579 PUBLICATION

Pancreatic cancer: The analysis of prognostic factors in patients with pancreatic cancer with distant metastasis

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Purpose: Because of difficulties in early detection of pancreatic cancer, significant number of patients are diagnosed with distant metastatic lesions. Pancreatic cancer with distant metastas is a rapidly progressive disease, and candidates of systemic chemotherapies should be selected under consideration of their short survival time. We analyzed prognostic factors in patients with pancreatic cancer with distant metastasis retrospectively to identify the significant prognostic factors.

Methods: 69 patients with pancreatic cancer who admitted to the center from Oct. 1992 to Dec. 1997 with distant metastasis but without any therapies. They were histologically or cytologically diagnosed as adenocarcinoma of the pancreas. Twenty-nine patients received systemic chemotherapies with or without radiation therapy and the others received the symptomatic treatment. Pretreatment clinical variables (age, sex, performance status (WHO), location of primary tumor, site of metastasis, presence of ascites, pain, chemotherapy, total bilirubin, hemoglobin, platelet count, albumin, total cholesterol, cholinesterase (ChE), tumor markers (CEA, CA19-9), prothrombin activity) were examined by using univariate analysis. Significant variables were analyzed in Cox proportional hazards model to identify the independent prognostic factors.

Results: The overall median survival time (MST) of all patients was 61 days, and 1 year survival rate was 0%. Significant poor prognostic factors were over the age of 60 years old, the presence of ascite, a total bilirubin >2 mg/dl, a prothrombin activity <70%, a ChE <180 mg/dl, and a performance status >1 ($p < 0.01$). The presence of pain, having chemotherapies, metastatic hepatic lesions or a higher level of tumor makers (CEA, CA19-9) were not significantly related to MST. The independent poor prognostic factors using Cox proportional hazards model were a presence of ascites, a serum ChE level of <180 mg/dl, and a age > 60. Higher hazard ratios were recognized as the following order: ascites, ChE, and age factors. MST of the patient without ascites was 85 days and, that of with ascites was 25 days. MST of those with a serum ChE level of <180 mg/dl were 34 days, and a age over 60 was 45 days respectively.

Conclusion: This study indicated that patients who had poor prognostic factors such as a presence of ascites, ChE < 180 mg/dl, or age > 60 should not be eligible for chemotherapies because of their extremely short survival time.

580 PUBLICATION

Selective arterial cytostatic infusion combined with chemoembolization in hepatic tumors

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Purpose: Liver is a very frequent site of malignant tumors with a conventionally low success rate of treatment locally and low survival generally. Thus, an alternative therapy is to be initiated rather than i.v. chemotherapy or major hepatic surgery.

Material and Methods: In 53 patients in 132 cycles all together 708 cytostatic infusion was given combined with 120 chemoembolization.

Results: In 41 patients the progression of the malignant process stopped or regressed. In 9 cases the progression was not effected and in 3 (very much advanced diseases) a deterioration was observed. The complication rate was very low of 2% (14 cases of 708 cycle). The most common result of the treatment was the decrease or halt of the spread and growth of the focal intrahepatic disease frequently with signs of necrosis.

Conclusion: Intraarterial anticancer chemotherapy is indicated in focal hepatic malignancies based on its acceptable clinical results and low morbidity being comparable to those of intravenous chemotherapy.

581 PUBLICATION

Neoadjuvant radiotherapy and chemiotherapy for advanced esophageal cancer

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Purpose: To determine the results of radiotherapy alone and combined with chemotherapy in the treatment of stage III esophageal carcinoma.

Methods: From 1990 to 1998 42 patients with stage III esophageal cancer, mean age 65.3 years, were treated in the Department of Radiation Therapy at the University of Rome "La Sapienza". Twentytwo patients underwent concomitant radiochemotherapy with external beam radiation, 45–50 Gy; 1.8 Gy 5/W, and chemotherapy, 5 FU 750 mg/m^2; day 1–5 and CDDP 50 mg/m^2 day 1. Twenty patients received radiotherapy alone, 50–60 Gy; 1.8 Gy 5/W. In selected patients, a boost of intraesophageal brachytherapy with 192 Ir, 10–20 Gy was administered.

Results: Of the 22 patients received radiochemotherapy, 9 have been subsequentely operated, 6 were pT0, nine patients had a complete response and 4 a partial response. Among 20 patients submitted to radiotherapy alone, 10 had complete response, 4 of them developed distant metastases after 4–7 months and 10 had a partial response. Acute toxicity particulary esophagitis (grade III: 3 cases) and hematologic side effects (grade III: 4 cases) were observed in patients treated with chemoradiotherapy (33%) and in patients treated with radiotherapy alone (25%).

Conclusion: Radiotherapy alone seems to have a significative local control in the advanced esophageal cancer, combined with chemotherapy even decreases the rate of distant metastases.

582 PUBLICATION

Weekly gemcitabine (GEM) and 5-fluorouracil (5-FU) in pancreatic carcinoma. Phase I-II study

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Introduction: 5-FU and GEM are the most active drugs in the treatment of pancreatic cancer. A randomized study comparing GEM and 5-FU showed an improvement of RR and clinical benefit in the group of pts treated with GEM. In order to evaluate toxicity dose limiting (TDL), the maximum tolerated dose (MTD), the efficacy of the association 5-FU and GEM also in term of clinical benefit, we began a phase I–II study with escalating doses of both drugs.

Methods: Inclusion criteria were: locally advanced or metastatic measurable adenocarcinoma of pancreas; PS (ECOG) = 2; normal hematological, hepatic, renal and cardiac function; life expectancy more than 3 months. Previous chemotherapy was not allowed. Three steps of 7 patients were projected. Chemotherapy was administered on days 1, 8, 15 every 4 weeks. I step: GEM 1000 mg/mq IV + 5-FU 1000 mg/mq IV bolus. II Step: GEM 1000 mg/mq IV + 5-FU 2000 mg/mq IV in 24 hours ci. III Step: GEM 1200 mg/mq IV + 5-FU 2250 mg/mq IV in 24 hours continous infusion. Up to now 17 pts were enrolled, 14 in the first 2 steps and 3 in the third step. All pts are evaluable for toxicity and clinical benefit, 14 are evaluable for response. Their main characteristics are: median age 54 y, 10 M/7 F, 5 stage IVA, 12 IVB, median PS (ECOG) 1.

Results: Altogether 77 courses of chemotherapy were delivered (37 step I, 33 step II, 7 step III); chemotherapy in day 15 was omitted in 5% of courses of step I and in 9% of the courses of step II. Grade 3–4 toxicity was observed only in step II: neutropenia in 12%, anemia in 6%, ALT/AST increase in 6% of courses. We observed 4 PR (2 in step I, 1 in step II e 1 in step III). Ten out of the 17 pts showed a clinical benefit from chemotherapy.

Conclusions: This schedule appears feasible at all the steps until now evaluated. Toxicity was accettable, clinical benefit was significant, response needs further evaluation.

583 PUBLICATION

Phase II trial of gemcitabine-UFT-leucovorin (ILV) in advanced carcinoma of the pancreas: Preliminary results

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Purpose: to evaluate the therapeutic activity and the tolerance of the combination Gemcitabine-UFT-LV in patients with advanced pancreatic cancer.

Patients and Method: 25 patients were included since sept-97, median age 59 (limits 45–71), male/female 14/11. Five patients (20%) had locally advanced disease and 20 (80%) metastatic disease. Fifteen patients (60%) had a performance status of 60–70, 14 (56%) moderate to severe pain and 17 (68%) weight loss greater than 5%.

Treatment consisted of gemcitabine 1500 mg/m^2 on days 1 and 14, i.v. l-LV 250 mg/m^2 in 2 hours on day 1 followed by oral l-LV 7.5 mg/12 hours for 14 days, and UFT 390 mg/m^2/day for 14 days. Courses were repeated every 28 days for a minimum of 3 per patient.

Results: 121 courses were administered, median 4.8 per patient (1–10). WHO grade 3–4 toxicities: diarrhea in 5 patients (20%), leucopenia in 2 (8%) and thrombocytopenia in 1 (4%). Twenty-two patients are evaluable for response so far: 3 had a partial response (14%, 95%CI 2–35%), 12 stable disease (54%) and 7 a progression (32%). Clinical improvement appeared in 13 patients (59%). The median time to progression was 6 months and the median survival 8 months.

Conclusions: although preliminary, these results suggest that the combination of gemcitabine-UFT-ILV is moderately active, convenient for the patient and has an acceptable toxicity.

584 PUBLICATION

Phase II study of docetaxel as first line chemotherapy (CT) in metastatic adenocarcinoma of the pancreas

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Introduction: The therapeutic outcome obtained with CT in metastatic pancreatic cancer is poor. A response rate of 22% (95% CI 6–34%) has been reported in 30 pts. with metastatic disease for Docetaxel (D) in an earlier phase 2 study. Based on these results D was investigated in a confirmatory phase 2 study.

Patients: 15 pts. with bidimensionally measurable metastatic disease were entered onto the study and were evaluable for response and safety. Male/Female ratio: 8/7, median age 58 (39–64), median WHO PS: 1 (0–2).

Treatment: D was given at a dose of 100 mg/m^2 i.v. over 1 h. every 21 days.

Results: 15 pts. received a total of 55 cycles with a median no. of 3 cycles/patient (range 1–8).

Safety: Short lasting neutropenia of NCI-CTC grade 4 and anaemia grade 3/4 occurred in 73% and 13% of pts. respectively. The incidence of non hematological toxicities of NCI-CTC grade 3/4 was asthenia 13%, vomiting 6%, stomatitis 6% and edema in 6% of pts. respectively.

Response: 1 PR (7% [95% CI 0–32%]) was achieved. In addition 10 (67%) pts. had stable disease resulting in a tumor growth control rate (PR/NC) of 74% (95% CI 45–92%). The median time to progression of disease was 5 month.

Conclusion: The present trial confirmed the results of newer phase 2 studies. However, the high rate of tumor growth control and the relatively long median time to progression suggest that patients may benefit from treatment with Docetaxel.

585 PUBLICATION

Necrotic solitary nodule of the liver: Case reports and pathogenetic hypothesis

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Introduction: we observed 2 cases of a rare and non tumoral lesion of the liver, misinterpreted as (necrotic) tumor: the necrotic solitary nodule. It is a lesion well delimited by a dense hyalinised fibrotic capsule with a necrotic center in a granular tissue. Different aetiophatogenetic hypothesis have been postulated: evolution of a liver hemangioma or other benign lesions, traumas, parasitics or abscess infections, hematomas.

Methods: The first case concerns a 43 years female with continuous abdominal pain. US showed a polylobated lesion (35 × 35 × 38) at segment 8, with an hypoechoic core and an hyperechoic edge associated with cholelithiasis. Color-doppler signaled a compression of the celiac axis (Dunbar syndrome). Arteriography revealed a subtotal stenosis of the celiac tripod due to compression. CT scan confirmed the same lesion at segment 8 without contrast enhancement. FNAB-CT guided showed an highly-cellulated tissue with a necrotic core. The patient underwent surgery: cholecystectomy and correction of Dunbar syndrome (liberation of the celiac tripod from the fight pillar of the diaphragm; mechanic dilatation of the celiac tripod through trasversal arteriotomy sutured with 7/0 prolene). Follow-up revealed a progressive reduction in diameter of the lesion suggestive for an ischemic pathogenetic role. The second case concerns a 69 years male, with an hypoechoic lesion (32 × 32 × 30 mm) at segment 6 as occasional US finding during the staging for prostatic cancer. FNAB-CT guided was positive for malignant cells. Surgical treatment consisted in a wide excision of the lesion. Histologically it was highly cellulated, completely necrotic: solitary necrotic nodule.

Conclusion: The diagnosis of this rare lesion is accidental. According with literature (50% of cases), we founded an associated tumor. Thus, the correct diagnosis is achievable only with an histologic exam as demonstrated in the second clinical case reported.

586 PUBLICATION

Phase II trial of gemcitabine (GEM), 5-Fluoruracil (5-FU) and leucovorin (LV) in advanced pancreatic cancer (PC)

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Purpose: PC remains as one of the deadliest diseases. The high incidence of unresectable and disseminated disease has led clinical investigators to recognize that improved palliation of PC will require more effective systemic therapy. Many studies have failed to evaluate the palliative benefit of treatments, although many patients consider such benefit to be the utmost importance. Gemcitabine (GEM), a novel nucleoside analogue and 5-Fluorouracil (5-FU) are the most active agents in PC. Their combination could result in higher activity.

Methods: A multi-institutional phase II study was initiated in November 97, to determine the clinical benefit, response rate and toxicity of the combination chemotherapy regimen. Schedule was: G 1000 mg/m^2 iv., 5-FU 600 mg/m^2 bolus iv. and LV 25 mg/m^2 iv. All drugs were given weekly for 3 weeks every 4 weeks. 18 pts. were accrued, male/female 12/6, median age 60.5 years (r 39–76), PS (ECOG) 0–2, 1–3, 2–13. All pts. were symptomatic: pain, weight loss, anorexia, impaired (PS); 11 pts. had locally advanced and 7 pts. had metastatic disease.

Results: 4 pts. achieved a PR and 11 a SD (RR 22.2%) (95% CI 6.4–47.6%). Median survival for all the pts. was 11 months. We observed only 11.2% of grade 3–4 hematological toxicity (WHO).

Conclusions: This chemotherapy regimen shows promising activity with low toxicity in this chemoresistant malignancy.

587 PUBLICATION

Cryosurgery for locally advanced pancreatic cancer

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Cancer of the exocrine pancreas remains a therapeutic challenge and continues to have a por prognosis. Only 10–15% of patients present with localized disease amenable for surgery with curative intent. Most patients with unresectable cancer die within 6 months of diagnosis, and thus novel treatment methods are needed. The aim of the study was to evaluate results of cryosurgery in patients with unresectable pancreatic cancer. Fifty-three patients with mean age 62.6 (range 26–74) with locally advanced exocrine pancreatic cancer were operated on in our Department. In 11 cases tumour was located in the head of the pancreas, in the body or tail in 25 cases. Seventeen patients had total pancreatic cancer. Cryosurgery alone was performed in 32 patients, other 21 underwent combined operative procedure consisted of cryosurgery and cholecystojejunostomy in patients with jaundice or gastrojejunostomy in patients with gastric obstruction. Cryosurgery of primary lesion in pancreas and solitary metastases in liver was performed in 5 cases. The size of the lesion determined the size of the cryoprobe to be used. In cases of big tumours (more than 5 cm in diameter) we performed destruction with two freeze-thaw cycles. The process of destruction was monitored effectively with intraoperative ultrasonsgraphy. Patient follow-up ranged from 8 to 40 months. Three patients (5.6%) died within 30 days after operation. Causes of death were disease progression in two cases and hepatorenal syndrome in one. Postoperative complications occurred in 14 cases (26.4%) and included pneumonia, wound infection and pancreatic fistula. Fifty patients (94.3%) were alive at 8 months of follow-up. The 1-, 2-, 3-year survivals were 64.1%, 28.3%, and 13.2%, respectively. Two patients lived 40 months. Thus, cryosurgery proved to be effective for the management of patients with locally advanced pancreatic cancer.