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Prognostic relevance of lymph node metastases and adjuvant treatment for patients with invasive intraductal papillary mucinous (IPMNs) of the pancreas

E. Vasile[1], M. Del Chiaro[2], N. Funel[3], A. Sainato[4], S. Caponi[1], M. Coppola[4], D. Campani[3], A. Falcone[1], U. Boggi[2], F. Mosca[5]. *[1]Azienda Ospedaliera-Universitaria Pisana Istituto Toscano Tumori, U.O. Oncologia Medica 2 Universitaria, Pisa, Italy; [2]Azienda Ospedaliera-Universitaria Pisana Istituto Toscano Tumori, U.O. Chirurgia Generale e Trapianti nell'Uremico e nel Diabetico, Pisa, Italy; [3]Azienda Ospedaliera-Universitaria Pisana Istituto Toscano Tumori, U.O. Anatomia Patologica 3, Pisa, Italy; [4]Azienda Ospedaliera-Universitaria Pisana Istituto Toscano Tumori, U.O. Radioterapia, Pisa, Italy; [5]Azienda Ospedaliera-Universitaria Pisana Istituto Toscano Tumori, U.O. Chirurgia Generale 1 Universitaria, Pisa, Italy*

Background: IPMNs of the pancreas are a group of intraductal mucin-producing cystic neoplasms with clear malignant potential. However, the natural history of invasive IPMNs (papillary mucinous carcinomas) is not well known and there are few data regarding the prognostic factors and the role of adjuvant treatment for these patients. The purpose of our retrospective analysis was to evaluate clinical and pathological factors associated with prognosis following pancreatic resection for invasive IPMNs.
Material and Methods: The database of pancreatic surgical resection at our institution was explored from 1/2004 to 3/2009 and matched with the pathological data on the resected specimens to identify patients resected for an invasive IPMN. A retrospective review of clinical and pathological features and outcome was conducted.
Results: Thirty-two patients (15 men and 17 women) who underwent a radical surgical resection for an invasive IPMN were identified. Median age was 68 years (range 37−87). Most patients (26, 81%) had a T3 tumor. Eighteen (56%) patients had positive nodes (median number 4; range 1−12). The median number of resected nodes was 31 (range 11−97). Two postoperative deaths occurred within two months of surgery related to cardiac complications. Eighteen (56%) patients received gemcitabine as adjuvant chemotherapy; four cases were treated also with adjuvant radiotherapy mainly because of inadequate surgical margins.
After a median follow up of 18 months, 13 patients experienced a disease progression and 7 died; the sites of progressive disease were: lung and liver in 3 cases each, peritoneum in 2, pancreas remnant and abdominal lymph nodes in 1 case each, multiple site in the remaining 3 patients. The estimated median disease-free survival (DFS) was 24.9 months.
The presence of lymph nodes metastases was the main prognostic factor in our series with a median DFS of 30 months for node negative vs 12.8 months for node positive patients. Adjuvant chemotherapy seemed beneficial for node positive patients (DFS 16.5 vs 8.5 months for treated vs untreated patients). Among node positive patients a lymph node ratio >0.1 resulted associated with worse outcome (DFS 11.9 vs 16.7 months with ratio <0.1).
Conclusions: Our results confirm that node positive invasive IPMNs has a dismal prognosis. The role of adjuvant treatment for these patients seems promising but should be further investigated. An early surgical approach for this disease should be advocated.

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A phase II study of erlotinib in patients (pts) with advanced pancreatic cancer (APC) who are refractory to gemcitabine (G)

R. Iyer[1], N. Khushalani[1], W. Tan[1], A. Litwin[1], C. LeVea[1], A. Hutson[1], C. Tucker[2], W. Ma[1], M. Fakih[1], A. Adjei[1]. *[1]Roswell Park Cancer Institute, Medicine, Buffalo, USA; [2]OSI Pharmaceuticals, Medicine, Denver, USA*

Background: Erlotinib + G is the only approved doublet for treatment of pts with APC. We examined the effect of erlotinib alone on progression free survival (PFS) in pts who were not candidates for or were refractory to G.
Materials and Methods: Pts with APC who had received either 0 or 1 prior therapy for APC, with ECOG performance status (PS) 0, 1 or 2 were included in this prospective trial. Primary endpoint was PFS and secondary endpoints were response rate (RR), overall survival (OS), quality of life (QOL) and toxicity. Correlation between primary and secondary clinical outcomes with smoking status, steady state concentrations of erlotinib in week 3 of treatment, rash development and *k-ras* mutation status of tumors was conducted. Treatment: Erlotinib 150 mg PO daily for 3 week cycles, restaging occurred q6 weeks and response was assessed by standard RECIST criteria. EORTC PAN-26 QOL tool was used. Statistical analyses were performed by the Kaplan-Meier method, log-rank test, Cox proportional hazards model and the Wilcoxon rank sum test.
Results: Eighteen pts were enrolled, 15 are evaluable for response (3 symptomatic deterioration). Pt characteristics: Median age 64.5 yrs (range 48−84 yrs) sex M/F: 9/9; PS 0/1/2: 13/3/2; Stage III/IV:0/18. Prior therapy 0/1: 4 (22%)/14 (78%). Median cycles: 2 (range 0.24−4.6). Median PFS was 1.38 months (95% CI: 1.35−1.41). The study was closed before accrual of the planned 34 pts for futility, as these findings are consistent with that expected from supportive care alone. Median OS was 3.1 months (95% CI: 2.8−4.3); Best response was stable disease in 4/18 (22%); progression 11/18 (61%) and nonevaluable in 3/18 (16%). Smoking status (n = 16) was correlated with PFS-current smokers (n = 5), past smokers (n = 9) and never smokers (n = 2) had a PFS of 1.2, 1.38 and 4.2 months respectively (long rank p value 0.02). Past/current smokers had 39% lower median steady state concentrations of OSI 774 and OSI 420 compared to never smokers (all values were within the wide range from population PK studies). QOL scores (baseline and post-therapy) had no statistical association with OS (P-value = 0.1166) or PFS (P-value = 0.212). *K-ras* mutation status will be presented. No grade 3 or 4 treatment related toxicities were seen. Fatigue, anorexia, nausea, diarrhea and anemia were frequent grade 1/2 events (n > 5). Rash was infrequent in this population [grade 1 (n = 3); grade 2 (n = 4)].
Conclusions: In pts with APC refractory to or not candidates for G, clinical benefit rate of erlotinib (CR+PR +SD) is 22% with median disease control time of 9.3 weeks. As expected in this APC population PFS and OS were short.

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Exploring the role of CA 19−9 level as a predictor of survival in patients with advanced pancreatic adenocarcinoma

T. Bekaii-Saab[1], A. Majumber[2], E. Trolli[2], J. Thomas[2]. *[1]Ohio State University Medical Center, Medicine and Pharmacology, Columbus Ohio, USA; [2]Ohio State University Medical Center, Medicine, Columbus Ohio, USA*

Background: Pancreas cancer is the 4th leading cause of cancer mortality. CA 19−9 is a tumor associated antigen that is considered to be a sensitive serum marker for pancreatic cancer. We hypothesized that patients treated with gemcitabine based chemotherapy presenting with normal levels of CA 19−9 upon diagnosis will show improved survival compared with those with elevated Ca 19−9 at presentation. We also hypothesized that lower Ca 19−9 levels after surgical resection could predict for a longer disease free survival (DFS).
Methods: Data was obtained from a chart review of 123 patients with metastatic pancreatic adenocarcinoma at the Ohio State University. We collected both demographic and medically pertinent (CA 19−9, progression, survival, and treatment). Data was analyzed using Kaplan-Meier survival curves and simple log-transformed correlation.
Results: A total of 31 patients who were initially resected and eventually progressed were analyzed. There was a negative association between DFS and log transformed CA19−9 level in those patients prior to the initiation of treatment for recurrence. Pearson correlation was calculated (−0.36). This association is statistically significant (p = 0.0465). We also analyzed data on all 123 patients including 93 patients who had elevated CA19−9 level and 30 patients who had normal levels. For patients with elevated CA19−9 level, median overall survival was 12 months (95% CI; 9.5, 17.3). For patients with normal CA19−9 level prior to treatment, median overall survival was 36 months (95% CI; 19, NA). Using the log-rank test to compare the KM curves for OS, a significant difference (p = 0.0002) was found in OS between the 2 groups of patients. Finally, we analyzed trends in Ca 19−9 levels on 89 patients who underwent gemcitabine based therapy. The group included 40 patients with a maximal decrease of CA19−9 level of ⩽50% and 49 with a maximal decrease of more than 50% during therapy. For patients with ⩽50% decrease in maximum CA19−9 level, median overall survival was 8.5 months (95% CI 6, 11). For patients with >50% decrease in maximum CA19−9 level, median overall survival was 21.5 months (95% CI;15, 23). Using the log-rank test to compare the KM curves for OS, there was a significant difference (p = 0.0002) in survival between the two groups of patients.
Conclusion: We showed that higher Ca 19−9 levels following resection could predict for a shorter DFS. We also showed that treated patients who present with elevated CA 19−9 levels will have a worse overall outcome than those who present with normal levels. Finally, we confirmed that patients who experienced a decrease in their CA 19−9 levels to >50% of pretreatment levels will have significantly improved odds for more prolonged survival.