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Efficacy and safety findings from a phase II study of capecitabine (X) as first-line therapy in Japanese patients (pts) with metastatic colorectal cancer (MCRC): comparison with published Western data

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Background: The 3-weekly regimen of X (1250 mg/m^2 bid, d1–14, q3w) has demonstrated superior activity and improved safety over bolus 5-FU/LV (Mayo Clinic regimen) as first-line therapy in 2 large randomised phase III trials. We conducted a phase II study to investigate the efficacy and safety of the 3-weekly X regimen in Japanese pts with MCRC and compared our findings with the published pooled efficacy and safety results from the Western phase III trials [Van Cutsem et al. 2004; Cassidy et al. 2002].
Methods: Eligibility criteria were aligned with the randomised phase III studies. Pts received X 1250 mg/m^2 bid on d1–14, q3w. Overall response rate (ORR) and time to progression (TTP) were assessed according to WHO criteria. The most common adverse events (diarrhoea, hand–foot syndrome [HFS], stomatitis, appetite decreased, nausea, hyperpigmentation, vomiting, GOT increased, hyperbilirubinaemia and increased lymphocyte count) were compared across the studies.
Results: 60 chemo-naïve pts were enrolled in the Japanese study. In terms of baseline characteristics, there were minor differences in performance status, cancer type, no. of metastatic sites and previous radiation therapy in the Japanese and phase III studies. The ORR was 32% (95% CI, 20–45%) in the Japanese study compared with 26% (95% CI, 22–30%) in the Western studies. There was no significant difference in median TTP (5.4 months vs. 4.6 months). The following related adverse events (all-grades) occurred more frequently in the Japanese study: HFS (73% vs. 53%), stomatitis (35% vs. 24%), decreased appetite (33% vs. 17%), hyperpigmentation (38% vs. 2%), and hyperbilirubinaemia (67% vs. 48%). However, the rate of diarrhoea was lower (35% vs. 48%), and nausea (35% vs. 38%) and vomiting (15% vs. 23%) were similar. The rate of grade 3/4 related events in the Japanese and Western studies were: HFS (13% vs. 17%), diarrhoea (2% vs. 13%) and hyperbilirubinaemia (33% vs. 23%).
Conclusions: Efficacy and safety data from the Japanese phase II study are similar to published Western data. These findings suggest that the 3-weekly regimen of X is highly effective and well tolerated for Japanese and Western pts with MCRC.

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Cutaneous and non-cutaneous toxicity induced by biologic therapy with cetuximab (erbitux)

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Background: Therapy with monoclonal antibody anti-EGFR (cetuximab) represents an important progress in scenery of medic therapy in advanced colorectal cancer patients. Tolerability and, in particular, cutaneous and non-cutaneous toxicity pattern induced by this new biologic therapy is non yet clearly known. Aim of this study was to analyze and describe cutaneous and non-cutaneous toxicities in a group of advanced colorectal cancer patients treated with cetuximab.
Materials and methods: 44 consecutive metastatic colorectal cancer patients (rectum/colon: 12/32), M/F: 16/28, median age 61 years (27–79), have been treated with cetuximab in monotherapy (5 patients) or combined with irinotecan (39 patients). A total of 762 courses have been administered, with a median of 16 courses for every patient and a range of 3–48 courses.
Results: Cutaneous toxicity: more frequent seats: only face (50%); only trunk (18.2%); face + trunk (27.2%); only limbs (11.4%). Type and grade of cutaneous toxicity are shown in table 1.
Non-cutaneous toxicity: type and grade of non-cutaneous toxicity are shown in table 2:
Conclusions: Toxicity pattern induced by cetuximab is various in terms of type, organ involved and events' severity. In our experience we have registered different types of cutaneous toxicities, generally spontaneously reversible after temporary interruption of therapy. Finally, for the first time in literature, we have reported a characteristic ophthalmic toxicity (blepharitis) caused by cetuximab.

Table 1

Cutaneous toxicity	All grades (%)	Grade 3–4 (%)
Every grade	90.9%	34.1%
Folliculitis	84.9%	27.2%
Erythema	88.6%	22.7%
Peri-ungual toxicity	45.5%	15.9%
Blepharitis	27.2%	18.2%

Table 2

Other toxicities	All grades (%)	Grade 3–4 (%)
Diarrhea	68.2%	27.2%
Stomatitis	59.1%	6.8%
Emesis	54.5%	0%
Hypotension	13.6%	0%
Allergic reactions	0%	0%
Fever	31.8%	0%
Fatigue	27.2%	9.1%

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Phase I/II trial of capecitabine and gefitinib in patients with advanced colorectal cancer after failure of first-line therapy

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Background: Capecitabine is active in advanced colorectal cancer (ACC) and appears to have synergistic activity with gefitinib (IRESSA) *in vitro* (Magne et al, Clin Cancer Res 2003;9:4735–42). The study aimed to evaluate the safety and efficacy of gefitinib in combination with capecitabine in patients (pts) with ACC.
Methods: A multicenter Phase I/II trial (1839/0505) recruited pts aged *18 years with WHO performance status (PS) $\leqslant$2, adequate organ function, and measurable disease. The Phase I study combined gefitinib 250 mg/day with 2 escalating capecitabine doses (1000 and 1250 mg/m^2 twice daily on Days 1–14 of a 21-day cycle). The recommended dose of capecitabine (based on the safety and tolerability results from the Phase I study) was then evaluated in combination with gefitinib in a Phase II trial. Tumor status was assessed every 9 weeks using RECIST. Adverse events were assessed by NCI-CTC (V3).
Results: 10 pts have been enrolled in the Phase I study at doses of 250/1000 (n = 6) and 250/1250 (n = 4): median age, 62 years (range 47–71); male/female, 9/1; PS 0/*1, 7/3; median chemotherapy cycles, 6. The most common adverse drug reactions (NCI-CTC) during the first 2 treatment cycles were: diarrhea (Grade [G] 1, n = 5; G2, n = 1 for 3 weeks [dose-limiting toxicity]), asthenia (G1, n = 2; G2, n = 3), rash (G1, n = 5; G2, n = 1), elevated transaminases (G1, n = 1; G3, n = 1), anemia (G1, n = 3) and leukopenia (G1, n = 1). Two treatment interruptions were required, without associated dose reduction.
Based on these data, a dosage of 250/1250 was carried into the Phase II study, into which 22 pts have been enrolled: median age, 66 years (range 53–81); male/female, 16/6; PS 0/1/2, 11/11/0. The no. of metastatic locations were: 1 site, n = 5 (23%); 2–3 sites, n = 4 (18%); >3 sites, n = 13 (60%). The most frequent metastatic locations were: liver, n = 48 (52%); lung, n = 32 (34%); lymph nodes, n = 7 (7.5%). Twelve pts were evaluable for efficacy: 6 had stable disease and 6 had progressive disease. All pts were evaluable for toxicity. CTC 3–4 Grade AEs were: diarrhea (n = 5, 23%); asthenia (n = 2, 9%); mucositis (n = 1, 5%); febrile neutropenia (n = 1); dysphagia (n = 1); gastrointestinal disorder (n = 1) and dry skin (n = 1).

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.

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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