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Adjuvant PEFG (cisplatin, epirubicin, 5-fluorouracil, gemcitabine) or gemcitabine in pancreatic cancer: a randomized phase II trial

M. Reni[1], S. Cereda[1], G. Aprile[2], M.C. Tronconi[3], C. Milandri[4], P. Passoni[5], A. Rognone[1], G. Balzano[6], V. Di carlo[6], E. Villa[1]. *[1]Hospital San Raffaele, Oncology, Milan, Italy; [2]University Hospital of Udine, Oncology, Udine, Italy; [3]Istituto Clinico Humanitas Rozzano, Oncology, Milan, Italy; [4]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori Meldola, Oncology, Forli', Italy; [5]Hospital San Raffaele, Radiotherapy, Milan, Italy; [6]Hospital San Raffaele, Surgery, Milan, Italy*

Background: In 2003, at time of trial design, the role of adjuvant therapy in PA was debated and no recommended standard existed. Since in stage III and IV pancreatic adenocarcinoma (PA), PEFG regimen significantly improved progression-free survival and overall survival (OS) as compared with gemcitabine (G), we assessed the impact upon disease control of PEFG regimen and G in the adjuvant setting as well.
Material and Methods: After R0 or R1 resection for PA, patients with stage IB-III disease, aged 18−70 years, Karnofsky performance status (PS) >60 were randomized within 8 weeks from surgery to receive either G 1 g/m^2/weekly Q3 every 4 weeks (Arm A), or PEFG (cisplatin and epirubicin at 40 mg/m^2 each on day one, gemcitabine at 600 mg/m^2 on days 1 and 8 and 5-FU at 200 mg/m^2/day on days 1 to 28) every 4 weeks (Arm B). In both arms chemotherapy was administered for 3 months and followed by radiotherapy (54−60 Gy in 27−30 fractions) with concurrent 5-FU 250 mg/m^2/day. The primary endpoint was the probability of being disease-free at 1 year (DFS 1 y) from surgery. The Fleming design was used to calculate the sample size. Assuming P0 = 35% and P1 = 55%, a?.05 and b.10, the study was to enroll 51 patients per arm. The treatment regimen had to be considered of interest with >23 patients being DFS 1 y.
Results: Between August 2003 and August 2008, 102 patients were enrolled, stratified by center and resection margin and randomized (51 per arm). One arm B patient was ineligible due to metastatic disease, 1 arm A patient received PEFG regimen and 1 arm B patient withdrew consent. An intent-to-treat analysis on eligible patients was performed. Patients' characteristics were (A/B): median age 61/60, median PS 90/90, stage IB-IIA 25/15%; stage IIB 63/78%; stage III 12/7%; grade 3 29/46%; R1 35/29%; pre- and post-surgery surgery CA19.9 >upper limit of laboratory normal 69/81% and 29/33%, tumor size >2.9 cm 44/42%. To date, 50 A and 48 B patients are assessable for the primary endpoint: 23 (46%) and 31 (65%) patients were DFS 1 y. Main G3−4 toxicity was: neutropenia in 15/58% and thrombocytopenia in 0/11% of cycles.
Conclusion: This is the first randomized trial on single agent or combination chemotherapy as adjuvant treatment of PA. With a mature follow-up for 98% of patients, PEFG fulfilled the primary endpoint and warrants further study while G not yet.

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Analysis of dosimetric factors associated with gastrointestinal and blood toxicities in patients with locally advanced pancreatic cancer treated with concurrent chemoradiation therapy

K. Shibuya[1], A. Nakamura[1], Y. Matsuo[1], M. Nakamura[1], T. Shiinoki[1], T. Mizowaki[1], M. Mitsumori[1], M. Hiraoka[1]. *[1]Kyoto University Hospital, Radiation Oncology and Image-applied Therapy, Kyoto, Japan*

Background: We conducted a phase I/II study and established a regimen consisting of weekly low dose gemcitabine with concurrent radiotherapy (RT), which achieved prolonged survival (16.6M in median) in patients with unresectable pancreatic cancer, but experienced local failure in 30%. Dese escalation of RT would be necessary, but gastrointestinal (GI) and blood toxicities are often dose-limiting factors.
Purpose: This study analyzed the dosimetric factors associated with GI and blood toxicities in patients treated with the regimen established in the phase I/II study.
Material and Methods: In all patients, a total dose of 54 Gy was delivered in 30 fractions of 1.8 Gy/day. Gemcitabine was given weekly at a dose of 250 mg/m^2 during the 6-week course of RT. Treatment-related toxicities were assessed weekly during, and 4 weeks after, RT using the National Cancer Institute's Common Terminology Criteria for Adverse Events v3.0 (CTC3.0). The relations between GI toxicities including anorexia, nausea, vomiting or pain with irradiated absolute volume (V10, V20, V30, V40 and V50) of stomach, small intestine and colon. In the same way, the relations of leukopenia or thrombocytopenia with irradiated absolute volume of liver or spleen were analyzed.
Results: For 33 patients, the data on dose distribution were available. There was no significant correlation between total irradiated volume and toxicities. However, we recognized a significant correlation of V30, V40 and V50 of stomach with GI toxicities; the correlation coefficients (R^2) were 0.46 (p = 0.48), 0.49 (p = 0.0042) and 0.46 (p = 0.0078), respectively. There was no correlation observed among GI toxicities and the absolute volume of small intestine or colon. The observed grade of leukopenia tended to increase as volume of the liver increased, although there were no significant correlations. In the same manner, between the absolute volume of spleen and CTC 3.0 grade, there were no significant correlations, but the incidence of leukopenia of CTC3.0 $\geqslant$ grade 3 was significantly higher for patients with V20 $\geqslant$30 cm^3 (100%) than with <30 cm^3 (50%). The incidence of thrombocytopenia showed no correlations with the volume of either liver or spleen.
Conclusion: To reduce GI toxicities, the irradiated absolute volume of the stomach is important and minimizing the irradiated volume of the liver or spleen might be effective in reducing the incidence of severe leucopenia. These analyses might be helpful in escalating radiation doses using novel techniques such as IMRT for the treatment of pancreatic cancer.

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Long term analysis of Gemcitabine based chemoradiation after surgical resection for pancreatic cancer

E. Ippolito[1], G.C. Mattiucci[2], E. Ciurlia[2], S. Alfieri[3], A. Antinori[4], M. Balducci[2], A. Crucitti[4], D. Smaniotto[2], A.G. Morganti[1], V. Valentini[2]. *[1]Catholic University of the Sacred Heart, Radiotherapy, Campobasso, Italy; [2]Catholic University of the Sacred Heart, Radiotherapy, Rome, Italy; [3]Catholic University of the Sacred Heart, Digestive Surgery, Rome, Italy; [4]Catholic University of the Sacred Heart, Surgery, Rome, Italy*

Background: To evaluate the efficacy of adjuvant Gemcitabine (Gem) based chemoradiation (CT-RT) after surgery for pancreatic cancer.
Material and Methods: from 2000 to 2007, forty patients (pts) underwent postoperative 3D radiotherapy (prescribed dose to the nodal areas 39.6 Gy and 50.4 Gy to the surgical bed) plus concurrent chemotherapy (Gem: 100 mg/m^2 continuously infused for 24 h, weekly). After CT-RT pts received 5 cycles of chemotherapy (CT) with Gem (1000 mg/m^2; days 1, 8, every 3 weeks). Toxicity was evaluated according RTOG/EORTC scales. Local control (LC), metastases free survival (MFS) and overall survival (OS) were analyzed according to the Kaplan-Meier method. Comparison between prognosis groups was performed by log rank analysis. Cox proportional hazards regression model was applied for multivariate analysis.
Results: Thirty-eight pts (M/F: 25/13, median age: 65 yrs; range 45−75) were evaluable. Most of pts (n = 31; 81%) had duodeno-cephalo-pancreatectomy (pylorus preserving surgery: 71%), 2 (5.2%) a distal pancreatectomy, 3 (7.8%) a total pancreatectomy. Only five pts (13.1%) after surgery had resection margin microscopically involved (R1). No patient had residual disease (R2). The pathological stage was II-III (IIA: 40%; IIB: 50%; III: 10%). The postoperative course was complicated in 6 (15.7%) pts. Thirty-two pts (84.2%) completed CT-RT. Grade 3 toxicity was observed in 11 (28.9%) pts (gastrointestinal: 18.4%; haematological: 10.5%). Grade 4 toxicity was recorded in 4 (10.5%) pts. No patient showed late toxicity. Adjuvant CT was completed in 17 pts (44.7%). The median follow-up was 59 months (range: 15–113 months). The median OS was 23 months (SD: 24.6; 2-year rate: 47%; 5-years rate: 13.5%). Local control at 2- and 5-years was 84% and 82% respectively. Two- and 5-years MFS was 39.8% and 13.8% respectively, median 17 months. In the subgroup analysis the pylorus preserving surgery was related with improved OS, LC and MFS (p < 0.05). This latter result was confirmed at multivariate analysis (p < 0.05). Patients with tumour larger than 3 cm had poor long-term survival (p = 0.03). The rate of LC was decreased in pts with positive margin, especially in retro peritoneum (p = 0.05) and with complicated postoperative course (p = 0.03).
Conclusions: The rate of local control in patient treated with this schedule seems encouraging. Still the poor 2-year MFS suggests the need of an intensified multimodal approach.