Modern medical management of Pancreatic cancer

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CME presentation on January 8, 2014.
Objectives

- Discuss modern medical management of pancreatic cancer
- Discuss role of multi-disciplinary participation in treatment
- Present examples of actual cases treated using these strategies
- Answer audience questions
- Poll audience responses during interactive session
Disclosures

- I have been asked by CME office to present this lecture today
- I have not received any financial payments for this lecture
- I have prepared all slides myself
Scope of discussion

• Discussion in this lecture is limited to exocrine pancreatic cancer-adenocarcinoma unless specified otherwise.

• Endocrine tumors of pancreatic origin have better prognosis and are treated differently.
General

- Very aggressive cancer
- Highly lethal cancer
- Overall 5 year survival is around 1%
Incidence

• 2013 SEER estimates
  ▫ Estimated cases 45,220
  ▫ Estimated deaths 38,460
Risk factors

- Mostly unknown
- Possible link to tobacco – smoking – a consistent risk factor
- Chronic pancreatitis may be a risk factor
- Fruits and vegetable rich diet may reduce risk
- Increasing age is a risk factor
- Familial syndromes with increased risk for pancreatic cancer – only a very small number of cases – next slide
Familial syndromes with increased risk

- Familial breast cancer (Selective genetic mutations BRCA 2 more strongly associated than BRCA 1)
- Familial pancreatitis syndrome (cationic trypsinogen gene) – pancreatitis
- HNPCC-Hereditary non polyposis colon cancer (DNA mismatch repair gene mutations) – colon cancer, endometrial cancer
- Familial atypical multiple mole melanoma (p16 mutations – chromosome 9P) – Multiple nevi, atypical nevi and melanoma
- Ataxia telangectasia
- Peutz Jeghers syndrome (STK 11 / LKB 1 mutations) – hamartomatous GI polyps and pigmented skin macules.
- Only 10-20% are thought to have familial pre disposition
Risk factors

- Conflicting data about coffee and alcohol
- Diabetes may be an early manifestation rather than predisposing factor
Pathogenesis

• KRAS oncogene mutations are common

• Intra ductal proliferative epithelial lesions (PanINs – pancreatic intra-epithelial neoplasms) are considered precursors of invasive ductal pancreatic cancer
Screening

• No screening is available

• CA 19-9 is not useful for screening

• Optimal screening strategy for patients with strong family history of pancreatic cancer is not known.
Prevention

- Minimize known risk factors
- No specific prevention strategy is known
AJCC staging

Stage IA Pancreatic Cancer

Stage IB Pancreatic Cancer

From cancer.gov
AJCC staging

Beyond pancreas but not in celiac plexus or SMA

From cancer.gov
AJCC staging

Stage IIB Pancreatic Cancer
Positive nodes

From cancer.gov
Unresectable:
SMA or celiac plexus involvement

From cancer.gov
AJCC staging

Stage IV Pancreatic Cancer

Pancreatic cancer has spread to other parts of the body:

- Lung
- Liver
- Peritoneal cavity

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From cancer.gov
AJCC staging

• See AJCC website or cancer.gov for staging details

• Accurate staging is very important in treatment planning

• Prognosis is dependant on stage
# PROGNOSIS

<table>
<thead>
<tr>
<th>Stage</th>
<th>5 year survival</th>
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<tbody>
<tr>
<td>I</td>
<td>12%-14%</td>
</tr>
<tr>
<td>II</td>
<td>5%-7%</td>
</tr>
<tr>
<td>III</td>
<td>3%</td>
</tr>
<tr>
<td>IV</td>
<td>1%</td>
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</table>
Diagnostic testing to determine stage

- CT scan / Ultrasound / MRI
- ERCP / MRCP
- EUS
- Laparoscopy
- PET scan
TREATMENT OPTIONS

• First step: evaluate patient for possibility of surgical resection

• The benefits of therapy are modest at best, so clinical trials remains a sensible option.

• Multi-modality therapy is generally necessary for most
TREATMENT OPTIONS

• For patients with poor performance status, best supportive care is appropriate.
## Treatment summary table:

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Palliative care, pain control, biliary stent etc for all appropriate patients
Surgery for resectable tumors

• Surgery is only poetically curative treatment

• Only 20% or fewer patients are candidates for potentially curative surgery.

• Diagnostic procedures listed above help determine resectability of pancreatic cancer
Surgery for resectable tumors

• Goal of Surgery
  ▫ Ro resection – resection with clean margins

• Multi-disciplinary evaluation is necessary

• Neo-adjuvant therapy for clearly resectable tumors is not recommended at present time
Surgery: Eligibility

- No distant metastases
- No involvement of SMV or portal vein
- Clear fatty plane around SMA, hepatic artery and celiac plexus
Surgery: Eligibility

• Generally tumors more than 4 cm size are rarely resectable \( \rightarrow \) less than 10% resectability rate
• Invasion of superior mesenteric artery or major blood vessels \( \rightarrow \) unresectable tumor.
• Even when the tumor appears to be resectable, \( \rightarrow \) as many as 40% of patients will be found to have small metastases to the peritoneum or liver that were not detected on preoperative imaging studies.
Surgery: results

- Postoperative mortality rates in patients who undergo pancreaticoduodenectomy (Whipple’s procedure) are influenced by the experience of the surgeon and the treatment center.

- In patients who undergo potentially curative surgery, 5-year survival rates have not exceeded 20% to 24% (generally 5% to 25%).
Case : A

- 75 year old male in good health
- ECOG PS 1
- Pancreatic adenocarcinoma: S/P Whipple procedure. PT2No clinical Mo, stage IB.
Case: A

Diagnosis

Surgically resectable
Case : A

- NCCN guidelines recommends following current options:
  1. Adjuvant chemotherapy with Gemcitabine or FU or Capecitabine for six months
  2. Adjuvant Chemotherapy → chemo-RT→ chemotherapy (Gemcitabine (or FU) one cycle →6 weeks of RT with FU pump (or Xeloda or Gemcitabine) → by 3 cycles of Gemcitabine (or FU) as an example.
  3. Clinical trial.
Case : A: What would you choose for him

1. Adjuvant chemotherapy with Gemcitabine or FU or Capecitabine for six months
2. Adjuvant Chemotherapy $\rightarrow$ chemo-RT $\rightarrow$ chemotherapy (Gemcitabine (or FU) one cycle $\rightarrow$ 6 weeks of RT with FU pump (or Xeloda or Gemcitabine) $\rightarrow$ by 3 cycles of Gemcitabine (or FU) as an example.
3. Clinical trial.
4. No treatment – observation only
Case: A -

- Wait ...wait....
Case: A

- Pre chemo CT chest, Abdomen and pelvis: A vague 0.9 cm low attenuation area in liver, reported to be new since surgery, too small to biopsy

- Modified plan:
  - Chemotherapy → followed by repeat CT → chemo-RT → chemotherapy
Case: A - post chemo CT prior to chemo-RT

And then a new liver lesion

Biopsy was positive - stage 4
Case : A -

- Now stage 4 disease
- Switch to palliative FOLFIRINOX
- Good response so far
- 14 months post diagnosis
- Taking a break from chemotherapy
Case: A - Post FOLFIRINOX

Much better

Marker trend CA 19-9 – good correlation to disease
Post operative adjuvant therapy

- Surgery alone is not adequate for most
- Controversial – best option is unclear.
- Goal of adjuvant therapy → improve Overall survival.
Post operative adjuvant therapy

Surgery if resectable

Adjuvant chemotherapy

Adjuvant chemo-RT
Post operative adjuvant therapy

• A small, randomized trial suggested an improvement in median and long-term survival in patients who received postoperative 5-fluorouracil + radiation. This has long been considered standard of care in USA.

• However, the benefit of postoperative chemo radiation has not been confirmed in subsequent randomized trials.
Post operative adjuvant therapy

CONKO-1 trial from Germany

- Adjuvant Gemcitabine compared to surgery alone
- Considered European standard.
- 5 year: 21% vs 9%

3 year survival

- Surgery
- Gem: 36%
- --: 19%
Post operative adjuvant therapy: (ESPAC)

- A recent trial in Europe
- Median survival 23 months

- Similar median survival between adjuvant Gemcitabine versus FU-LV.
- Either of regimen can be considered.
Post operative adjuvant therapy

- A US trial (RTOG 9704):
- 3 year follow up: suggested improved outcome in pancreatic head tumors with post operative Gemcitabine → FU-RT → Gemcitabine versus FU-RT (3 year survival of 31% versus 22%).
- 5 year follow up: with further follow up there appears to be no major survival advantage
Post operative adjuvant therapy

- NCCN guidelines:
  - “No definite standard has been established in the adjuvant treatment ... “
Post operative adjuvant therapy

- No one best option
- Customize management based on individual prognostic factors and comorbid conditions

Options include
- Adjuvant chemotherapy
- OR adjuvant chemo-RT
Unresectable tumors

- For patients with locally advanced but unresectable disease
- Options:
  - Chemo – radiation
  - Chemotherapy → Chemo – radiation
  - Palliative chemotherapy
  - Participation in clinical trial
Unresectable tumors

• Chemotherapy and radiation for unresectable tumors
  ▫ **FU with RT is considered standard in USA**
  ▫ Newer agents such as Gemcitabine, Capecitabine and targeted agents are under study
  ▫ Might be better in patients with uncontrolled pain since RT may help pain.

• Chemotherapy alone for unresectable tumors
  ▫ Reasonable choice
  ▫ European trial indicated that Induction chemo-RT with maintenance Gemcitabine was no better than Gemcitabine alone.
Unresectable tumors

• No one best option
• Customize management based on individual prognostic factors and comorbid conditions
Surgery: Borderline resectable

- No distant metastases
- Venous involvement of SMV or portal vein (distortion or narrowing of vein)
- Gastro duodenal artery encasement
- Direct abutment of hepatic artery
- Abutment around SMA no more than 180º circumference
- Refer to surgical literature for latest criteria
Borderline resectable tumors

- Current trials are focusing on neo-adjuvant therapy → attempt at surgical resection
Neo-adjuvant therapy: Options

- Neoadjuvant chemotherapy
  - Surgery if resectable
  - No surgery if unresectable
  - Adjuvant chemotherapy + RT
  - Chemo-RT
Neo-adjuvant therapy: Options

- Neoadjuvant chemotherapy + RT
  - Surgery if resectable
    - Adjuvant chemotherapy
  - No surgery if unresectable
    - Adjuvant chemotherapy
Neo-adjuvant therapy: Options
Neo-adjuvant therapy

- Some patients may develop metastatic disease during neo-adjuvant therapy prior to any definitive local therapy could be done
Neo-adjuvant therapy

- No one best option
- Customize management based on individual prognostic factors and comorbid conditions
Case B

CT

- 74 year old female
- Borderline resectable candidate by EUS criteria
- Possible T3N0M0 clinical - Stage IIA or possibly T4N0-III
Case B: What would you chose?

1. Surgical resection attempt → adjuvant chemotherapy or adjuvant chemo-RT.
2. Neo-adjuvant chemotherapy → surgery (if tumor is down staged and becomes resectable) → adjuvant therapy.
3. Neo-adjuvant chemotherapy + RT → surgery (if tumor is down staged and becomes resectable) → adjuvant therapy.
4. Neo-adjuvant chemotherapy → definitive chemotherapy + RT (non surgical option).
5. Neo-adjuvant chemotherapy → pre-op chemotherapy + RT → surgery if resectable.
Case B: She chose

- Neo-adjuvant chemotherapy $\rightarrow$ surgery (if tumor is down staged and becomes resectable) $\rightarrow$ adjuvant therapy.
Case B:

Update

- Two cycles of Gem-Oxaliplatin
- Too high to biopsy
- Complete 4 cycles
- Re-assess
- Will need liver biopsy

New liver lesion
Chemotherapy for metastatic tumors (stage 4 cancer)

- Therapy is palliative.
- Best option is unclear
Case C

- 52 year old female
- Stage 4 pancreatic adenocarcinoma
- Biopsy of liver x 2 negative, third one positive
- ECOG PS 0-1
- New onset diabetes mellitus
- Wants aggressive treatment
Case C
Case C

Liver mets

Liver mets
Case C: What would you give her

1. Gemcitabine alone
2. Gemcitabine + Tarceva
3. Gemcitabine + Cisplatin or FU or Xeloda.
4. Gemcitabine + FU or Xeloda.
5. FOLFIRINOX
6. Palliative care alone
Case C

Treatment given

- Started FOLFIRINOX
- Good response
- Doing well 8 months later with major response

Post treatment
Case C : Tumor marker correlation
Chemotherapy for metastatic tumors (stage 4 cancer)

- **Single agent: First line**
  - Gemcitabine is currently the first-line therapy of choice for patients with metastatic disease and good performance status.
  - Mild to moderate activity seen with Gemcitabine, FU, Taxanes, Platinum and Irinotecan
Chemotherapy for metastatic tumors (stage 4 cancer)

- **First line**
  - Gemcitabine was superior to FU in randomized trial (better pain control and improved appetite and weight – Clinical benefit).
  - Clinical benefit 24%, response rates less than 10%, 1 year survival 18%.
Chemotherapy for metastatic tumors (stage 4 cancer)

- Combination regimens: First line
  - Most of the older trials of combinations have failed to show survival advantage over Gemcitabine alone.
Chemotherapy for metastatic tumors (stage 4 cancer)

• Recent data: First line
  ▫ Combination may provide slight benefit in good performance status patients only.
  ▫ Combination therapy may not provide any advantage in poor performance status patients.
Chemotherapy for metastatic tumors (stage 4 cancer)

- Combination regimens: First line
  - Recent data:
    - Gemcitabine + oral Erlotinib was slightly better than Gemcitabine alone in Progression free survival and survival
    - Median survival 6.2 vs. 5.9 months
    - One year survival 23% versus 17% - statistically significant.
Chemotherapy for metastatic tumors (stage 4 cancer)

• Combination regimens: First line
  ▫ Recent data:
    • Gemcitabine + oral Capecitabine was slightly better than Gemcitabine alone in Progression free survival and survival.
Chemotherapy for metastatic tumors (stage 4 cancer)

• Combination regimens: First line
  ▫ **Recent data:**
    • FOLFIRINOX has shown improved responses compared to Gemcitabine alone (median overall survival 11.1 vs. 6.8 months).
Chemotherapy for metastatic tumors (stage 4 cancer)

• Combination regimens: First line
  ▫ Recent data:
    • Nab-Paclitaxel-Gemcitabine has shown improved responses compared to Gemcitabine alone (median overall survival 8.5 vs. 6.5 months).
    • 1 year survival: 35% vs 22%
    • 2 year survival: 9% vs 4%
    • Good PS only: PS over 70%

Second line

• A recent German trial (CONKO 3) reported benefit of second line FU-LV-Oxaliplatin over FU-LV in patient failing first line Gemcitabine.
• Med survival - (26 weeks versus 13 weeks)
Summary of chemotherapy for stage 4:

- Gemcitabine alone or Gemcitabine containing combination is considered standard of care.
- Gemcitabine containing combination should be used in good PS patients.
- No one best option
- Customize management based on individual prognostic factors and comorbid conditions
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Palliative care: Pain control, billiary stent, thrombosis prevention and treatment, depression management, nutritional management etc for all appropriate patients
Is long term survival possible?
Case D

• 72 year old man
• Very active
• Stage 4 disease – adenocarcinoma
• Wanted aggressive therapy
• Was seen at a major cancer center – not satisfied with options provided
Case D

March 2008: Liver mets

Stage 4 cancer

- Chemotherapy x 2 cycles
- Stabilization and borderline response
• Chemo-embolization
• Severe chemical hepatitis
• Needed high dose steroids
Case D

2010

- Post Chemo-embolization
- Necrotic cystic area remains
Case D

2010

- 2010 liver mets outside of chemo-embolized field
Case D

2010

- Biopsy positive pancreatic mass
Case D

September 2013
Case D

- Has now been treated with multiple chemotherapy regimens
- Remains alive and well after 68 months
- Very active
- Has been off chemotherapy for 8 months with stable disease
- Diagnosis: around April 2008
- Last follow up November 2013
Thank you
Extra slides
Do your see or treat patients with pancreatic cancer?

- Yes
- No
Did you learn any new information today?

- Yes
- No
Was information discussed relevant to your practice?

- Yes
- No
Was information discussed free of any bias?

- Yes
- No
Will you change your approach to pancreatic cancer treatment based on this CME?

- Yes
- No
Were objectives for this CME met?

• Yes
• No
Overall rating for today's presentation

- Highly satisfied
- Satisfied
- Neutral
- Unsatisfied
- Highly unsatisfied
Thank you