next step will be to use the validated model to select patients who do not need (immediate) surgery.

6048 POSTER

A comparison of efficacy of first-line chemotherapy regimens for metastatic colorectal cancer (mCRC): FOLFIRI+ bevacizumab vs. XELIRI+ bevacizumab

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Background: FOLFIRI in combination with bevacizumab (BV) is a standard treatment option in first-line Cht for mCRC. Capecitabine is an oral prodrug of 5-FU, which is converted to 5-FU by three enzymatic steps. It can maintain a constant level of 5-FU without complications. The primary endpoint was to determine the efficacy of XELIRI/BV and to compare it to FOLFIRI/BV. The secondary endpoints were overall survival (OS), time to progression (TTP) and evaluation of side effects of BV.
Methods: Pts with histologically proven, previously untreated mCRC, older than 18 years, ECOG PS 0−2 and adequate organ and hematological functions were included to receive a combination of irinotecan 180 mg/m^2 iv day 1, BV 5 mg/kg iv day 1, LV 400 mg/m^2 iv day 1, 5-FU 400 mg/m^2 bolus iv day 1and 5-FU 2400 mg/m^2 in continuosly 46-hour infusion, repeated every 2 weeks, or irinotecan 250 mg/m^2 iv day 1, BV 7.5 mg/kg iv day 1 and capecitabine 1000 mg/m^2, po twd day 1−14, repeated every 3 weeks.
Results: From February 2005 to December 2007 139 pts with mCRC were included. Median age was 58 years (31−77), M/F = 61.9%/38.1%. Of 139 44 pts were treated with FOLFIRI/BV and 95 pts with XELIRI/BV. On analysis of results, data of all pts were available. Median duration of treatment was 22 weeks (2−36 weeks) in FOLFIRI/BV group and 20.1 weeks (3−36 weeks) in XELIRI/BV group. RR were CR 15.9% (7 pts), PR 22.7% (10 pts), SD 36.4% (16 pts), PD 20.5% (9 pts) in FOLFIRI/BV group and CR 11.6% (11 pts), PR 33.7% (32 pts), SD 41.1% (39 pts), PD 7.4% (7 pts) in XELIRI/BV group. Median TTP was 13.9 months in FOLFIRI/BV group and 17.6 months in XELIRI/BV group (95% CI). Median OS was 43.3 mo in FOLFIRI/BV group and 63.6 mo in XELIRI/BV group (p = 0.112). In 40 pts, BV was discontinued because of severe side effects. Deep venous thrombosis was detected in 7 pts, pulmonary embolism in 2 pts, colon perforation in 1 pt, any hemorrhagic event in 4 pts, G 3−4 hypertension in 2 pts, proteinuria G 3−4 in 8 pts. None of pts died because of side effects.
Conclusions: XELIRI/BV is at least as effective as FOLFIRI/BV in first-line treatment of mCRC. The results of efficacy of both regimens in our pts are comparable with the results from previous phase III studies in first-line treatment of bevacizumab + chemotherapy. Median OS was longer in XELIRI/BV, but it was not statisticaly significant. The observed adverse effects of BV in our study are comparable to those previously reported in mCRC.

6049 POSTER

Phase II trial of combined chemotherapy with irinotecan, S-1, and bevacizumab in patients with metastatic colorectal cancer

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Background: A study comparing the effectiveness and safety of irinotecan plus S-1 (IRIS) with that of a combination of 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) as second-line treatment in patients with advanced, recurrent colorectal cancer (FIRIS trial) is ongoing in Japan. We previously reported that IRIS is very effective as first-line treatment (33rd ESMO in 2008). Bevacizumab, a molecular targeted agent, is positioned as a standard regimen for the treatment of advanced colorectal cancer. We examined the effectiveness and safety of the IRIS regimen combined with bevacizumab.
Materials and Methods: Eligible patients had to have mCRC with a confirmed diagnosis of adenocarcinoma, an age of $\geqslant$20 years, a ECOG performance status (PS) of 0−1, and no history of prior chemotherapy. S-1 40−60 mg twice daily p.o. was given on days 1−14 and irinotecan 100 mg/m^2 and bevacizumab 5 mg/kg i.v. were given on days 1 and 15 of a 28-day cycle. The primary endpoint was safety. The secondary endpoints included overall response (OR), progression-free survival (PFS), and overall survival (OS).
Results: The target number of 53 patients was enrolled as of March 2009. The results are reported for 45 patients with evaluable lesions. The clinical characteristics of the patients were as follows. The median age was 63 years (interquartile range, 48 to 82). The male:female ratio was 3:2. The performance status on the Eastern Cooperative Oncology Group scale was 0. At interim analysis, median follow-up was 162 days. On safety analysis, the incidence of grade 3 or 4 neutropenia was 27%. The incidences of other grade 3 or 4 adverse reactions were as follows: diarrhea, 13%; anorexia, 7%; stomatitis, 2%; hypertension, 11%; and gastrointestinal perforation, 0%. The overall response rate was 53%. Twenty-four patients (53%) had a partial response, 17 (38%) had stable disease, none had progressive disease, and 4 (9%) were not evaluable. Median progression-free survival and overall survival were not reached.
Conclusions: Our results suggest that IRIS plus bevacizumab is a well-tolerated, highly effective chemotherapeutic regimen that is easy to administer. The latest data will be reported at this meeting.

6050 POSTER

Clinical features of interstitial lung disease induced by FOLFOX or FOLFIRI for colorectal cancer

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Background: Either infusional fluorouracil, leucovorin and oxaliplatin (FOLFOX) or infusional fluorouracil, leucovorin and irinotecan (FOLFIRI) has been recognized as one of the standard chemotherapy for colorectal cancer. Chemotherapy-induced interstitial lung disease (ILD) is rare, and few patients with ILD following FOLFOX or FOLFIRI have been reported. The aims of this study are to clarify and evaluate the clinical features of ILD after treatment of FOLFOX or FOLFIRI for colorectal cancer.
Material and Methods: We identified 734 patients with colorectal cancer treated with FOLFOX or FOLFIRI from April 2005 to December 2008 at National Cancer Center East Hospital by using computerized data base of the institution. ILD was defined when a chest computed tomography revealed interstitial infiltrates and the other pulmonary disease was clinically excluded. We categorized patients with ILD into improved ones and dead ones.
Results: Of 734 patients, 449 (92) received FOLFOX (with bevacizumab), 55 (18) FOLFIRI (with bevacizumab) and 230 (93) both FOLFOX and FOLFIRI (with bevacizumab). Eleven (1.5%) patients developed ILD, which consisted of 7 improved ones and 4 dead ones. All patients with ILD were men, and 10 of 11 patients were heavy smoker. Of 11 patients, 10 patients had any pulmonary shadows except lung metastases before chemotherapy. FOLFOX has been ever administered for all of the ILD patients. Six patients developed ILD during FOLFOX therapy, one occurred on the 137th day after completion of adjuvant chemotherapy with FOLFOX, and four developed ILD during the other regimens (FOLFIRI in three patients and fluorouracil/leucovorin plus bevacizumab in one). Median Brinkman Index was 700 (range, 0–1000) in the improved patients and 1085 (range, 380–1380) in the dead ones. Median days from the last dose of any chemotherapy to the episode were 8 days (range, 0–137 days) in the improved patients and 1.5 days (range, 0−10 days) in the dead ones. Median days from the episode to start of the treatment were 8.5 days (range, 0−14 days) in the improved patients and 13 days (range, 5−21 days) in the dead ones.
Conclusions: This study was the first systemic analysis to investigate the incidence of ILD induced by FOLFOX or FOLFIRI. The incidence of ILD was not so common, but it is life-threatening complication. We should be careful to the onset of ILD not only during, but also after chemotherapy for colorectal cancer.

6051 POSTER

Balancing pros and cons of the addition of Bevacizumab (BEVA) to first-line chemotherapy (CT) for advanced/metastatic colorectal cancer (MCRC): Meta-analysis of randomized clinical trials exploring absolute benefits

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Background: Although the addition of BEVA to CT has provided a significant survival benefit for MCRC, the magnitudes of both the advantages and the drawbacks (with particular regard to vascular toxicities) have not been extensively weighted. With these perspectives, a literature-based meta-analysis was conducted.

Methods: Hazard Ratios (HR) with 95% Confidence Intervals (CI) were extracted from prospective, randomized clinical trials (RCTs, either phase II/III) for primary end-points. The log of event-based relative risk ratio (RR) with 95% CI were derived for secondary endpoints through a random-effect model. Primary outcomes were both Progression Free Survival (PFS), and Overall Survival (OS). Secondary end-points were: 1) objective response rate (ORR), 2) partial response rate (PR), 3) grade 3−4 hypertension (HTN) rate, 4) grade 3−4 bleeding rate, and 5) grade 3−4 proteinuria rate. Absolute differences (AD) and the number of patients needed to treat/harm (NNT/NNH) were calculated. Heterogeneity test and a meta-regression analysis with clinical predictors for outcomes were conducted as well. A sensitivity analysis according to the trial phase-design was accomplished. Calculations were accomplished using the SPSS and the CMA v 2.0 software.
Results: Five trials (2,728 pts), 2 phase II (313 pts) and 3 phase III (2,415 pts), were selected.

End-points		Pts (RCTs)	HR/RR 95% CI)	p-value	Het. (p)	AD (%)	NNT/NNH
Primary	PFS	2,624 (4)	0.62 (0.48, 0.69)	*<0.0001*	*0.001*	17.1	6
	OS	2,624 (4)	0.78 (0.66, 0.94)	*0.007*	*0.14*	8.6	12
Secondary	ORR	2,728 (5)	1.16 (0.97, 1.38)	*0.085*	*0.034*	–	–
	PR	1,336 (4)	1.24 (1.06, 1.46)	*0.006*	*0.19*	6.5	15
	HTN	2,728 (5)	4.87 (3.12, 7.61)	*<0.0001*	*0.93*	6.2	16
	Bleeding	2,570 (4)	1.72 (0.96, 3.07)	*0.07*	*0.52*	–	–
	Proteinuria	2,570 (4)	2.10 (0.64, 6.84)	*0.21*	*0.56*	–	–

The benefit in primary outcomes was obtained regardless of the study setting (interaction test: $p = 0.057$ and $p = 0.93$, respectively) between phase II and phase III pooled results. According to the meta-regression analysis, female gender and rectal primary site were significant predictors for PFS benefit ($p = 0.003$, $p = 0.005$).
Conclusions: Notwithstanding all the implications related to costs and the significant HTN risk, the significant outcome improvement provided by BEVA in first-line treatment of unselected MCRC patients, should be considered when choosing the appropriate up-front therapy. Nevertheless, a targeted-based approach would be pursuit as well in order to maximize the efficacy of treatment.

6052 POSTER

Capecitabine single agent or in combination in the routine first-line treatment of a predominantly elderly population with metastatic colorectal cancer (MCRC)

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Background: Most controlled trials on new treatments suffer from a lack of representativity of patients (pts), especially in solid tumor diseases typically prevalent in the senium. The purpose of this ongoing non-interventional observation study is to obtain data on usage, efficacy and safety of capecitabine (Cape) (Xeloda®) in a large unselected patient cohort with specific focus on elderly pts.
Material and Methods: Between February 2005 and February 2009 data on 461 pts with MCRC were recorded in detail on standardized forms until detection of disease progression or up to a maximum of 12 cycles, followed by an additional long-term survey for survival.
Results: The cohort showed a high median age of 73 years (y), with 26% ⩽65 y (stratum A), 34% 66−75 y (B), 36% 76−85 y (C), and 4% >85 y (D). 57% were male, with ECOG performance status 0/1/⩾2 in 23%/50%/27%. 66% suffered from liver and 28% from lung metastases. 34% had previously received adjuvant chemotherapy. The median duration of cape treatment was 5.3 months (mo), with only a slight decrease from 5.6 to 4.7 across the age groups. Half of the pts received cape monotherapy, with a strongly increasing trend by age (A: 29%, B: 51%, C: 61%, D: 70%, $p < 0.0001$). 2-/3-drug combinations were applied in 37%/13%, XELOX in 26%, XELIRI in 6%, bevacizumab was used in 13% and cetuximab in 3% of pts. The median of the overall average daily cape dose per patient was 1803 mg/m^2 and rather constant until the age of 75 y, but lower in older pts. It amounted to 1656 and 1980 mg/m^2 in the groups with or without a concurrent second cytostatic drug, respectively. Dose adaptations were performed in 22%/41% of cycles/pts. Overall best response in an intent-to-treat approach was 8% CR and 33% PR, adding to an overall response rate of 40%, considerably declining with age (A: 51%, B: 41%, C: 34%, D: 25%, $p = 0.0015$), probably at least in part due to the decreasing treatment intensity. Hematoxicity grade 3/4 was observed in less than 10% of pts. Hand-foot skin reaction (HFS) was reported in almost half of the pts, but grade 3 HFS was observed in only 3%. Diarrhea was the predominant gastrointestinal toxicity (grade 2/3/4 in 12%/4%/0%).
Conclusions: Capecitabine, administered either as single agent or part of a combination treatment, proved to be safe and effective in the routine practice of colorectal cancer treatment. Obviously, the oral treatment is a preferred option in elderly patients and/or those unfit for combined cytotoxic treatment.

6053 POSTER

Phase II study of capecitabine, irinotecan (CAPIRI) plus bevacizumab in chemotherapy naive stage IV colorectal cancer, results in 120 patients

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Background: Bevacizumab is an active monoclonal antibody when combined with chemotherapy (Hurwitz. N Engl J Med 2004). Bolus 5FU can be substituted by an infusion increasing the tolerance and probably the efficacy (FOLFIRI), and the infusion of 5FU can be substituted by oral fluoropirimidins (CAPIRI). We chose a reduced dose of irinotecan based in a previously phase I-II study conducted in our hospital (Am J Clin Oncol 2003; 26:107−11) and we employed an empirically reduced dose of capecitabine after the first experience with this combination without monoclonal antibodies (Clin Colorectal Ca 2005; 5(1): 50−6). Irinotecan was chosen instead of oxaliplatin because of the cumulative neurotoxicity of that drug.
Material and Methods: Naive chemotherapy patients (pts) with advanced colorectal cancer were entered into the study with capecitabine (850 mg/m^2/12 hrs po on days 1−14), irinotecan (240 mg/m^2 iv on day 1) and bevacizumab (7.5 mg/Kg on day 1), in a 3-week cycle. The primary end point was overall survival and secundary were time to progression and relation between CEA, karnofsky (KPS), age, number of organ involved (NOI), RAS status and evolution.
Results: From April 2005 to April 2008, 120 pts were enrolled. Median age were 64 years (limits: 40−79 years), KPS 70% (limits: 60−90%). The overall response (OR) rate was 63.3% and the disease stabilization was 30%. The bivariate analyses only found a significant relation between low values of CEA and responses ($p < 0.001$). Time to progression was 18 month (95% CI, 14.3−21.6). but it was different between patients with CEA response (50% reduction), 20 month, and patients without CEA response, 12 month ($p = 0.002$). KPS and NOI were related with survival in bivariate but not in multivariate analyses. The main grade 2−4 toxicities were: diarrhea in 55 pts (grade 3−4 in 16), hand-foot syndrome in 54 pts (grade 3−4 in 2), neutropenia in 40 pts (grade 3−4 in 8), any hypertension in 74 pts (grade 3−4 in 2), any proteinuria in 75 pts (none was grade 3−4), thrombotic events in 7 pts or bleeding in 55 pts (mainly epistaxis); 5 live threatening adverse events: 1 neutropenic toxic death, 2 pulmonary thromboembolism, 2 grade IV diarrhea with secondary renal insufficiency.
Conclusion: There seems to be a relation between the value of CEA at diagnosis and response, and between CEA response and time to progression. Results indicate that the combination of CAPIRI plus bevacizumab has a remarkable anti-tumor activity that is consistent with other combinations published (Schmiegel. J Clin Oncol 2007; 25(20): 4034) and has an acceptable safety profile.

6054 POSTER

Management of isolated non-resectable liver metastases in colorectal cancer patients: a case-control study of isolated hepatic perfusion with melphalan versus systemic chemotherapy

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Purpose: To compare the median overall survival of patients with isolated non-resectable liver metastases in comparable groups of patients treated with either isolated hepatic perfusion (IHP) with melphalan or with systemic chemotherapy.
Patients and Methods: All patients with isolated liver metastases from colorectal cancer origin, who underwent IHP with 200 mg melphalan between August 1994 and December 2004, through both the portal vein and hepatic artery, were included in this study. The control group consisted