIc 18.8%. Irradiation was given with a single daily fraction of 1.8 Gy to a total dose of 50.4 Gy. Five patients treated with the parallel opposed (AP-PA) fields and four-field box technique was used in 65 patients. Chemotherapy (CT) consisted of the combination of 5-fluorouracil and leucovorin. Thirty patients received 1 to 2 cycles of CT before concurrent CRT, while 39 has started with CRT simultaneously after surgery. The median interval between surgery and radiotherapy (RT) was 58 days and RT was completed in median 42 (30–73) days. Clinical and pathologic variables including age, sex, clinical stage, operative method, tumor differentiation, number of removed and metastatic lymph nodes, AP/PA or box treatment designs, administration of CT before RT and having late complications were analyzed using univariate and multivariate Cox models.
Results: The median follow-up was 25 (5.5–65) months. Late severe intestinal toxicity appeared in 7 patients and 5 of them had required intestinal resections, the others had occlusive crises responded to medical treatments. Local recurrence and distant metastasis were detected in 5 (%7.2) and 7 (%10.1) patients respectively.
Median progression-free and overall survivals (OAS) were 55 and 58 months. Univariate analysis showed that number of metastatic lymph nodes, AP-PA field technique, late complications and having 1 to 2 course of chemotherapy before CRT had significant impact on overall survival (OAS). In multivariate analysis, high number of metastatic lymph nodes ($p = 0.001$, HR:1.12), AP-PA field technique ($p = 0.004$, HR:8.14) and late complications ($p = 0.033$. HR: 0.21) were independent poor prognostic factors for overall survival.
Conclusion: High number of positive lymph nodes, AP-PA radiotherapy technique and late complications were independent prognostic factors for survival in patients with rectal carcinoma treated with surgery and postoperative CRT. Our results show that appropriate RT technique should be utilized for rectal cancer patients in order to improve survival.

705 PUBLICATION

Transanal excision of rectal villous adenomata is an effectine alternative to more major surgery in high risk patients

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Background: Flat adenomata are frequently unsuitable for endoscopic snare removal techniques, but those within the lower rectum may be amenable to simple transanal excision. The aim of our study was to evaluate the complication and recurrence rates in all patients who had undergone a transanal excision for rectal villous adenomata under the care of single colorectal surgeon.
Material & methods: All patients who had undergone this procedure over nine year period were identified from consultant's logbook and all casenotes were retrieved for retrospective analysis.
Results: A total of 56 trans anal excisions were performed in 35 patients. The male:female distribution was equal and the patients ranged in age from 44 to 89 years (mean age 68). Many were frail, a number having significant co-morbidity with 11 classified as ASA grade 3 or 4. All had confirmed tubulovillous adenomata with low to high grade dysplasia. The distance of the lesions were ranging 4 cm-10 cm (mean 6 cm) from anal verge. Recurrence developed in 5 patients (14%), of which 3 underwent repeat excision, 2 elderly patients having multiple repeat procedures over many years. There was no significant mortality or morbidity.
Conclusions: Transanal excision is a successful alternative to major surgical operations in relatively poor risk patients with large rectal villous adenomas, with no significant mortality and morbidity.

706 PUBLICATION

Comparision of rectal bleeding clinic with conventional out patient clinic for detection of early colorectal cancer.

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Background: To study the effectiveness of a Rectal Bleeding Clinic in detecting premalignant colonic lesions and early colorectal cancers in comparison with conventional out-patient clinics (OPD).
Materials & methods: All 2,175 consecutive patients referred to the RBC from November 1997 to Aug 2004 were assessed by detailed history, clinical examination and flexible sigmoidoscopy underwent subsequent colonoscopy. The final definitive histology of each patient was confirmed from the histology department database, which was also used to identify a control group of 92 consecutive patients with colorectal cancer diagnosed in conventional OPD.
Results: Two hundred and thirty patients (10.6%) had significant neoplastic lesions. Of these 139 had adenomatous polyps and 92 patients had invasive cancer. Of the invasive cancers, forty one (45%) patients had Duke's A lesions, as compared to 10 (10%) of the control group of patients coming through the OPD during this period, as shown in the table below.

Duke's stage	RBC	OPD
A	41 (45%)	10 (10%)
B	29 (29%)	43 (46%)
C	17 (19%)	31 (36%)
D	4 (4%)	5 (5%)
X	3 (3%)	3 (3%)
Total	*92*	*92*

Twenty patients ages 40–49 years were diagnosed as having neoplastic lesions (eleven with low grade dysplasia, one with high grade dysplasia and eight with invasive cancer).
Conclusions: A rapid access RBC enables detection of a higher proportion of potentially curable early colorectal cancers than conventional clinics, in addition to a large number of pre-malignant lesions which can be treated endoscopically with subsequent colonoscopic surveillance.

707 PUBLICATION

Capecitabine, oxaliplatin and irinotecan combination: a first line treatment for metastasic colorectal cancer, preliminary results of a phase II study

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Background: Oxaliplatin, Irinotecan and Capecitabine are active drugs in colorrectal cancer. This drugs have been found to act sinergistically, both, at "in vivo" and "in vitro" studies. The aim of this study is to determinate the safety and efficacy of this combination in metastasic colorrectal cancer (MCRC) as first-line treatment.
Methods: 34 eligible and untreated patients with MCRC were included in this trial. All patients received, Oxaliplatin 85 mg/m^2 day 1, Irinotecan 150 mg/m^2 day 1 and Capecitabine 800 mg/m^2 bid for 7 days, cycles were repeated every 14 days.
Results: From November 2004 to May 2005, 34 patients were enroled into the study with the following characteristics: male/female (64.7%/35.3%), median age 57 (32–68), performance status 91.2% I, 8.8% II, metastasic locations: 85.3% liver, 79.4 lung, 25% retroperitoneum. The median number of cycles received per patient was 6 (1–12). Response was as follows: 5.9% complete response, 73.5% partial response, 20.5% stabilization. No progressions during treatment were found.
NCI-CTC grade III/IV hematologycal toxicities presented as follows: 8.8% Anemia, 11.8% leucopenia, 32.4% neutropenia, 2.9% plaquetopenia. Non-hematologycal toxicities presented as follows: 14.7% vomiting, 14.7%