Interferon-based adjuvant chemoradiation therapy after pancreaticoduodenectomy for pancreatic adenocarcinoma

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Background
Historically, 5-year survival rates in patients with locally advanced pancreatic cancer have been dismal (<10%), even following a Whipple resection. Disease recurrence is typically both local and distant. Further advances in the management of pancreatic cancer led to the incorporation of chemotherapy and radiotherapy following surgery, with a subsequent improvement in 2-year survival from 18% to 43% according to the GITSG studies. In 2000, Nukui et al reported the results of a phase II study using more aggressive chemoradiation in addition to interferon for the treatment of locally advanced pancreatic cancer. The study employed continuous infusion 5-FU, weekly cisplatin, and subcutaneous interferon concurrent with radiation in the post-operative setting. The rationale for interferon was possible enhancement of tumoricidal effects of certain chemotherapeutic agents. The authors reported a 2-year survival rate of 84% with this aggressive treatment approach. This current article by Picozzi et al serves as an update to the results reported by Nukui et al in 2000.

Materials and Methods
- A cohort of 43 patients were evaluated, all with ductal adenocarcinoma of the pancreatic head and of pancreatic origin
- Primary tumors of the distal common bile duct, ampulla, and duodenum were excluded
- All patients underwent pancreaticoduodenal resection (Whipple)
- Approximately 6-8 weeks following resection, patients were begun on concurrent chemo-radiation as well as interferon therapy
- Radiation therapy was external beam, 45 Gray (Gy) – 54 Gy, given over 5 weeks in 25 daily fractions, delivered to the pancreatic bed
- Chemotherapy consisted of continuous infusion 5-FU (200mg/m2) on days 1-35 and weekly cisplatin (30mg/m2) on days 1, 8, 15, 22, and 29
- Interferon was given as a subcutaneous injection, 3 million units QOD for 5 weeks
- All patients received adjuvant chemotherapy in the form of 5-FU (200mg/m2) on days 64-105, then again on days 120-161
- Several factors were analyzed, including resection type, blood loss, nodal status, treatment toxicity, and survival
- Follow-up was obtained by telephone contact, and evidence of relapse was determined by physical examination, CXR, and CT scans
- Statistical evaluation was done using Kaplan-Meier analysis

Results
- Between 1995-2002, 43 patients were accrued, with a median patient age of 62 years
- Median patient follow-up was 21.8 months (range of 4-86 months)
- All but 7% of patients had pylorus-preserving surgery, and 2 had total pancreatectomies
- Two percent of patients had stage I disease, 12% had stage II, 72% had stage III, and 14% had stage IVa disease
- Eighty-four percent of patients had positive lymph nodes with an average of 2.2 nodes per patient
With regard to histology, 26% were poorly differentiated, and there was perineural invasion in 68% of samples. A total of 19% patients had gross or microscopic positive margins. Ninety-five percent of patients completed their radiation course. Ninety-three percent of patients received greater than 85% of the intended 5-FU dose, while the last dose of cisplatin was held in 28% of patients. With regard to adjuvant chemotherapy, 56% of patients got 100% of the intended 5-FU dose, and 70% received >85% of the intended dose. Treatment-related toxicity was mostly gastrointestinal, with grade 3 toxicity in 70% of the patients; 70% had some form of delay in their chemoradiotherapy, while 43% of patients were hospitalized for treatment-related toxicity. Actuarial overall survival at 1, 2, and 5 years was 95%, 64%, and 55% respectively; disease-free survival was 67%, 52%, and 52% at 1, 2, and 5 years respectively.

Discussion

When compared to other studies using adjuvant chemotherapy, the results of this study demonstrate the highest survival rates to date, and thus are very encouraging. However, this improvement in survival comes at the cost of significantly increased treatment-related toxicity requiring hospitalization in 42% of patients. Though toxicity was high, there was no treatment-related mortality. There was no mention of the performance status of enrolled patients, but one should assume that patients were carefully selected for this aggressive treatment regimen. All surgeries were performed at a single institution with one surgeon performing 91% of the resections; it will be interesting to see if the same results will hold when surgery is performed at other centers.