Clinical Aspects of Pancreatic Cancer

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Lecture Overview

1) Incidence, Etiology, Diagnosis and Staging
2) Treatment:
   - Surgery (localized disease)
   - Chemotherapy (advanced disease)
3) Combined Modality Therapy: The Dartmouth Experience

Topic #1: Incidence, Etiology, Diagnosis and Staging

Epidemiology

- 31,000 cases/year in USA. 30,400 deaths…
- Median survival 3-6 months
- 5 year survival of 4%.

Pathology of Pancreatic Cancer

- Adenocarcinoma of Ductal Epithelium (>80%)
- 70% of cancers occur in proximal pancreas

Pathology Continued

- Early vascular dissemination and nodal spread
- Most patients have subclinical liver mets at presentation
- Disease confined to pancreas in < 20% of cases

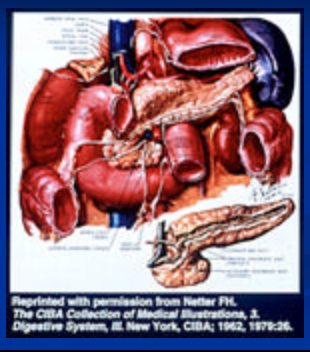
Risk Factors - Environmental

- Cigarette Smoking
- Age > 50 years
- Pancreatitis
- ? Industrial Chemical Exposure / ? Diet

Risk Factors - Genetic

- 3 - 5% of pancreas cancer likely familial
- Hereditary Pancreatitis
- Familial Atypical Multiple Mole Melanoma
- No specific gene yet identified in familial clusters of pancreatic cancer (Evans, J Med Gen, 1995)

Anatomy of the Pancreas



Reprinted with permission from Netter FH. *The CIBA Collection of Medical Illustrations*, 3. *Digestive System*, III. New York, CIBA; 1962, 1979:26.

Signs and Symptoms

- Pain (>70%)
- Biliary obstruction
- Weight loss (>90%)
- Microcytic anemia (50%)
- Nausea / vomiting
- Gastric Outlet Obstruction
- DVT / Trousseau's Syndrome

Evaluation of Suspected Pancreatic Neoplasm

Clinical Suspicion
↓
Fine Cut CT Scan
↓
Endoscopic Ultrasound (ERCP) & Biopsy
↓
Tumor Board Presentation
↓
Laparoscopy
↓
Treatment Decision

Staging of Pancreatic Cancer Using the TNM System[a] (cont)

Stage	Group Staging Criteria		
I	T1-T2	N0	M0
II	T3	N0	M0
III	Any T	N1	M0
IV	Any T	Any N	M1

Adapted with permission from Beahrs OH et al, eds. *Manual for Staging of Cancer*. 4th ed New York, Lippincott-Raven Publishers; 1992:109.

Topic #2: Treatment

Pancreatic Cancer Treatment

Surgical Resection

Radiotherapy

Chemotherapy

Multi-Modality Therapy

Surgical Resection

- Only chance for cure--in patients with limited disease
- Majority of 'resectable' tumors are unresectable at laparotomy
- Margin (+) resection offers no benefit

Surgery

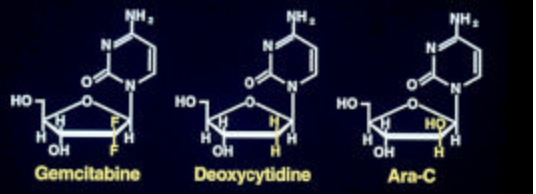
- Whipple Procedure: long term survival 10%
- Surgical mortality relates to hospital volume of Whipple procedures (Birkmeyer, 1999)
- Median survival of 6-10 months with locally advanced, unresectable disease

Chemotherapy for Advanced Disease

Gemcitabine (Gemzar)

- Nucleoside Analog
- Approved for advanced disease

Chemical Structure[31]



- Gemcitabine is a nucleoside analogue.

Adapted with permission from Heinemann et al. *Cancer Res.* 1988; 48:4024.

Gemcitabine in Chemo-naive Patients

Multicentre, single-blinded, randomized trial (126 pts)

Gemcitabine 1000 mg/m^2 weekly x 3 q 28 days

vs

5-Fluorouracil 600 mg/m^2 weekly

- Endpoints: clinical benefit response, survival, time to progression, tumor response

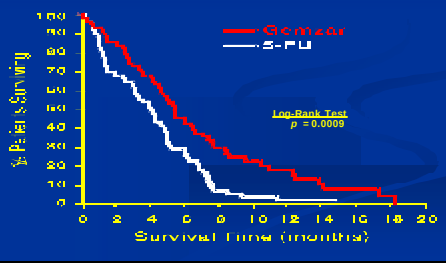
Burris et al, *J Clin Oncol* 1997

Gemcitabine vs 5FU

	GEMZAR	5-FU	*p*-
Clinical Benefit Response	24%	5%	0.0022
Median survival	5.7m	4.4m	0.0025
Time to progression	2.1m	0.9m	0.0013
12-month survival	18%	2%	—

Burris et al, J Clin Oncol 1997

Phase III Gemzar vs 5FU: Overall Survival



Gemcitabine Doublets in Pancreatic Cancer

- Gemzar + 5-FU
- Gemzar + cisplatin
- Gemzar + irinotecan
- Gemzar + Taxotere
- Gemzar + Xeloda
- Gemzar + Tarceva
- Gemzar + Erbitux
- Gemzar + Avastin

CALGB 89904

CALGB 89904

Metastatic Pancreatic Cancer

PI: Kulke,Tempero

- Gemzar 1000 mg/m^2 d 1,8,15 Cisplatin 50 mg/m^2 d 1,15 q 28 days
- Gemzar 1000 mg/m^2 d 1,8 Docetaxel 40 mg/m^2 d 1,8 q 21 days
- Gemzar 1000 mg/m^2 d 1,8 Irinotecan 100 mg/m2 d 1,8 q 21 days
- Gemzar 10mg/m2/min x 150 mins (150 mg/m2) d 1, 8,15 q 21 days

CALGB 89904

- No standard dose Gemzar arm
- All arms "well tolerated" but no regimen clearly superior
- Failed to alter the standard of care

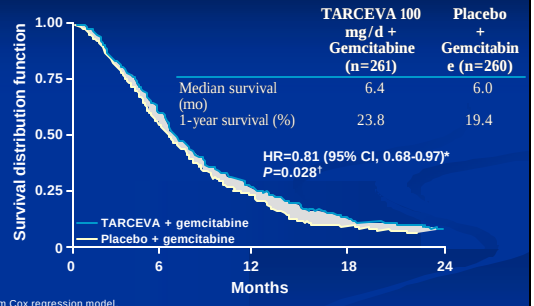
Gemzar / Tarceva

- Tarceva (erlotinib) small molecule EGFR inhibitor
- Approved for advanced NSC Lung Cancer
- Randomized trial of Gem +/- Tarceva

Gemcitabine +/- Tarceva

Response	Gem/Tarceva 100mg/d (n=261)	Gem/placebo (n=260)	*P* Value*
CR + PR (%)	**8.6**	**7.9**	**0.87**
Median response duration (wk)	**23.9**	**23.3**	

Gem +/- Tarceva: Overall Survival



	TARCEVA 100 mg/d + Gemcitabine (n=261)	Placebo + Gemcitabine (n=260)
Median survival (mo)	6.4	6.0
1-year survival (%)	23.8	19.4

*From Cox regression model.
†From 2-sided log-rank test.
TARCEVA® (erlotinib) PI. 2005.

Gemzar / Tarceva

- Survival improved by 12.8 days. No change in response rate
- Increased toxicity/cost
- Approved by FDA after split advisory board vote, November 2005

Gemzar / Xeloda

- Xeloda (capecitabine) oral pro-drug converted to 5-FU
- Approved for advanced CRC and breast Ca
- Favorable toxicity profile

Gemzar / Xeloda

- Phase III European trial of 533 pts
- Gem 1000/m2 +/- Xeloda 1660m2/day x21 days
- Result: Combination improved….

Response	(7 vs 14%)
Median Survival	(6 vs 7.4 months)
One year Survival	(19 vs 26%)

Cunningham, et al. ECCO abstract 2005

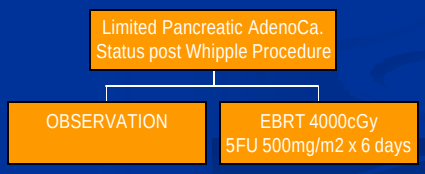
Summary: Advanced disease

- Gemzar remains the backbone of first line therapy
- Numerous doublets have shown improved response rates—value unclear.
- Addition of Tarceva or Xeloda to Gemzar results in small improvement in survival
- Standard of care remains elusive

Topic #3: Combined Modality Therapy

Chemoradiotherapy-Historical

GITSG: Postoperative Treatment



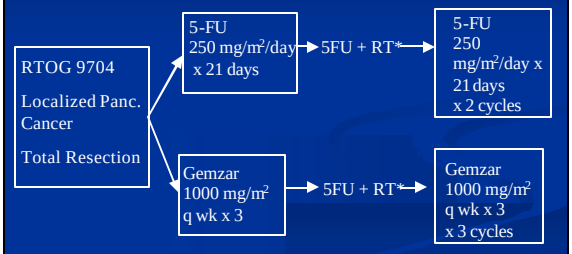
GITSG Adjuvant

- Median Survival 11 months vs 20 months
- 1 in 4 patients had significant delays in starting treatment
- Adjuvant 5FU/ radiation widely used in USA

Chemoradiotherapy

- Multiagent regimens not superior, may increase toxicity
- Optimum timing/agents unclear
- Data limited by multiple small studies
- European data suggest no benefit to post-operative chemoradiotherapy (Neoptolemos, NEJM 2004)

RTOG Adjuvant Trial- closed



* 50.4 Gy @ 1.8 Gy fx x 5.5 wks, 5FU 250 mg/m²/day during RT

Gemcitabine as Radiosensitizer

- Potent radiosensitizer *in vitro*
- Sensitization occurs at non-cytotoxic concentrations and correlates with dATP depletion
- Every 3 day dosing interval most active in human tumor xenografts
- A number of studies have investigated Gem / XRT

Phase I Study of Twice weekly Gemcitabine and Concomitant External Beam Radiotherapy in Patients with Pancreatic Adenocarcinoma

J. Marc Pipas MD , Sandra E. Mitchell MD, Richard J. Barth Jr. MD, Raul-Vera Gimon MD, Joerg Rathmann MD, Louise P. Meyer MS ARNP, Richard S. Wagman MD, Lionel Lewis MD, Joerg Rathmann MD, Thomas A. Colacchio MD, Raymond Perez MD

International Journal of Radiation Oncology, Biology, Physics
September, 2001

Gemcitabine / Radiotherapy

Radiotherapy:
Total dose 5040 cGy in 28 fractions

Gemcitabine:
Twice weekly over x 12 doses concurrent with XRT

(Infusion completed prior to that day's radiation)

Pipas, et al. Int J Rad Onc B Phys, 2001

Results

- 21 patients enrolled (mean age of 64 years)
- MTD for twice weekly gemcitabine with radiotherapy 50mg/m2
- Dose limiting toxicity (DLT) is gastritis/GI bleeding at gemcitabine 60mg/m2

Pipas, et al. Int J Rad Onc B Phys, 2001

Results

- Six patients with response (two partial responders)
- Five patients underwent complete surgical resection with extensive treatment effect in specimen
- Three were unresectable prior to treatment

Gemcitabine / Radiotherapy

" Neoadjuvant chemo-radiotherapy with twice-weekly gemcitabine is standard of care at DHMC for patients presenting with limited or locally advanced pancreatic adenocarcinoma"

Docetaxel / Gemcitabine followed by Gemcitabine and External Beam Radiotherapy in Patients with Pancreatic Adenocarcinoma

J. Marc Pipas MD, Richard J. Barth Jr. MD, Bassem Zaki MD, Michael J. Tsapakos MD, Michael A. Bettmann MD*, Justin M. Cates MD PhD, Arief A. Suriawinata MD, Gregory H Ripple MD, John E. Sutton MD, Stuart R. Gordon MD, Carol E. McDonnell CCRP, Raymond P. Perez MD, Nancy Redfield ARNP, Louise P. Meyer, ARNP, John F. Marshall MD, Bernard F. Cole PhD, Thomas A. Colacchio MD

Annals of Surgical Oncology
December 2005

Treatment

Day 1, 15, 29: Taxotere 65mg/m2 IV over 60 min
Gemcitabine 4000mg/m2 IV over 30 min

Day 43: EBRT x 6 weeks (5040 cGy total dose)
Gemcitabine 50mg/ m2 biw x 12 doses

*Restage after 4 week rest and consider resection attempt

DMS 0117

- 24 patients
- Mean patient age 65 years (range: 43-83)
- At Diagnosis:

Thirteen (54%) unresectable
Seven (29%) borderline resectable
Four (17%) resectable

DMS 0117: Results

- All patients received 3 cycles of induction chemo.
- All but one received full course of XRT
- Thirteen patients hospitalized during treatment
- No neutropenic fever, no deaths on protocol

DMS 0117: Results

- No local tumor progression through therapy
- Twelve patients (50%) met RECIST criteria for response
- Two other patients met criteria for response but had small liver mets at surgery

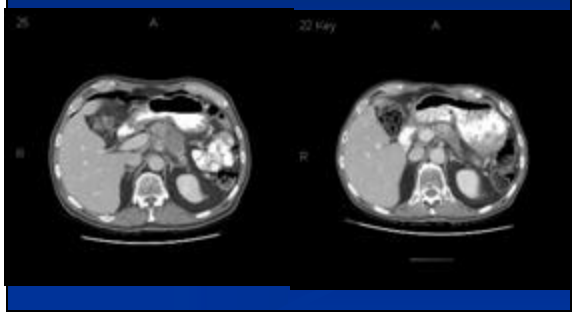
DMS 0117: Surgery

- Seventeen patients underwent tumor resection
- Thirteen (76%) were margin (-) resections
- Nine of 13 were unresectable or borderline prior to Rx.

DMS 0117

- Two patients died post operatively
- No local recurrence in any resected patient
- At mean F/U of 22 months 10 patients alive, 5 without disease

Pre & Post treatment Scans



DMS 0117: Conclusions

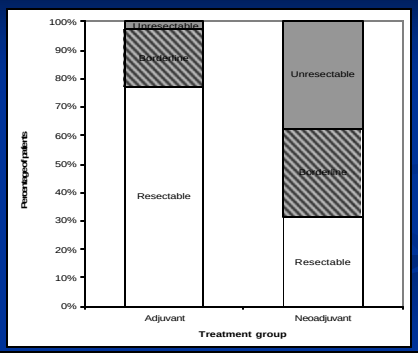
- Combination neoadjuvant therapy is active with acceptable toxicity
- Tumor downstaging occurs in some patients, enabling complete resection of disease

Does Neoadjuvant Therapy Improve Disease Control ?

Local Recurrence Rates

- Greer, et al (New England Surgical Society, 2005)
- Retrospective review of 93 pancreatic cancer resections at DHMC between 1993-2004
- Data collected regarding: resectability at presentation, therapy (adj vs neoadj) and type of surgery performed

Resectability Based on Initial CT Reading



Local Recurrence

Resection and Adjuvant Therapy: (N=39)

Local Recurrences – 13 (33%)

Neoadjuvant Therapy and Resection: (N=35)

Local Recurrences – 2 (6%)

Adjuvant vs Neoadjuvant Therapy

- "Despite marked bias toward more advanced tumors, the neoadjuvant group have a lower risk of local relapse"
- Trend toward improved time to local recurrence in the patients undergoing neoadjuvant therapy

Future Directions:

Bio-Chemo-Radiotherapy

Epidermal Growth Factor Receptor

- Over expressed in pancreatic cancer from 30% to 89% in advanced disease (Korc, 1992)
- Associated with increased tumor aggressiveness and worse prognosis

Cetuximab (Erbitux, IM-C225)

- Mouse-Human chimeric anti-EGFR mAb
- Inhibits tumor cell growth, enhances chemotherapy
- Phase II data with Gemzar in advanced pancreatic cancer (12.5% RR)
- Xenograft data for Cetuximab/Gemzar/ Radiotherapy

DMS 0432

Pancreatic Adenocarcinoma
No Distant Metastases
|
V
Stratification by EGFR status of tumor
|
V

CETUXIMAB: 400mg/m2 IV loading one week prior to radiation
250mg/m2 IV q Tue x 6 weeks with XRT

GEMCITABINE: 50 mg/m2 IV q Tues & Fri x12 doses with XRT

RADIOTHERAPY: 5400cGy over 28 fractions in single daily doses

|
V
Rest four weeks
Assess for surgery

D0432 Patient Demographics

- Ten patients enrolled to date, mean age >70 years. Eight patients evaluable for response
- No local progression. One pt with liver mets post treatment
- Two partial responses (25%)
- No relation of EGFR (+) to response

D0432 Toxicity

- 80% Grade III-IV hematotoxicity
- 70% admitted (GI toxicity, stent obstruction, weakness)
- One episode Cetuximab anaphylaxis
- Two pts with ischemic strokes, one death (age 81).

Surgery

- Six pts taken to surgery all with margins (-)
- One each unresectable and borderline prior
- No recurrences to date (median F/U=9 months)

Interim Analysis

- Gem/Erb/IMRT -- modest efficacy with high resectability rates
- Toxicity likely due to increased intensity of treatment as well as elderly patient demographic

Conclusions

- Neoadjuvant therapy is active and tolerable for pancreatic cancer
- Tumor downstaging may allow for complete resection
- Neoadjuvant therapy appears to result in improved local control of disease
- Much work is yet to be done…….!!!