Material and Methods: The inclusion criteria were; (1) histologically proved adenocarcinoma of colon or rectum, (2) age ⩾20 years, (3) no prior treatment, (4) at least one target lesion by RECIST ver1.0 criteria, (5) ECOG Performance Status 0−1. Patients (Pts) were randomized to receive either S-1 (40−60 mg bid) and oral LV (25 mg bid) for one week and L-OHP (85 mg/m^2) on day 1, repeated every 2 weeks (SOL; Group A) or L-OHP (85 mg/m^2), *l*-LV (200 mg/m^2), and 5-FU (400 mg/m^2, bolus) on day 1, followed by 5-FU (2400 mg/m^2, ci, 46 hours), repeated every 2 weeks (mFOLFOX6; Group B). The number of the enrolled pts was set to achieve the probability that a point estimate of hazard ratio (HR) of progression free survival (PFS; primary endpoint) less than 1.0 is 80% or more. This trial was supported by Taiho Pharmaceutical CO., LTD and Yakult Honsha CO., LTD. ClinicalTrials.gov Identifier: NCT00721916.
Results: From July 2008 to July 2009, 107 pts were randomized, and 105 were eligible (56 to Group A and 49 to Group B). A cut-off date for the primary analysis was 31 March 2010. The median PFS for Group A and Group B was 9.6 and 6.9 months (HR = 0.83; 95% CI, 0.49–1.40), indicating that the primary endpoint was met. Response rate was 55.4% for Group A (31/56; 95% CI, 41.5–68.7) compared to 53.1% for Group B (26/49; 95% CI, 38.3–67.5), and disease control rate (CR + PR + SD) was 92.9% for Group A (52/56; 95% CI, 82.7–98.0) compared to 85.7% for Group B (42/49; 95% CI, 72.8–94.1). Median OS have not been reached at this time, but 1-year survival rate was 86.0% for Group A and 79.0% for Group B. The incidences of grade 3/4 adverse drug reactions were; neutropenia (19.6% Group A, 41.2% Group B), lymphopenia (14.3% and 5.9%), sensory neuropathy (19.6% and 2.0%), anorexia (12.5% and 7.8%), fatigue (10.7% and 5.9%) and diarrhea (10.7% and 3.9%).
Conclusions: SOL shows promising activity with well-tolerated toxicities compared to mFOLFOX6.

6119 POSTER

High Level of Thymidine Phosphorylase Gene Expression in Tumour Tissues is Associated With Response to Oral Uracil and Tegafur/leucovorin Chemotherapy in Patients With Colorectal Cancer

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Background: 5-Flurouracil (5-FU)/ leucovorin (LV) and oral uracil and tegafur (UFT)/LV are widely used as standard adjuvant chemotherapy for colorectal cancer (CRC). We previously reported that folylpolyglutamate synthase (FPGS) and g-glutamyl hydrolase (GGH) regulate the reduced folate levels in CRC tissue when oral LV was administered. In the present study, we examined the relationship between mRNA expressions of pyrimidine and folate metabolism-related enzymes in CRC tissues and the efficacy of UFT/LV treatment.
Material and Methods: Seventy-six well- or moderately-differentiated CRC patients without prior treatment who were scheduled to undergo surgery were enrolled. These 76 patients subsequently received oral treatment with UFT/LV for 2 weeks and underwent surgery 3 days after the final dose administration. We evaluated the tumour response on the resected specimens. We assessed pathological response based on the extent of residual cancer cells and granulation tissues, and graded on a scale from 0 to 4. A patient with scale 3 or 4 was defined as a “responder”. The mRNA expressions of pyrimidine-related enzymes (6 genes) and reduced folate-related enzymes (8 genes) were quantitatively evaluated using a RT-PCR assay. These candidate genes were evaluated based on differences in the log-transformed mRNA expression levels between responders and non-responders. A multivariate logistic regression model with a stepwise regression was used to assess the independent effect on the response to oral UFT/LV treatment.
Results: Pathological responses were observed in 19.7% (15/76) of the patients. There was no significant difference in response rates between well and moderately differentiated histologic types. The median values of relative thymidine phosphrylase (TP) mRNA expressions were 0.0019 and 0.0012 for responders and non-responders, respectively. The expression level of TP mRNA was significantly higher in responders than in nonresponders ($p = 0.011$). There were no significant differences between pathological response and other gene expressions on univariate analysis. On multivariate logistic regression analysis including clinical parameters, TP remained independent predictor of the response.
Conclusion: The TP mRNA expression levels in primary CRC tissues may be useful for predicting the efficacy of oral UFT/LV treatment in patients with CRC.

6120 POSTER

Personalized Dose Management for 5-fluoruracil Based Chemotherapy Regimens to Lower Severe Toxicity by Cancer Patients

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Background: Doses of chemotherapy drugs are administered based on body surface area (BSA), determined by height and weight of the patient. This standard does not reflect the difference in absorption and metabolism by each patient, which causes big blood drug level variations. We investigated the blood level of 5-fluoruracil (5-FU) in 3 chemotherapy regiments for treatment of colorectal cancer to determine the individual dose management with less side effects for each patient compared to standard dose treatment.
Material and Methods: A group of 56 patient with colorectal cancer were first divided into two subgroups according to the stage of the disease: 21 patients receiving adjuvant chemotherapy and 35 treated for metastatic disease. Three chemotherapy regiment were chosen: 5-FU (day 1 and day 5) + leucovorin (every 21 days), FOLFOX every 21 days and FOLFIRI every 21 days. 5-FU individual plasma concentrations were determined in four different ways − once on day 1 at the end of 2 hours infusion, twice at the 20th and 46th hour of pump infusion, measuring the concentration on the first, second and third day of the infusion and on the first, second, third and fourth day of the 5-FU infusion with a chromatography method. Another group of 50 patients receiving the same standard dose chemotherapy based only on BSA (without any dose adjustment) was used as a control group to follow up toxicity, intensity of treatment and period to progression.
Results: The area under the time/concentration curve (AUC) of 5-FU (according to Gamelin FU dose adjustment table) for patients treated in adjuvant aspect: AUC 15−20 mgh/l resulted in recommendation for a 15% higher dose for 2 patients; AUC 20−24 mgh/l − 1 patient with no dose correction; AUC 30−35 mgh/l − 1 patient with a lower dose recommendation. Results for patients with metastatic disease: by AUC under 10 mgh/l − 13 patients recommended for a high dose, AUC 10−15 mgh/l − 4 patients for 15% higher dose and AUC 20−24 mgh/l − 5 patients with no dose changes. From the results without any recommendation of dose adjustment: by 7 patients plasma concentrations of 5-FU could not be measured, the other 30 results are either with too high or too low AUC values. The concentration by follow up of patients on first, second and third day was different.
Conclusions: Personalized dose management based on testing of blood drug levels has the potential to lessen severe side effects of chemotherapy drugs and to deliver the more accurate treatment to patients and a better quality of life.

6121 POSTER

Phase II Trial of Combination Therapy With Bevacizumab and S-1 in Elderly Patients With Unresectable or Recurrent Colorectal Cancer (BASIC)

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Background: Chemotherapeutic regimens for elderly patients with advanced or recurrent colorectal cancer, such as combined treatment with 5-fluorouracil, leucovorin, and bevacizumab, often do not include oxaliplatin or irinotecan, because many patients are in poor physical condition. However, treatment with 5-fluorouracil and leucovorin requires the placement of a percutaneous port as well as other precautions, causing stress for patients as well as healthcare workers. From the viewpoint of ease of treatment, it is clinically important to confirm the therapeutic effectiveness of bevacizumab combined with S-1, an oral 5-fluorouracil derivative. In this study, we evaluated the efficacy and safety of combined therapy with S-1 and bevacizumab in elderly patients who had advanced or recurrent colorectal cancer.
Materials and Methods: The study group comprised elderly patients 65 years or older who had a histologically confirmed diagnosis of advanced or recurrent colorectal cancer and were scheduled to receive first-line chemotherapy. As for the treatment regimen, bevacizumab (5 mg/kg) was given intravenously on days 1, 15, and 29, and S-1 (80 to 120 mg/day

according to body-surface area in two divided doses daily, after meals) was administered orally on days 1 to 28 of a 42-day cycle, which was repeated. The primary endpoint was progression-free survival (PFS). Secondary endpoints were time to treatment failure (TTF), response rate (RR), overall survival (OS), treatment completion status, and the incidence and severity of adverse events.
Results: From October 2007 through March 2010, a total of 56 patients were enrolled. Their median age was 75 years. The RR was 54% (95% confidence interval [CI], 40% to 67%), the median TTF was 7.6 months (95% CI, 6.1 to 9.1), and the median PRS was 9.4 months (95% CI, 7.6 to 11.0). The main Grade 3 or higher averse events were hypertension (18%), diarrhea (9%), and neutropenia (7%).
Conclusions: Our results suggest that combination therapy with S-1 and bevacizumab can be administered safely and continuously and is therapeutically effective in elderly patients with advanced or recurrent colorectal cancer.

6122 POSTER

Impact of Cetuximab-based Therapy and KRas Genotypes in Japanese Patients With Chemotherapy-refractory Metastatic Colorectal Cancer

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Background: Clinical trials have demonstrated that cetuximab improves the response rate and survival of patients with metastatic KRAS wild type colorectal cancer and this agent was approved in July 2008 in Japan. This retrospective study evaluated the treatment outcome and clinical relevance of KRAS mutational status in chemotherapy-refractory Japanese metastatic colorectal cancer patients treated with cetuximab-based therapy.
Materials and Methods: The study included 65 patients with metastatic colorectal cancer who received cetuximab-based therapy from August, 2008 to October, 2009 at the Department of Surgery and Science, Kyusyu University and related facilities. The tumours were retrospectively screened for KRAS mutations (codons 12 and 13) using direct sequencing and the association between KRAS mutations and the treatment outcome was also analyzed.
Results: Cetuximab was administered in 2nd line therapy to 4 (6.2%), in 3rd line therapy to 28 (43.1%), and in $\geqslant$ 4th line therapy to 33 patients (50.8%). Cetuximab monotherapy was administered to 11 patients (16.9%), combination therapy with CRT-11 for 39 (60.0%), and with FOLFIRI for 15 (23.1%). A partial response and stable disease was observed in 19 (29.2%) and 23 (35.4%) patients, respectively. There was no therapy-related death. Grade 3−4 neutropenia and anemia was observed in 21 (32.3%) and 9 (13.8%) patients, respectively. A skin rash was observed in 50 patients (76.9%), and among them, 3 patients (4.6%) experienced a Grade 3 of skin rash. The median progression-free survival was 3.5 months and the 6-month overall survival (OS) rate was 75.4%. An ongoing KRAS mutational analysis revealed that 23 wild type and 9 mutant tumours (codon 12 mutation: 8 cases and codon 13 mutation: 1 case) were included in the subjects. A KRAS mutation was associated with resistance to cetuximab-based treatment (0% vs. 47.8% of responders among 9 mutant and 23 wild type patients, respectively; $P < 0.05$) and a tendency to show a poorer survival (1-year OS rate: 0% vs. 60.3% in 9 mutant and 23 wild type patients, respectively; $P = 0.0764$).
Conclusions: Cetuximab-based therapy was therefore demonstrated to be effective for chemotherapy-refractory metastatic colorectal cancer patients. Appropriate management of the skin toxicity associated with cetuximab therapy is necessary to allow for both adequate drug administration and to improve the patients' quality of life. These results indicate the clinical relevance of KRAS mutations for predicting the efficacy of cetuximab-based therapy in Japanese metastatic colorectal patients.

6123 POSTER

Panitumumab in Patients With Metastatic Colorectal Cancer (mCRC) − Single Center Experience

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Background: Panitumumab (Pmab) has demonstrated to provide clinical benefits in randomized, controlled trials (RCTs) both in combination with chemotherapy (CT) or in monotherapy in patients (pts) with mCRC with wild-type (WT) KRAS. There are limited data of the efficacy and safety of pmab in clinical practice.
Material and Methods: We retrospectively analyzed all pts treated with pmab in our center from Jan07-Dec10. Demographic variables, clinical outcomes until Dec10, and adverse events were collected by reviewing pts files. Efficacy variables were analyzed only for KRAS WT pts. Overall survival (OS) was calculated from the initiation of first-line treatment for metastatic disease, and progression-free survival (PFS) from the initiation of pmab.
Results: From 2007 to 2010, 67 pts were treated with pmab: 48 pts (72%) were KRAS wild-type, 17 pts (25%) had unknown KRAS status, and 2 pts (3%) were KRAS mutant. The median age was 63 years (range 31−77); 33% women; 90% ECOG 0−1 and 10% ECOG 2. Pmab was administered as first-line treatment in 55% of cases (median 11 cycles), second-line in 34% (median 9 cycles) and third-line or later in 11% (median 3 cycles). The most common concomitant CT was FOLFOX/XELOX (64%), followed by irinotecan (27%), FOLFIRI/XELIRI (3%) and 5-fluorouracil/capecitabine (1.5%). Pmab monotherapy was used in 4.5% of the pts. Median follow-up time since pmab initiation was 10 months (m) (range 0.6−45). For pts with WT KRAS, median PFS (by Kaplan–Meier) was 12.0 m (95% confidence interval (CI) = 6.0, 18.0). In the subset of pts receiving pmab as first-line, median PFS was 15.5 m, compared to 8.5 m in pts undergoing second-line and 1.5 m in third-line or later. Overall response rate was 56.3% (27/48): Partial response 74, 56 and 0% in first, second and other lines respectively Median OS was 26.0 m (95% CI: 18.0, 34.0). 52.1% pts were alive at time of analysis. In the overall sample, grade 3/4 adverse event rates were similar to those reported in clinical trials: acne-like skin or ungueal toxicity, 11.5%; diarrhea, 11.7%; other, 21.3%. Pmab was suspended due to toxicity in 8 cases (12.3%) mostly due to toxicity associated with CT treatment.
Conclusions: Pmab showed similar efficacy results than RCTs in a non-selected cohort of WT KRAS mCRC pts. Pmab was well tolerated and observed toxicities did not exceed the rates reported in prior clinical trials.

6124 POSTER

The Role of Bevacizumab (B) in the Maintenance Treatment After Chemotherapy (CT) for Metastatic Colorectal Cancer (mCRC) Patients (pts) − an Italian Multicenter Retrospective Analysis

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Background: Maintenance treatment with B is considered an option for mCRC pts in responding pts after a first line CT + B, but few data are available on its real benefit on progression-free survival (PFS).
Methods: Data were obtained by reviewing the clinical chart of pts treated in any single institution from 2005 to 2010. Two-hundred-twenty mCRC pts treated with first line CT + B achieving a response [partial (PR) or complete (CR)] or a stable disease (SD) were considered eligible. 118 pts had received B maintenance (BM) whereas 102 did not (noBM). The two groups were homogeneous for main characteristics. First-line therapy in the BM vs noBM group included FOLFIRI regimen (96 vs 73 pts), FOLFOX (18 vs 28 pts) and FUFA (4 vs 1 pts). The median age of pts was 62 ys (range 34−80) for BM and 65 ys (range 32−82) for noBM. K-ras status was analyzed in 115 pts with an higher percentage of wild-type (wt) in the BM group (65 vs 50 pts, $p = 0.04$). A CR or PR have been achieved in 56% of pts in the BM group and 49% of noBM group, while a SD was observed in 34% and 31% of pts respectively for the BM and noBM group. The median number of BM cycles administered was 7 (range 3−25). PFS analysis of was conducted on the entire population comparing BM and noBM and by response to prior CT+B (PR and CR versus SD).
Results: At a median follow-up of 18 months (1–109), the median PFS was 13 months (C.I.95%: 11−15) vs 8 months (C.I.95%: 7−10) $p < 0.0001$, and the 1-year PFS 53.% vs 28% for BM and noBM respectively. According to the response, pts with CR/PR had a mPFS of 15 months (CI 95% 12−19) vs 10 months (CI 95% 10−12) $p = 0.004$, and a 1-year PFS of 62.6% and 33.7% for the BM vs noBM group respectively. No difference in PFS was found in pts showing SD after first-line CT + B: the 1 year-PFS was 37.1% in the BM group and 37.3% in the noBM group, the mPFS was respectively 12 mo (CI 95% 10−13) and 8 mo (CI 95% 7−10) ($p = 0.11$). Furthermore, no difference was observed in PFS comparing, in the BM group alone, CR/PR vs SD nor when the k-ras status was considered.
Conclusion: In our retrospective analysis the maintenance strategy with B shows a longer PFS in pts responding to the first line chemotherapy + B whereas for pts who achieving an SD no difference was observed. Results from ongoing randomized phase III studies addressed to explore the issue of maintenance treatment are needed.