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

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**

**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**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Group Staging Criteria</th>
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<tbody>
<tr>
<td>I</td>
<td>T1-T2</td>
</tr>
<tr>
<td>II</td>
<td>T3</td>
</tr>
<tr>
<td>III</td>
<td>Any T</td>
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<tr>
<td>IV</td>
<td>Any T</td>
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**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
Gemcitabine in Chemo-naive Patients

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

Gemcitabine 1000 mg/m² weekly x 3 q 28 days 

vs

5-Fluorouracil 600 mg/m² weekly

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

Burris et al, J Clin Oncol 1997

Gemcitabine vs 5FU

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>GEMZAR</th>
<th>5-FU</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Benefit Response</td>
<td>24%</td>
<td>5%</td>
<td>0.0022</td>
</tr>
<tr>
<td>Median survival</td>
<td>5.7m</td>
<td>4.4m</td>
<td>0.0025</td>
</tr>
<tr>
<td>Time to progression</td>
<td>2.1m</td>
<td>0.9m</td>
<td>0.0013</td>
</tr>
<tr>
<td>12-month survival</td>
<td>18%</td>
<td>2%</td>
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Burris et al, J Clin Oncol 1997

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, Temporero

Gemzar 1000 mg/m² d 1,8,15
Cisplatin 50 mg/m² d1,15 q 28 days

Gemzar 1000 mg/m² d 1,8
Docetaxel 40 mg/m² d 1,8 q 21 days

Gemzar 1000 mg/m² d 1,8
Irinotecan 100 mg/m² d 1,8 q 21 days

Gemzar 10 mg/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**

<table>
<thead>
<tr>
<th>Response</th>
<th>Gem/ Tarceva 100mg/d (n=261)</th>
<th>Gem/ placebo (n=260)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR + PR (%)</td>
<td>8.6</td>
<td>7.9</td>
<td>0.87</td>
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</table>

| Median response duration (wk) | 23.9                          | 23.3                  |

**Gem +/- - Tarceva: Overall Survival**

- 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

- Limited Pancreatic AdenoCa.
- Status post Whipple Procedure

EBRT 4000cGy
5FU 500mg/m2 x 6 days

OBSERVATION

Limited Pancreatic AdenoCa.
Status post Whipple Procedure

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)

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
RTOG Adjuvant Trial - closed

RTOG 9704
Localized Panc. Cancer
Total Resection

S-FU
250 mg/m²/day
x 21 days

Gemzar
1000 mg/m²/q wk x 3

S-FU + RT*

S-FU
250 mg/m²/day
x 21 days
x 2 cycles

Gemzar
1000 mg/m²/q wk x 3
x 3 cycles

* 50.4 Gy @ 1.8 Gy fx 5.5 wks, S-FU 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


International Journal of Radiation Oncology, Biology, Physics
September, 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

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)

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


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
Seventeen patients underwent tumor resection.

Thirteen (76%) were margin (-) resections.

Nine of 13 were unresectable or borderline prior to Rx.

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.

Combination neoadjuvant therapy is active with acceptable toxicity.

Tumor downstaging occurs in some patients, enabling complete resection of disease.


Data collected regarding: resectability at presentation, therapy (adj vs neoadj) and type of surgery performed.
Resectability Based on Initial CT Reading

Resectable
Borderline
Unresectable

0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

Resectability Based on Initial CT Reading

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
Stratification by EGFR status of tumor

**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 x 12 doses with XRT

**RADIOTHERAPY:**
- 5400cGy over 28 fractions in single daily doses
- Post four weeks
- Assess for surgery

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**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...