Conclusion: The combination of C + G appears to be active and well tolerated as first-line treatment in pts with advanced/metastatic pancreatic cancer.

770 PUBLICATION

A phase II study of S-1 in patients with metastatic pancreatic cancer

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Background: The purpose of this study was to evaluate the efficacy and toxicity of S-1 in patients with metastatic pancreatic cancer. S-1, an oral anticancer agent, contains tegafur, gimeracil (CDHP: a dihydropyrimidine dehydrogenase inhibitor), and potassium oxonate (Oxo: an orotate phosphoribosyl transferase inhibitor) at a molar ratio of FT:CDHP:Oxo = 1:0.4:1.
Methods: Patients with histological or cytological diagnosis of measurable metastatic pancreatic adenocarcinoma not amenable to surgery or radiotherapy were eligible for the study. Other eligibility criteria included a Karnofsky performance status of 80 to 100%; an age of 20 to 74 years; adequate haematological, renal and liver functions; no prior chemotherapy; and written informed consent. S-1 was administered orally at 40 mg/sm twice daily for 28 consecutive days and then 14 days rest period as one course. Administration was repeated until the appearance of disease progression or unacceptable toxicity.
Results: Forty-one patients from seven institutions were enrolled. One patient deteriorated before receiving treatment and was excluded. Out of the 40 eligible patients, 15 patients had partial responses, for an objective response rate of 37.5% with a 95% confidence interval of 22.7–54.2%. And 11 patients had no change, 13 had progressive diseases, and one patient was not evaluated. The median survival time was 8.8 months (95% c.i.: 7.5–10.8 months). A clinical benefit response was achieved in four of the ten evaluable patients. The major drug-related toxicities were gastrointestinal toxicities such as anorexia (12.5%), diarrhoea (7.5%), nausea (7.5%), neutropenia (7.5%), though most of them were manageable. There was no drug-related death.
Conclusions: S-1 is effective and well tolerable as a single agent chemotherapy in patients with metastatic pancreatic cancer.

771 PUBLICATION

Combination of gemcitabine & cisplatin chemotherapy in unresectables gall bladder cancer

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Background: Adenocarcinoma of the gall bladder accounts for approximately 4% of all malignant neoplasm of the gastro-intestinal tract. Though surgical resection is the treatment of choice, majority of the cases are unresectable. Different chemotherapeutic agents including 5Flurouracil, Mytomycin C, Cisplatin, Methotrexate, Etoposide and Doxurobicin have been tried single or in combination. Partial response lasting from weeks to several months have been observed only in about 10%-20% of the cases and the median survival for patients with gall bladder cancer is approximately at around 4 months. Gemcitabine is a pyrimydine analogue of Deoxycytidine and has shown strong anti tumour activity in a variety of solid tumours. Cisplatin has synergistic activity with Gemcitabine. The aim of our study was to see the response rate of Gemcitabine and Cisplatin combination in unresectable gall bladder cancer and to see the tolerability in Indian-Asian pollution.
Materials and Methods: During period from November 2002 to December 2004 we selected consecutive 48 gall bladder cancers. All patients has histologicaly proven unresectable measurable gall bladder cancer. The inclusion criteria were performance status more than 60% (Kornofsky), no prior radiotherapy and normal liver (bilirubin <2) and kidney function (creatinine <2). All patient received Gemcitabine (1000 mg/m^2 intravenously over 30 minute) on day 1 and day 8 and Cisplatin (100 mg/m^2 divided D1 to D3) every 21 days. Response assessment was done by CT Scan after 3 cycles of chemotherapy. All 48 patients are eligible for efficacy and toxicity analysis.
Result: There were 9 (18.75%) complete responders, 15 (31.25%) partial responders, 13 (27.08%) with stable disease and 11 (22.91%) shows disease progression. The median time to progression was 20 weeks with range of 12–26 weeks. The median duration of response was 15 weeks (range 5.5–60 weeks). The median over all survival was 22 weeks (range 11–27 weeks) with 1year survival rate of 20.4%. WHO grade III or IV anaemia was seen in 8 & 5 patients respectively. Ten patients each experienced grade III or IV neutropenia while grade III or IV thompocytopenia was seen in 5 & 3 patients respectively.
Conclusion: The present study shows the Gemcitabin & Cisplatine combination was very useful in advanced unresectable gall bladder cancer. It was well tolerated by the the patients.

772 PUBLICATION

Treatment of advanced gallbladder cancer with gemcitabine (gem) or gemcitabine-cisplatin (gem-cispl)

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Gallbladder carcinomas (GBC) are often diagnosed at an advanced/metastatic stage amenable only to palliative surgery but in this case median survival is only around 8 to 12 weeks. Results of chemotherapy for advanced GBC are extremely poor with traditional treatment based on 5-FU.
Since 1997 we have been studying the effect of Gem. We retrospectively reviewed data of two different protocol treatments, we made possible. In both trials pts had similar characteristics, they all pts had measurable locally or metastatic GBC with histological or cytological proof, no prior chemotherapy nor radiotherapy. The main endpoint was RR and secondary endpoints were treatment toxicity and overall survival. We retrospectively review pts data and outcomes.
In first trial 26 pts were treated with Gem 1000 mg/m^2 i.v. for 30 minutes weekly for 3 weeks out of every 4 until disease progression and/or toxicity. In second cohort, 44 pts received Gem 1200 mg/m^2 and Cis 35 mg/m^2 on d1 and 8, every 21d for a total of 6 courses. Treatment was discontinued in case of unacceptable toxicity or disease progression. RR was evaluated by abdominal CT scan. Pts were treated on an outpatient basis.
Result: A total of 108 and 204 chemotherapy courses were given, 27% of pts for Gem alone and 63% of pts for Gem-cispl received at least 6 courses and 27% and 25% respectively received <2 courses. Twenty-five pts and 42 pts received at least one complete course of chemotherapy and were, therefore, evaluated for response. For Gem monotherapy the RR, CR and PR were 35/0/35% respectively, and for Gem-cisplt were 45/9/36%. All 26 and 44 pts were evaluated for toxicity. Four and 1 died due to disease progression, one pt died due to renal toxicity in the arm Gem-cispl. In one pt occurred hepatotoxicity grade 4 in arm gem alone. The main grade 3 hematology toxicities included thrombocytopenia (0% vs 2%), neutropenia (3.8% vs 23%) and anemia (3.8% vs 14%) in the group gem vs Gem-cispl respectively. Median survival time was 8.7 mos vs 7 mos for the entire population, 14.1 mos vs 9 mos for responders, and 6.1 mos vs 5 mos for non-responders.
Conclusion: Gem is active against advanced, unresectable recurrent and/or metastatic GC with a good tolerability. The low toxicity profile of Gem should be considered when a treatment choice is to be made for a patient with advanced GBC. Gem-cispl look like more active but survival was similar. A possible explanation may be that the treatment duration that was only six cycles in case of Gem-cispl.

773 PUBLICATION

Phase I study of docetaxel, cisplatin and 5-fluorouracil(TPF) as first-line chemotherapy in patients with advanced esophageal cancer. –Hokkaido Gastrointestinal Cancer Study Group (HGCSG) study-

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Background: This study was conducted to determine the maximum-tolerated dose (MTD), dose-limiting toxicity (DLT), and efficacy of a combination chemotherapy using docetaxel, cisplatin and 5-fluarouracil (TPF) in patients with advanced esophageal cancer.
Methods: Patients with previously untreated measurable metastatic esophageal cancer were included in this trial. Patients received this combination chemotherapy repeated every 28 days until progression

disease. Starting dose (dose level 1) were docetaxel 50 mg/m^2 on day 1, fixed dose intravenously cisplatin (15 mg/m^2/day) and continuous infusion 5-FU (800 mg/m^2/day) on day 1–4. Nine patients received this combination chemotherapy (TPF) at the two different dose level. DLT was defined as follows (according to NCI-CTC version 2.0); Grade 4 neutropenia lasting for more than 4 days, Grade 4 anemia and thrombocytopenia, Grade 3 neutropenia accompanied fever (⩾38ºC), and Grade 3 non-hematological toxicity (except for nausea, appetite loss, general fatigue). Maximal Tolerated Dose (MTD) is determined when the incidence of critical toxicity exceeds 50% at a certain dose level.
Results: MTD was dose level 2: docetaxel 60 mg/m^2, cisplatin 15 mg/m^2, and 5-fluorouracil 800 mg/m^2/day. DLTs were diarrhea on level 1, and febrile neutropenia, diarrhea, and stomatitis on level 2. The major toxicity were Neutropenia (Grade 3 and 4, 56%), Leukocytopenia (Grade 3, 44%), Anemia (Grade 3, 11%), Diarrhea (Grade 3, 33%) and stomatitis (Grade 3, 11%). The overall response rate was 44.4% and recommend dose's response rate was 66.7%.
Conclusions: The recommended dose of docetaxel in this study was determined to be 50 mg/m^2. This combination chemotherapy of recommended dose appeared to be highly active with a response rate of 66.7% and to have acceptable toxicities. Phase II multicenter study has already started.

774 PUBLICATION

Epirubicin, cisplatin and capecitabine for advanced biliary tract adenocarcinoma: a phase II study

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Background: Advanced biliary tract cancers (BTC) are associated with a very poor prognosis. Although numerous chemotherapeutic agents have been tested, the role of palliative chemotherapy in BTC has not yet been clarified. New therapeutic strategies are thus needed to improve the efficacy and survival, and we designed this study with new effective drug combination.
Materials and Methods: Patients with recurrent or metastatic BTC received a combination of epirubicin 50 mg/m^2, cisplatin 60 mg/m^2 on day 1, and capecitabine 1,000 mg/m^2 twice daily as an intermittent regimen of 2 weeks of treatment followed by a 1-week rest. Treatment was repeated every 3 weeks.
Results: Of 42 patients registered (14 with extrahepatic and 14 with intrahepatic cholangiocarcinoma, 6 with gallbladder cancer, 8 with ampulla of Vater cancer), one patient withdrew his consent and never received protocol therapy. The median age was 57 years (range, 36–69) and 5 had Zubrod performance status of 2. Objective responses were, which maintained for a median of 7 months), observed in 15 patients (36%) with 10 stable diseases. With a follow-up duration of 16 months, the median survival time was 8 months (95% confidence interval, 5–10 months). In total, 177 chemotherapy cycles were delivered, with a median of 5 cycles per patient (range, 0–9). Toxicity was mainly myelosuppression and mucositis. One patient died of hepatic failure between treatment cycles. For all patients, response to treatment was positively correlated with survival.
Conclusion: This combination chemotherapy with epirubicin, cisplatin and capecitabine feasibly offered promising antitumor activity in patients with advanced BTC.

775 PUBLICATION

Irinotecan and gemcitabine (IrinoGem) combined with 3-D conformal radiation therapy for locally advanced pancreatic cancer

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Background: Chemoradiation for locally advanced pancreatic cancer may improve local control and long-term survival. The combination of irinotecan (Irino) and gemcitabine (Gem) (IrinoGem) is active in pancreatic cancer and has an acceptable toxicity profile (Rocha Lima et al, JCO, 2002). Both drugs are also radiosensitizers. Therefore, we conducted a phase I/II study to evaluate the feasibility and efficacy of IrinoGem combined with radiotherapy (RT) in patients (pts) with localized, unresectable pancreatic cancer.
Material and Methods: Pts received 2 induction cycles of Gem 1000 mg/m^2 and Irino 100 mg/m^2 administered on days 1 and 8 of each 3-week treatment cycle. This was followed by 3 cycles of low-dose IrinoGem with concurrent abdominal radiation. Gem was administered at a fixed dose of 300 mg/m^2 and doses of Irino were escalated in successive cohorts from 20 mg/m^2 to 50 mg/m^2, by increments of 10 mg/m^2. RT was delivered by 3-D conformal technique to the pancreas and lymphatic drainage at 1.8 Gy daily fraction to a dose of 50.4 Gy.
Results: Sixteen pts entered the study between 11/2002 and 1/2004. Their median age was 66 y (range, 48–80 y) and performance status was 1/2 in 10/6 pts. All pts received 28 induction cycles and 11 pts continued with 33 cycles combined with RT. Treatment was stopped during the induction phase in 5 pts (toxicity 1, stent complications 1, refusal 1, tumor progression 2). Grade III-IV adverse events were diarrhea, vomiting, fatigue and mucositis in 5/16 (31%) pts during the induction phase and fatigue in 1/11 (9%) pts receiving concurrent chemotherapy and RT. There was no grade III-IV hematological toxicity. Thirteen pts were eligible for efficacy. Nine pts (70%) achieved clinical benefit response (CBR). One pt (8%) had an objective partial response, 7 pts (54%) had stable disease and 5 pts (38%) progressed, 2 of them during the induction phase. Release of major vessels encasement by the tumor was noticed in 2 pts, and one of them underwent R0 pancreatectomy. Median time to tumor progression was 6 m (range, 1–32+ m) and overall survival ranged from 2 to 32+ m, with a median of 13 m. Five pts are alive 1 y (1 pt), 2 y (3 pts) and 3 y (1 pt) after start of treatment.
Conclusions: This schedule of IrinoGem and RT is well tolerated and can provide CBR and disease control in pts with localized, unresectable carcinoma.

776 PUBLICATION

Phase I/II study of S1 plus docetaxel in patients with advanced or recurrent gastric cancer

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Background: S1 and docetaxel (TXT) show significant single-agent efficacy in gastric cancer and are synergistic in vivo studies. We performed a phase I/II study of S1 and docetaxel combination chemotherapy to determine the maximum-tolerated dose (MTD), recommended dose (RD), and efficacy in unresectable or recurrent gastric cancer.
Methods: Docetaxel was administered intravenously on day 1 and S1 was administered orally on days 1–14. Treatment was repeated every 3 weeks. Doses of each drug in the phase I study were as follows: TXT/S1- level 1 60/60; level 2A 60/80; level 2B 75/60; level 3 75/80 (mg/m^2). Phase II study is being conducted with RD based on the phase I study.
Results: Fifteen patients (median age 52) were enrolled in this phase I study and 9 patients (median age 52) were enrolled in this phase II study. No dose-limiting toxicities (DLTs) occurred at level 1, 2A, and 2B. At level 3, 2 of 3 (66.7%) patients developed DLTs (1 patient: grade 4 neutropenia with fever, 1 patient: grade 4 neutropenia with grade 3 stomatitis). Therefore, the dose at level 3 was determined as the MTD and the dose at level 2B was determined as the RD. The response rates of the phase I study were as follows: level 1 0% (0/3); level 2A 33.3% (1/3); level 2B (RD) 66.7% (4/6); level 3 66.7% (2/3). The response rate of the phase II study was 66.7% (4/6 evaluable patients: 1 CR, 3 PR, 1 SD, and 1 PD). Two patients (age 66 and 64 years old) developed fatal toxicity (grade 4 neutropenia with fever and shock) during the phase II study. The phase II study was well tolerated by the other 7 patients (all except 1 patient were younger than 60 years old). Additional phase I study with level 2A for the patients older than 60 years (n = 3) was conducted. No DLTs occurred at this level and the toxicities were easily manageable.
Conclusion: Level 2B (TXT/S1 at 75/60 mg/m^2) for the younger (<60 years old) patients and level 2A (TXT/S1 at 60/80 mg/m^2) for the older patients are the RD of this combination chemotherapy. This combination regimen showed a high response rate and tolerable toxicities in patients with advanced or recurrent gastric cancer. The phase II study is now under way.

777 PUBLICATION

Salvage surgery after failure of oncologic therapy for anal cancer

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Background: After primary oncologic therapy for epidermoid anal cancer some 20%-30% will have either residual disease or experience locoregional recurrence. Extensive surgical resection remains the only treatment with a possible curative outcome in these cases. We report the results in patients operated in our institution.
Material and Method: Retrospective assessment of patients operated for cure with abdominoperineal resection (APR) for residual or recurrent epidermoid anal cancer after primary oncologic therapy from 1990 through 2003.