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The efficacy, toxicity and pharmacokinetic findings of S-1 in patients (pts) with advanced biliary tract cancer (BTC): a phase II trial

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Purpose: The aim of this trial was to investigate the efficacy, toxicity, and pharmacokinetics of S-1 in BTC pts. S-1 is a novel oral anticancer agent and contains tegafur (FT: prodrug of 5-fluorouracil), gimeracil (CDHP: dihydropyrimidine dehydrogenase inhibitor), and oteracil potassium (Oxo: orotate phosphoribosyl transferase inhibitor) at a molar ratio of FT:CDHP:Oxo = 1:0.4:1.

Patients and Method: Eligibility criteria were pathologically proven BTC with measurable tumor lesions, age 20-74 years, Karnofsky performance status (KPS) 80-100%, adequate hematological, renal, and liver functions, no prior radiotherapy or chemotherapy, and written informed consent. S-1 was administered orally (40mg/m^2) bid for 28 days with 14 days' rest period as one course.

Results: Nineteen BTC pts were registered between July 2000 and January 2002. Pts characteristics were sex (M/F) 12/7, median age: 59 years (range, 44-71), primary tumor (gallbladder/extrahepatic bile ducts/ampulla of Vater) 16/2/1, and KPS (100%/90%/80%) 8/10/1. Pharmacokinetic study was done on day 1 in the initial eight pts. Median number of courses was 2 (range, 1-12). The overall response rate for 19 eligible pts was 21.1% (4PR, 9NC, 5PD, 1NE; 95% C.I., 6.1-45.6%) with median response duration 203 days. Median survival was 252 days (95% C.I., 89-321 days). The grade 3 (NCI-CTC) anorexia and fatigue occurred in 2 pts respectively (10.5%). Also grade 3 anemia, neutropenia, γ -GTP increase, hyponatremia, fever, stomatitis, nausea and diarrhea occurred in 1 patient respectively (5.3%). There was no grade 4 toxicity. Pharmacokinetic parameters (5-fluorouracil: Cmax 146.9 ± 62.1 ng/mL, AUC0-12 770.5 ± 282.2 ng·h/mL, Tmax 4.0 ± 0.0 h, T1/2 1.9 ± 0.3 h) after single oral administration of S-1 in pts with BTC were similar to those with gastric, colorectal, breast (Clinical Cancer Research, 5, 2000-2005, 1999), and pancreatic cancer (American Society Clinical Oncology, abs.682, 2002).

Conclusion: Our results suggest that S-1 has promising activity for BTC and is well tolerated with easily manageable toxicity. That will be confirmed in following larger phase II trial.

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Molecular mechanism of down-regulation by CPT-11 of thymidylate synthase highly expressing in gastrointestinal cancer xenografts during combined treatment with oral fluoropyrimidines

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Background: 5-Fluorouracil (5-FU) is widely used to treat gastrointestinal cancers, however, it has been reported to be less effective in patients with cancers highly expressing thymidylate synthase (TS). CPT-11 is also used clinically as the first and/or second line-therapeutic drug. The combined treatment with 5-FU and CPT-11 resulted in synergistic antitumor activity as demonstrated in vitro and in vivo studies. We have investigated the mechanism of synergistic antitumor effect of the combination of S-1, a prodrug of 5-FU with CPT-11 using human gastrointestinal tumors with low or high TS activity.

Methods: CPT-11 (75 mg/kg) was administered weekly, twice, to mice bearing 4-1-ST, AZ521, SC-2, KM12(20)C and KM12C/5-FU tumors. Thereafter, their tumors were removed and activities and mRNAs of 5-FU-metabolizing enzymes were measured. Furthermore, proteins relating to G1/S phase signaling were detected by Western-blot analysis. In therapeutic experiments, CPT-11 was administered weekly, twice, and S-1, an oral prodrug of 5-FU, was given once daily for 14 consecutive days.

Results: When treated with CPT-11, TS activity in 4-1-ST, AZ521, and KM12C/5-FU tumors with higher TS pretreatment levels significantly decreased but that in SC-2 and KM12C tumors with lower TS pretreatment levels did not change. The levels of TS mRNA in all tumors tested was not altered by treatment with CPT-11. These results suggest the transcriptional regulation of TS gene by signals induced during inhibition of topoisomerase I by CPT-11. The expression of phosphorylated Rb and E2F1 proteins in highly TS-expressing tumors was down-regulated by CPT-11. We detected the complex of CDK4, cyclin D1 and p27 regulating Rb-E2F system (phosphorylation of Rb and activation of F2F) and found that such complex tended to decline by the treatment with CPT-11. In therapeutic experiment using 5-FU-resistant tumors (KM12C/5-FU), CPT plus oral S-1, showed a significant synergistic antitumor effect as compared to CPT-11 and S-1 alone, and seemed to be almost same as that in parental KM12C tumors with lower TS treated with CPT plus S-1.

Conclusion: Our results can conclude that combined treatment with CPT-11 and S-1, a new oral 5-FU prodrug, would contribute to treat patients with gastrointestinal cancers showing not only low TS but also high TS activity.

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Combination of docetaxel with 5-fluorouracil and cisplatin in patients with advanced gastric cancer (AGC)

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Purpose: Docetaxel is an active agent for treatment of AGC. Since 1997 we have performed phase II studies to assess an efficacy and toxicity of docetaxel in combination with 5-FU and cisplatin for treatment of AGC patients.

Patients and Methods: In pilot study 25 pts (18 men and 7 women) with chemotherapy-naïve AGC were treated with docetaxel 75 mg/m2 i.v. day 1, 5-FU 300 mg/m2 bolus days 2,3,4, cisplatin 60 mg/m2 day 5. The regimen was repeated every 3 weeks.

Results: Population characteristics and results of the trial are shown below.

N. of pts	25
Available pts: for response	23
for toxicity	25
Median age	53
Karnofsky PS 100/90/80/70	1/12/9/3
Positive markers (CEA, Ca 19.9)	64%
OR/ SD/ PD	8/9/6
Response rate	3 4, 7%
Stabilization	39%
Clinical benefit response	52%
Median response duration	6 months
Median time to progression	7 months
Median survival	10,5 months

The most often seen grade III-IV toxicities (per cycle) included asthenia (30%), neutropenia (39%), diarrhea (15%), stomatitis (10%).

Conclusion: The combination is an active for treatment of AGC. Combination of docetaxel with 5-FU and cisplatin produces a high response rate, long-term median time to progression and overall survival with acceptable toxicity. The results of ongoing phase III study is awaiting with great interest.

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Sentinel node biopsy (SNB) for colon cancer: personal experience

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Background: Many studies have demonstrated the usefulness of SNB technique, especially in staging breast cancer and melanoma. Some Authors have also tested the utility of SNB in colorectal cancer patients. They found metastases in sentinel lymph nodes (SLN) only in about 20% of cases, with skip metastases ranging from 4 to 38%.

Methods: From March 1999, 47 consecutive patients (18 males and 29 females) with colon cancer entered the present study. During surgery, 1 ml of isosulfan blue was injected under the serosa around the tumour. After 5 minutes, one to three blue nodes were identified in all 47 patients (median of two). Routine histopathological examination (haematoxylin eosin, H&E) was performed on all the traditionally resected nodes, whereas H&E and immunohistochemistry with cytokeratines were used on 10 sections of each SLN.

Results: Among the 47 patients, in 10 patients whose SLNs were negative, all other non-SLNs were also negative. In 17 patients SLNs were positive for metastases, both having additional non SLNs positive. In 16 out

of 47 (34%) we noticed cytokeratines-positive cells in SLNs only, being the other nodes negative. Our skip metastases rate was 8.5% (4/47 patients).

Conclusion: We found that SLN reflects the status of all the other pericolic nodes. Thus, a more accurate analysis performed on SLN in colon cancer may help to identify an additional patient population who should be treated with adjuvant chemotherapy.

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Efficacy of intraoperative cytological examination

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Background: The aim of the study was to assess the efficacy of intraoperative cytological examination.

Materials and methods: The efficacy of the method was analyzed on the basis of 2647 specimens obtained from 553 patients who were operated in 2002. Cytological specimens included bioptates, scrapes, imprints and body cavity fluids. We examined 609 bioptates of primary tumors and tumor-like masses from different sites, 44 liver bioptates, 756 lymph node scrapes, 330 surgical margins' scrapes (mainly breast, bronchi and esophagus) , 232 scrapes and imprints from serosae, 213 scrapes and imprints from peritomoral tissues, 463 samples of pleural and peritoneal fluid. Cytological smears were stained using Pappenheim's modified method (azur-eosin staining) . The results of intraoperative cytological assessment were compared to the conventional histopathological examination.

Results: An overall accuracy of intraoperative cytological examination was 98,3%: false negative results were observed in 1%, false positive – 0,7%. The accuracy of intraoperative cytological examination for different cytological specimens was as follows: lymph node metastases – 99,2%, primary tumors – 95,9%, surgical margins – 99,7%, serosae – 97,8%, peritumoral tissues – 98,1%, hepatic lesions – 97,7%.

Conclusion: Intraoperative cytological examination is a highly accurate method of morphological diagnosis. Still some cytograms of malignant tumors were misinterpreted. In case of lymph nodes micrometastases and high-grade sinus-hystiocytosis were the reasons of failure. In case of fluids and serosae non-specific mesothelial changes accounted for false results. In some instances it was difficult to differentiate tumor cells from non-specific inflammation.

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Analysis of G/A SNP change at position 2494 in the E-cadherin gene in Italian patients with sporadic, diffuse gastric cancer

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Current investigations are studying new E-cadherin gene (CDH1) mutations that may be causative of diffuse gastric cancer susceptibility. Recently, a novel CDH1 germline variant with G/A nucleotide change at cDNA position 2494 has been found in Japanese patients with familial diffuse gastric cancer. The consequent amino acid variation (Val/Met) may alter the binding activity of B-catenin and the adhesive function of the E-cadherin protein. Data on the 2494 G/A nucleotide change in sporadic cases of diffuse gastric cancer and in patients of Western origin are lacking. We have investigated its frequency in Italian cases of sporadic, diffuse gastric cancer and healthy controls.

Peripheral blood samples were collected from consecutive patients with sporadic, diffuse gastric cancer and healthy controls who were natives of the District of Urbino, Region Marche, Central Italy. After DNA extraction, standard techniques for molecular analyses were used to investigate the 2494 G/A germline nucleotide change in CDH1 cDNA.

None of 48 patients and 48 controls showed the G/A 2494 nucleotide change. Assumed a binomial distribution of the mutation among individuals and according to zero mutations in 48 patients, the 95% upper bound for the underlying mutation **frequency** was 7.4%.

The novel CDH1 nucleotide change is uncommon in Italian patients with sporadic, diffuse gastric cancer. In this setting, further analyses in large population-based studies are not advisable.

202 POSTER

Should gastrectomy be performed for metastatic stomach carcinoma?

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Background. The prognosis of patients with metastatic stomach carcinoma is extremely poor, and there exists controversy on the adequate surgical treatment in terms of safety and benefit.

Material and methods. We reviewed the outcome of 56 patients with metastatic gastric cancer in whom total or subtotal gastrectomy ± metastasectomy was performed. The sites of metastases were as the follows: peritoneum (18 patients), distant lymph nodes (16), liver (10), ovary (5), other sites and multiple sites (6). There were 33 males and 23 females; the mean age was 55 years. Tumor-related complications were registered in 40 patient, anemia (17) and pyloric stenosis (15) predominated. The primary tumor penetrated the serosa in 40 patients, involved two thirds or the whole stomach in 32 patients. Lymph nodes were positive in 33 patients. The study population was divided into two equal groups: 28 patients treated between 1975 and 1995, and 28 patients treated between 1996 and 2002.

Results. In the second period of the study, the portion of total gastrectomies increased from 39 to 57%, of extended (D2 or more) lymphadenectomy from 7 to 36%. At the same time the incidence of anastomotic leaks decreased from 14 to 7%, intraabdominal infection from 14 to 0%, pneumonia from 18 to 7%; overall number of patients with complications from 36 to 11%. Postoperative mortality was 25% in the former period and 3.5% in the latter. Complete resection of all metastatic sites was performed in 20 (36%) cases, partial resection in 9 (16%) cases. Median survival of the whole group (excluding postoperative deaths) was 8.2 months. Cumulative survival was as the follows: 6 months 76%, 1 year 34%, 2 years 8%. There were only 2 long-term survivors (43 and 115 months), both had distant lymph node metastasis.

Conclusions. Gastrectomy, including extended and combined resections, may be performed safely independently of the degree of metastatic extension. It should be performed to patients with metastatic gastric cancer to overcome or to prevent fatal tumor complications. In appropriate cases (P1, H1 etc.), compete metastasectomy may increase the effectiveness of adjuvant therapy and give a patient a chance for cure.

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Outcome of patients receiving radiation with or without chemotherapy for squamous cell carcinoma of the esophagus

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Purpose: Several studies showed chemoradiotherapy for patients with esophageal cancer was superior radiotherapy alone. There were few studies whether these results were reproduced in practice. Primary objective of this study was to determine outcome of patients with esophageal cancer treated in our institution who received radiation therapy with or without chemotherapy.

Material & methods: From 1994 to 2001, 216 patients with squamous cell carcinoma of the esophagus without distant organ metastases were treated with curative intent using radiation therapy alone or combined chemotherapy at National Cancer Center Hospital, Tokyo. There were 186 males and 30 females. The age at diagnosis ranged from 40 to 89 years with a median of 64.5 years old. Forty-eight percent of patients (103 patients) had clinical stage (CS) 1 disease, 17% (37 patients) had CS 2 disease, and 35% (70 patients) had CS 3 disease. Fifty-one patients were treated with radiotherapy alone, and 165 patients were treated with radiotherapy and chemotherapy concurrently. Most of patients treated with chemotherapy were taken cisplatin and fluorouracil.

Results: At the time of the analysis, 128 patients were alive and 88 patients were dead. The median duration of follow-up for the patients alive was 27.0 months. A survival rate of all patients at 2 years was 63.6%. Patients, tumor and treatment-related factors were found to be significantly associated with survival on univariate analyses. At 2 years, patients with CS 1 disease had a 88.3% survival rate, compared with 56.3% for the patients with CS 2 and 33.7% for the patients with CS 3 ($p<0.0001$). Patients who had chemotherapy with radiotherapy concurrently had a 68.5% 2-year survival rate, whereas those who did not had a 2-year survival rate of 44.8% ($p=0.0038$). Two-year survival rate for patients who presented with a serum albumin level e3.7g/dl was 70.7%, compared with 58.2% for patients with <3.7g/dl ($p=0.0459$). Survival rate was lower for patients with