Management of Metastatic Pancreas Cancer

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Disclosures

- None to report

Overview

- 56,770 adults diagnosed in the US per year (29,940 men, 26,830 women)
- 45,750 deaths in the US per year (23,800 men, 21,950 women)
- 10^{th} most common cancer in men, 9^{th} in women, but 4^{th} most common cause of cancer death in men and women
- 7% of all cancer deaths
- 5 year survival 9%
- 15-20% are resectable at the time of diagnosis; 5 year survival with advanced disease is 3%

Overview

- Median survival of untreated metastatic pancreatic cancer reported as 3.5mo
- 2017 GI ASCO SEER analysis from 1993-2013 reported median survival of 2mo for newly diagnosed pts with metastatic pancreatic cancer, essentially unchanged over 2 decades
- Percentage of patients surviving less than 2mo went from 63.5% in 1993 to 50.6% in 2013
- Percentage of patients surviving longer than 1yr went from 4.9% in 1993 to 12.7% in 2013

Why So Dismal?

- Single agent chemotherapy in advanced disease with limited efficacy
- Data from MSKCC, Dana Farber in the early 1990s with single agent 5FU with response rates of <10%, median OS of 2.5mo (MSKCC), 6mo (Dana Farber)
- Data from MSKCC in the mid-90s with single agent gemcitabine demonstrated a response rate of 11%
- However, “clinical response rate” (>50% reduction in pain, analgesic use, 20pt improvement in KPS) was 27% in a mid-1990s phase II study– in patients who had progressed on prior 5FU

5FU vs Gemcitabine

- 1997 study of gemcitabine vs 5FU (1,000mg gemcitabine weekly 3 on/1 off, 5FU 600mg/m2 weekly) demonstrated a clinical response rate of 23.8% for gemcitabine vs 4.8% for 5FU, and 18% survival rate at 12mo for gemcitabine vs 2% for 5FU
- However, overall survival still limited at 5.65 and 4.41mo for gemcitabine and 5FU respectively
- However, based on these results, gemcitabine was approved by the FDA for treatment of advanced pancreatic cancer in 1996

Maybe Capecitabine or S-1

- 2002 study from US Oncology with single agent capecitabine with 24% clinical response rate, but only 7.3% objective response
- 2013 Japanese/Taiwanese GEST study (834 patients!) with S-1 showed noninferiority of S-1 vs gemcitabine in overall survival, improved response rate (21 vs 13%)

Gemcitabine Combinations

- Gemcitabine plus 5FU– E2297 from 2002 showed no benefit for overall survival, response rates <10%, PFS of 2.2 and 3.4mo
- Gemcitabine plus capecitabine– 2 European phase III trials (2007, 2009) failed to demonstrate overall survival benefit for the combination; however, a meta-analysis of these trials plus a separate phase II trial suggested an overall survival benefit
- Gemcitabine plus S-1– data conflictory, can’t get it

Gemcitabine Plus Erlotinib

- Phase III NCIC trial
- 569 patients
- Addition of erlotinib increased 1yr survival to 23% from 17%
- Overall survival 6.2 vs 5.9 months
- Erlotinib approved in 2005

Gemcitabine Plus Others

- 2010 study of gemcitabine plus cetuximab without any improvement in median survival, response rate, or progression free survival (745 patients)
- 2009 phase III trial of bevacizumab with gemcitabine/erlotinib without improvement in overall survival, 4.6 vs 3.6mo progression free survival benefit (607 patients)
- Gem/cis, gem/ox, gem/irinotecan are all negative combinations (2005-2010; E6201 demonstrating no benefit for FDR gemcitabine or gem/ox enrolled 832 patients)

GTX

- Gemcitabine, docetaxel, capecitabine
- 2009 study demonstrated a 21.5% response rate and a median overall survival of 14.5mo
- 2011 evaluation from JHU/MSKCC/US Oncology demonstrated median overall survival 11.6mo (25mo in the locally advanced cohort) and an 11% response rate

Gemcitabine and Nabpaclitaxel

- 2011 study in 67 patients with 48% response rate, median survival 12.2 months
- MPACT trial (861 patients) published in 2013 with OS 8.5mo in gemcitabine/nabpaclitaxel arm vs 6.7mo in gemcitabine arm, 5.5 vs 3.7mo PFS, 35% alive at 1yr with combination vs 22% in gemcitabine alone group
- Combination approved in 2013

FOLFIRINOX

- 5FU, oxaliplatin, irinotecan
- Compared to gemcitabine in the phase III ACCORD 11 trial, published in 2011
- Original enrollment 342 patients, trial stopped after 250 patients
- 32% vs 9% response rate
- Overall survival 11.1 vs 6.8 months
- PFS 6.4 vs 3.3 months
- NO trials directly comparing FOLFIRINOX vs gemcitabine/nabpaclitaxel

Before You Give FOLFIRINOX

- Testing for BRCA mutations
- Testing for microsatellite instability or next-gen sequencing

BRCA

- About 5% of pancreatic cancers arise in setting of BRCA mutation
- Pancreas cancer olaparib ongoing trial (POLO) reported at ASCO 2019
- At least 16 weeks of platinum based therapy– if no progression, followed by maintenance olaparib vs placebo
- At 2 years, 22.1% of patients on olaparib had not progressed compared to 9.6% on placebo
- PFS 7.4 vs 3.8mo

MSI/NGS

- Tumor-agnostic mutations (e.g. NTRK)
- MSI/MMR-D pancreatic cancer is rare (<1%)
- No known efficacy for ‘standard’ immunotherapy in pancreatic cancer without MSI

Second Line Therapy

- Unclear and somewhat unknown efficacy
- HIGHLY individualized and based on tolerance to prior line of therapy, performance status, patient goals

Liposomal Irinotecan

- Nanoliposomal encapsulated, with theoretical improvement in uptake in tumor cells
- Phase III NAPOLI-1 trial, 417 patients with gemcitabine refractory disease, published in 2016
- Randomized to 5FU/leucovorin, liposomal irinotecan, or the combination
- Overall survival 6.1 vs 4.2mo with combination therapy vs 5FU/leucovorin alone, PFS 3.1 vs 1.5mo
- Response rate 16% vs 1%-- FDA approved in 2015

Other Options After Gemcitabine

- 5FU/oxaliplatin combination therapy or capecitabine/oxaliplatin combination
- Limited data regarding usage of FOLFIRINOX after gemcitabine
- Can also consider gemcitabine/oxaliplatin, oxaliplatin plus irinotecan
- Paclitaxel with some activity as single agent (10% response rate)

Options After FOLFIRINOX

- Gemcitabine/nabpaclitaxel (response rate 18%, PFS 5.1mo, overall survival 8.8mo)
- Gemcitabine +/- capecitabine
- Paclitaxel

Things To Consider

- Assessment of response by primary tumor changes can be unreliable
- Utilization of CA19-9 should always be accompanied by imaging restaging as well
- Focus on SUPPORTIVE CARE

Ongoing Clinical Questions

- Should we test everyone with next-gen sequencing?
- Should we do liquid biopsies?
- How do we choose who gets FOLFIRINOX vs gemcitabine/nabpaclitaxel?
- Who should get second (or third, fourth, etc.) line therapy?

Supportive Care

- Multidisciplinary and multi-pharmacologic approaches to pain control (oral opiates, patches, medications for neuropathic pain)– early utilization of celiac plexus neurolysis or palliative radiation therapy
- Aggressive multidisciplinary support for gastric outlet obstruction and delayed gastric emptying
- Early and continued referrals/interventions for psychosocial support/treatment for depression
- Early referral to dietician for anorexia/cachexia, _and_ early utilization of pancreatic enzyme replacement therapy

Should We Anticoagulate?

- Subgroup of 273 ambulatory pancreatic cancer patients from the CASSINI trial presented at ASCO 2019
- 10.1% vs 3.7% of patients on placebo vs rivaroxaban had a DVT/PE
- Number needed to treat to avoid one event was 16
- Bleeding risk not higher in the rivaroxaban arm


EVERYBODY BLAMES EVERYTHING ON THE LAWYERS
THE LAWYERS BLAME EVERYTHING ON THE DOCTORS..WHO DO THE DOCTORS BLAME?
THE GOLF PRO
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