Poster Sessions

Gastrointestinal cancer

1058 POSTER

Detection of disseminated tumor cells by immunocytology: standardization through computerassisted analysis

I. Vogel, C. Röder, D. Henne-Bruns, B. Kremer, H. Kalthoff. *University Hospital Kiel, General and Thoracic Surgery, Kiel, Germany*

Purpose: Preoperative detection of disseminated tumor cells can be regarded be a good selection-criteria of patients with high risk of tumor recurrence. To standardize the evaluation of immunocytologically detected disseminated tumor cells an automated screening systems will be helpful.

Methods: We analyzed cytospins from bone marrow aspirates of 242 patients with gastrointestinal carcinoma. Immunocytological analyses were performed with: 1. EPIMET-Kit™ (Baxter) and 2. with a cocktail of antibodies (tumor-associated antigens (TAA)): C1-P83 (CEA), Ca-19-9, Ra-96. (APAAP-method). The evaluation of 106 cells was performed by the author independently by conventional light microscopy and with the ChromaVision™-system.

Results: EPIMET-Kit: In 97.1% corresponding results for conventional and automated technique were found. TAA-cocktail: For further characterization of the tumor cells additionally analyses with the TAA cocktail was performed in 66 specimens. Corresponding results between conventional and automatic analyses were observed in 95.5% (63/66) of the patients. Comparison of the paired samples analyzed with both methods showed in 71% identical results.

Conclusion: After individual adjustment the automated computerassisted analysis with the ChromaVision™-systems allows an precise detection of disseminated tumor cells in less time (40%) than conventional analyses and therefore seems to be extremely useful for standardization.

The differences between the two detection methods might reflect the heterogeneity of the disseminated tumor cells.

1059 POSTER

Limited treatment-related toxicities are observed with cisplatin and 5FU during definitive chemoradiation for anal cancer

A. Hung[1], M. Ballo[1], C. Crane[1], M. Delclos[1], J. Ajani[2], T. Brown[2], B. Feig[3], J. Skibber[3], N. Janjan[1]. *[1]UT M.D. Anderson Cancer Center, Radiation Oncology, Houston, U.S.A; [2]UT M.D. Anderson Cancer Center, Medical Oncology, Houston, U.S.A; [3]UT M.D. Anderson Cancer Center, Surgical Oncology, Houston, U.S.A*

Aim: To document the well-tolerated nature of definitive chemoradiation for patients treated for anal carcinoma with concurrent cisplatin and 5-FU.

Methods: A retrospective analysis was performed among 92 patients with M0 squamous cell carcinoma of the anus treated between 1989-1998. By AJCC criteria, 5 patients had T1 disease, 44-T2, 28-T3, 10-T4, and 5-Tx. 70% [N=65] were node negative; 7 patients had N1 disease, 13-N2, and 7-N3 disease. The primary tumor and involved lymph nodes received 55Gy/30 daily fractions. The total dose to the pelvis was 50.4Gy. Cisplatin [4 mg/m2/day] and 5FU [250 mg/m2/day] were given as a continuous infusion, 5 days each week throughout the radiation course. Toxicity rates were evaluated and scored by RTOG criteria. Kaplan-Meier curves were generated for local control and overall survival.

Results: The median age was 58 years. There were 21 males and 71 females. Actuarial 5 year OS is 85%. The overall rate of local control is 82%; for T1 lesions, LC was 100%, 88% for T2, 74% for T3, 66% for T4. Local recurrences occurred in 16 cases; 15/16 local recurrences occurred within 16 months, and 9 patients have NED after APR. Median treatment time was the expected 42 days in >90% of cases; 7 patients required >46 days. Treatment compliance, due to socioeconomic reasons, was the cause of delays in 4 cases. 2 cases had prolonged courses because they developed upper GI bleeds that resulted in hospitalization. 1 case, previously treated with FAC for breast cancer, required hospitalization for fluid resuscitation that caused a treatment interruption. These patients represent 3 of the 5 cases [5%] of RTOG Grade 4 toxicity; the remaining cases did not sustain an interruption in XRT. 1 other case required parenteral support and the last case of Grade 4 toxicity was a perineal skin ulcer in the region of the tumor. RTOG Grade 3 toxicities were limited to the expected moist desquamation in the inguinal and perianal region [63 cases; 68%]. With good supportive care, other Grade 3 toxicities occurred in <10% of cases; Grade 3 diarrhea occurred in only 8 cases [9%], and nausea in 9[10%] cases. The only hematologic toxicity was grade 2 in 2 cases. Late toxicities occurred in 2 cases: chronic cystitis and a fistula.

Conclusions: Treatment-limiting toxicities are rare for chemoradiation for anal cancer with a regimen that uses cisplatin and 5FU. Therapeutic outcomes are comparable to those with more toxic regimens that use mitomycin-C and 5FU.

1060 POSTER

Gemcitabine and cisplatin chemotherapy for patients with metastatic esophageal carcinoma

S. Urba, S. Taylor, J. Paradelo, J. Abbruzzese, K. Chansky. *Southwest Oncology Group (SWOG), Seattle, USA*

A protocol was designed within SWOG to assess overall survival for patients (pts) with metastatic or recurrent esophageal carcinoma who were treated with gemcitabine and cisplatin chemotherapy. Pts could have received prior neoadjuvant therapy, but no previous chemotherapy for recurrent or metastatic disease, and no prior gemcitabine was allowed. The regimen was gemcitabine 1000 mg/m2 on Days #1, 8, and 15, and cisplatin 100 mg/m2 on Day #15. Cycles were repeated at 28 day intervals. Between 4/1/98 and 6/15/99, 62 eligible pts were enrolled from 37 institutions. 82% of pts had adenocarcinoma and 18% of pts had squamous cell carcinoma. 95% were males, and the median age was 57 (range 33-77). Three deaths occurred during treatment: 1 pt died from renal failure likely related to the cisplatin, 1 pt died from an arrhythmia, and 1 pt experienced severe depression and general decline. The most common Grade 3 or 4 toxicities were neutropenia - 16 pts (26%), leukopenia -15 pts (24%), lymphopenia - 10 pts (16%), nausea -10 pts (16%), vomiting - 6 pts (10%). The median survival is 7.2 months. Estimated 3-month survival is 81%, and 1-year survival is 20%. At this time, 7 pts remain alive (range of follow-up is 10-18 months). Conclusion: This regimen of cisplatin and gemcitabine was well tolerated, and survival compares favorably to the 50% 3-month survival previously observed for pts with metastatic esophageal cancer in former SWOG protocols. Other regimens of combination chemotherapy including gemcitabine will be investigated for esophageal cancer.

1061 POSTER

Bystander effect is dependent on gap junction in esophageal cancer

S. Matono, T. Tanaka, H. Yamana, S. Sueyoshi, U. Toh, H. Fujita, K. Shirouzu. *Kurume University, Surgery, Kurume, Japan*

Background: It has been recently reported that bystander effect (BE) in a gene therapy through herpes simplex virus thymidine kinase (HSV-TK)/ganciclovir (GCV) is mainly mediated by gap junction. We examined the relationship between BE and expression of gap junction protein, connexin (Cx), in esophageal cancer in vitro. Materials and Methods: We did our present study by using human squamous cell carcinoma cell lines, KE-series (8spesies), with the following procedures: 1) Immunohistochemistry, RT-PCR and Western blot for Cx26 and Cx43, 2) Dye transfer assays with Lucifer Yellow, and 3) Cell killing assay by using cells transfected with gene of HSV-tk and parent cells with GCV treatment. We further examined the effect of all-transretinoic acid in BE. Result: KE series expressed Cx43 mRNA in all cell lines used and protein in 3 of 8 cell lines and did not express Cx26 mRNA and protein. Localization of Cx43 protein was observed in cytoplasm and cell-cell contact area of KE-6 and in cell-cell interface of KE-8. Considerable GJIC capacity and BE was observed in KE-8 and

slight BE was seen in KE-6. When 10% HSV- tk+ cells were mixtured, about 50% of cells were killed in KE-8. All-trans-retinoic acid enhanced the GJIC and the BE by around 30% in KE-6. Conclusion: Our results suggest that Cx expression in cell-cell contact area is indispensable to BE induction in HSV-tk/GCV gene therapy. We can expect considerable effect of this gene therapy only for esophageal cancer expressing GJIC capacity. This gene therapy might become enough efficacious with Cx gene induction or up-regulation of GJIC by adequate chemicals,

1062 POSTER

A comparsion of different techniques in VX2 tumor cell implantation

Y.C. Lin[1], J.H. Chen[2], Y.H. Jen[2], K.W. Han[1]. [1] *Chunghsing University, Veterinary Medicine, Taichung, Taiwan;* [2] *China Medical College Hospital, Radiology, Taichung, Taiwan*

Introduction/Purpose: The liver might harbor primary tumors and is the most common site for metastases from gastrointestinal tumors and malignant melanoma. Early detection or exclusion of a neoplasm is important for appropriate treatment. The authors compared four methods for tumor implantation into the rabbit liver for experimental purposes.

Methods: Fifty-five New-Zealand white rabbits, each weighing about 2.8-3.2kg, were used for the experiment. The rabbits were divided into 4 groups. Four different implantation methods were used to induce VX2 carcinomas respectively. In group one (n=10), tumor cells were directly injected into rabbit liver. In group two (n=19), we used alcoholic cotton swap pressed on the injected site after injection. In group three (n=16), we injected agarose to the needle track after the tumor cells suspension was implanted to prevent cancer seeding. In group four (n=10), we directly transplanted 1 mm3 of the tumor block into both the left and right lobe of the rabbit liver. The growing of the tumor cells were evaluated by CT scan after two weeks of inoculation.

Results: The successful inoculation was defined as no tumor seeding in the needle tract, peritoneum, and subcutaneous area. The successful rate for the four groups (I, II, III, and IV) were 10%, 32%, 88%, and 92% respectively. Agarose injection followed tumor cells suspension injection has comparable success rate as that of direct tumor block transplantation.

Discussion/Conclusions: With highly successful implantation rate, direct injection followed by agarose prevention is a convenient technique and is very useful when multiple implantation sites are demanded.

1063 POSTER

Phase I/II clinical trial on the combination chemotherapy with CPT-11 and the new oral anticancer drug S-1 for advanced gastric cancer (AGC)

Y. Komatsu[1], H. Takeda[1], M. Kato[1], T. Sugiyama[1], M. Asaka[1], T. Miyagishima[2], Y. Kunieda[3], M. Tateyama[4], Y. Sakata[5]. [1] *Hokkaido University, Department of Gastroenterology, Sapporo, Japan;* [2] *2Kushiro Rousai Hospital, Internal Medicine, Kushiro, Japan;* [3] *3Wakkani City Hospital, Internal Medicine, Wakkanai, Japan;* [4] *4Tomakomai Nissho Hospital, Internal Medicine, Tomakomai, Japan;* [5] *Misawa City Hospital, Internal Medicine, Misawa, Japan*

Purpose: The purposes of this study is 1) To decide the recommended doses of CPT-11 in this combination chemotherapy, 2) To determine the side effects and safety of this combination therapy; 3) To evaluate the effectiveness, antitumor effect of this combination therapy for Advanced Gastric Cancer (AGC). Methods: Patients with AGC and chemotherapy-naive were entered this study. CPT11 was administered intravenously over 90-min on day 1 and day 15. S-1 was orally given from day 1 to day 14, twice a day after breakfast and supper.We established 3 dose escalation levels. While the dose of S-1 was determined, as just mentioned, the dose of CPT-11 was increased from 100 mg to 125 mg, and then to 150 mg. Results: Fifteen patients entered this study.Side effects observed as non- hematological toxicity (HT) were all mild, classified as grade 2 or lower, except for grade 3 non-HT observed at level 1 and grade 3 dermatitis at level 2.As for HT, grade 4 neutropenia occurred in one patient at level 1 and in 2 at level 2, but these side effects were within a tolerable range in the others.Then MTD has not yet been reached. The antitumor effect was observed in 3 patients at level 1, including one CR case, and 3 PR cases were observed at level 2. Thus a 50% efficacy rate was obtained. Conclusion: At the present time, although the clinical trial on this combination chemotherapy has been up to level 3, a 50% response rate, including one CR case, has been obtained, indicating that this regimen is effective in the treatment of AGC. Additionary, pharmacokinetics studies were performed.This study is now ongoing.

1064 POSTER

Gemcitabine (G) and cisplatin (C) in the treatment of locally advanced and/or metastatic pancreatic carcinoma

M. Oukkal, K. Bouzid, H. Mahfouf. *Centre Pierre et Marie Curie, Medical Oncology, Algiers, Algeria*

Purpose: G, an active agent in pancreatic cancer, has shown synergistic activity with C. We evaluated the efficacy and toxicity of the G plus C combination in patients with locally advanced unresectable and/or metastatic pancreatic carcinoma.

Methods: Inclusion criteria included: adults with advanced pancreatic carcinoma, measurable disease, no prior chemotherapy, ECOG performance status (PS) less than or equal to 2, adequate renal and liver function, good bone marrow reserve, life expectancy greater than or equal to 12 weeks, and informed consent. G 1250 mg/m2 was administered on days 1 and 8 with C 70 mg/m2 on day 1 every 3 weeks.

Results: From June 1997 to March 2001, 31 patients (21 males, 10 females) were enrolled with a median age of 56 years (range 34-71);. 17 patients had metastatic and 14 had locally advanced disease. At the time of the analysis, all patients were evaluable for toxicity and 28 were evaluable for response. Complete response (CR) was achieved in 2 (7.1%) patients and partial response (PR) in 7 (25%) patients, for an overall response rate (CR+PR) of 32.1%; 8 (28.6%) patients had stable disease and 11 (39.3%) had progressive disease. Clinical benefit response (based on reduction of analgesic consumption, increase in weight, and improvement of PS) was noted in 21 (67.7%) patients. Overall survival is 8 months. A total of 97 cycles was administered, with a median of 3.1 cycles (range 1-6). Severe toxicities (NCIC grade 3/4) evaluated over 97 cycles were thrombocytopenia in 8%, vomiting in 12%, anemia in 5%, and neutropenia in 2% of patients.

Conclusions: The combination of G and C is well tolerated and shows promising activity in pancreatic cancer, and confers a clinical benefit for most of the patients.

1065 POSTER

Chemoradiation with gemcitabine ('gemzar') in the treatment of biliopancreatic cancer: a phase I study

G. Macchia[1], L. Trodella[1], A.G. Morganti[1], S. Luzi[1], D. Smaniotto[1], S. Alfieri[2], G. Costamagna[2], V. Valentini[1], G.B. Doglietto[2], N. Cellini[1]. [1] *Radiology, Radiotherapy, Rome, Italy;* [2] *Surgery, Surgery, Rome, Italy*

Purpose: Aim of this study was to establish the maximal tolerated dose (MTD) of gemcitabine (once weekly) that could be safely administered when combined with radiation in advanced biliopancreatic malignancies; moreover to assess clinical and pathological response rate.

Material and Method: 15 patients (M/F: 9/6; median age: 63.4; pancreatic ca: 10 pts, biliary ca: 5 pts; T4N0: 9 pts, T3N0: 4 pts, T4N1:2 pts) entered into the study. Five patients were treated with chemoradiation after radical surgical resection. Eligibility criteria included: disease limited to the local regional area without evidence of liver or distant metastasis, age less than 75, ECOG performance score 0-2, WBC > 4000, PLT >100.000, Hb > 10.

External beam radiation was delivered with 9-10 MV photons by using a three-field technique. The prescribed external beam dose (ICRU 50) was 50.4 Gy. The initial dose of Gemcitabine was 100 mg/m2 administered as a short intravenous infusion once a week. Three patients were treated at each dose level and if no grade 3-4 WHO toxicity (considered as DLT) was recorded, the dose of the drug was escalated in increments of 50 mg/m2 till MTD was established.

Results: All patients were evaluable for acute toxicity. Fourteen patients completed the planned course of chemoradiation without interruptions. There were no treatment-related deaths. No DLT occurred at the first 4 dose levels (100 mg/m2 -250 mg/m2).

At the 5th dose level (300 mg/m2), 3 patient experienced DLT: 1 grade 3 gastrointestinal toxicity, 1 uncomplicated grade 3 leukopenia and 1 grade 3 change in liver biochemistry tests.

In addition, all 10 patients unresected were evaluated for response, of whom 4 had PD (1 local; 2 distant; 1 local and distant) and 6 had NC.

Conclusion: In conclusion, gemcitabine concomitant with pelvic radiotherapy has allowed out-patient administration with manageable toxicity. The main drug-related toxicities were gastritis, leukopenia and increased level of serum transaminases. Based on this study, it appears that the MTD for weekly short infusional gemcitabine combined with radiation is 250 mg/m2. Further studies aimed to improve the response rate after chemoradiation are needed. Moreover, different infusion modality, like continous infusion of gemcitabine, should be tested more accurately.