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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