Pain and Side-Effect Management

Pancreatic Cancer Action Network
Educational Seminar
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Overview

- Introduction
- 1st Case "Connie"
  - Helping with Connie's Challenges
- 2nd Case "Bob"
  - Focus on Bob's Challenges
- A few extra things
- Conclusion/Questions

Introduction

- On average, pts suffer 11 significant symptoms directly attributable to pancreas cancer
- Requires proactive team approach to manage symptoms aggressively & improve QOL
  - May need once or twice weekly visits
- Dramatic difference in QOL, particularly if combined with an effective chemotherapy regimen
- Hopefully this talk will highlight some points to share with your care team

Case #1: "Connie"

- 62 y.o. woman with borderline resectable pancreas cancer I was treating with neoadjuvant FOLFIRINOX
  - Suffered significant **nausea**, occasional vomiting
- At diagnosis she had significant mid-back pain
  - 6-8/10, waking her from sleep
  - Was given Norco, taking average of 12 tabs daily(yikes!)
- Lost 25 lbs in about 2 months before diagnosis
  - General lack of appetite
- Only when asked, she described "rope-like stools" that were floating in the bowl
  - Some cramping

Connie's Challenges

- Pain
- Nausea, vomiting, appetite loss
  - Cancer Anorexia-Cachexia Syndrome (CACS)
  - Chemotherapy-induced N/V
- Diarrhea, bloating, profound weight loss
  - Pancreatic exocrine insufficient (PEI)

Pain – Where To Start?

- Unfortunately, a common part of pancreas cancer
  - Mediated via the *celiac plexus*, a large nerve bundle that runs through the pancreas
- WHO Pain Ladder:
  - A prescribing guide escalating class of medications based on:
    - The severity of the pain
    - The response to the med on the prior step

Pain – Step 1

- Step 1: ibuprofen, Tylenol, ice, heat, etc
  - Basic over-the-counter remedies
  - Ibuprofen: careful of damaging kidneys
  - Tylenol/acetaminophen:
    - Not to exceed 2,000-4,000 mg/day
    - Excess amounts can cause liver damage
- Often only partially effective for pancreas cancer
  - Patients usually require Step 2 or 3

The Next Steps

- Standard of care is opioids (morphine/-like drugs)
  - Should be effective to regain most activities
  - Start with a dose **every 4 hrs** as needed (not 6 hrs)
  - Very helpful if you can keep notes or a pain diary
- Step 2: combination pill such as T#3, Norco or Vicodin
  - Limited by the 24-hr Tylenol (acetaminophen) intake
  - 325 mg in most of the combination pills
  - Usually limited to 6 or 7 tablets/day

Beyond Norco

- If you are:
  - Taking 6 or more combo pills/day
  - Have ineffectively controlled pain
- It's time for Step 3: morphine/-like drugs
  - Patients commonly have concerns
  - Much safer to switch to a pure opioid
  - The starting morphine and oxycodone doses are roughly equivalent to Norco 10/325 mg

"I don't want to become addicted"

- I hear this almost every day in practice
  - Incidence of new addiction in cancer pts is < 1%
- You don't become addicted just because you take a medicine a long time for pain
- Pts at highest risk are those with prior addiction
  - Smoking, drinking, heroine
  - If there is a history, be open w doctor and yourself
- One simple question: **"If a magic wand made all of your pain go away right now, would you still take the pain medicine?"**

Proper Opioid Use

- Fast-acting morphine* every 4 hrs as needed
  - Metabolized + gone by hour 4 (no rationale for 6 hrs)
  - If it does **not** manage the pain, talk to your care team as you likely require a dose increase
- Peaks and Valleys?
  - If you **have** to take it every 4 hours or have constant pain, you likely require a "slow-release" i.e. "long-acting" formulation to provide a sustained level of relief throughout the day
  - Options: the Fentanyl patch, MSContin**, or OxyContin**

*morphine or morphine-like drug; **the suffice "Contin" means continuous release

A More Targeted Approach

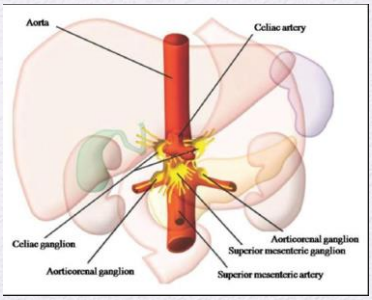
- Opioids have unwanted side effects such as:
  - Somnolence, constipation (though can be prevented)
- A nice adjunct is a Celiac Plexus Nerve block (CPN)
  - Under image guidance, ethanol is injected* to kill the nerve fibers in the celiac nerve root
  - Stops or minimizes pain signals from the area
- Effective in the majority of patients
  - Lower pain scores by 2.2 points
  - 50% less morphine used per day

Yan BM, 2007
Wong GY, JAMA 2004
Arcidiacono, Cochrane 2011

*By an anesthesiologist or Advanced Endoscopist (Interventional GI)

More About CPN

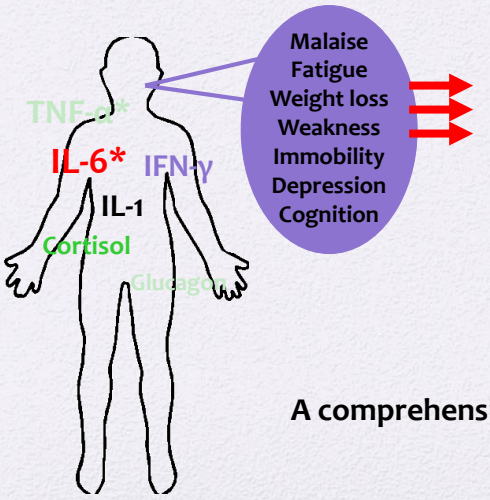
- Doctors used *wait to recommend CPN* only when the pain was unbearable…
  - But it has been shown that **the earlier, the better**
  - 1 study even showed superior outcomes if done at diagnosis
- Risks include:
  - Diarrhea, low blood pressure
  - Small risk of bleeding
  - Rare paradoxical increase in pain
    - Usually immediately



Now—to the GI Tract

- The predominant symptoms with pancreas cancer
- Nausea, appetite loss, food "just tastes bad"
  - Cancer Anorexia-Cachexia Syndrome (CACS)
  - Chemotherapy-induced N/V
- Diarrhea, bloating, gassy, profound weight loss
  - Loose stools, break apart in bowl, may float
  - Cramping, some urgency, maybe accidents
  - Pancreatic exocrine insufficiency (PEI)
- These all tie together, and must all be treated
  - Consult with a dietician specializing in cancer care

It's Not Just Weight Loss



Poor quality of life
(Patients & families)

- Family nagging to eat constantly
- The patient feels like they just aren't trying hard enough

A comprehensive plan can help a lot!

Illman J, 2005
Tisdale MG, 1997

"The Evil Humors"

Cancer Anorexia-Cachexia Syndrome

- Pancreas cancer secretes proteins, hormones that change the body metabolism
  - Tell your brain you're *not hungry* and ↑ nausea
  - Predispose to muscle loss selectively
- Controlling the whole syndrome makes this ***better***
  - An effective chemotherapy regimen
  - Addition of pancreatic enzymes ± olanzapine*
    - Start 2.5 or 5 mg nightly, may increase to 10 mg nightly
  - Pts gain weight back, recover their hunger & taste

*Not an FDA-approved indication

N/V from Chemotherapy

- Pre-medications given before chemo can be adjusted
  - Possibly add Emend (fos-/aprepitant) IV or pills
  - Decrease steroids if you get severe insomnia
- 1 med from each class as they work better **together:**
  - Compazine (prochlorperazine), Reglan (metoclopramide)
  - **Zofran (ondansetron)** or Kytril (granisetron)
    - Better coverage with 8 mg (not 4 mg)
    - Dissolving tablet often a bad idea
      - Bad taste association
      - Gets absorbed in the stomach anyway

Olanzapine (Zyprexa)

- Standard of care for chemo with mod-high risk of N/V*
  - Studies: show 5 mg twice daily effective
  - Makes people sleepy so I give all at bedtime
- Newer generation antipsychotic gave pts ***insatiable*** appetites
  - Used by palliative medicine for over a decade now
  - Reduces both N/V that occurs up to 7-days from chemo
  - Most effective for the constant experience of nausea
- **Usually ↑ blood glucose in DM** (minimal w/o DM)
- Very rare: hallucinations, "creepy crawlies"
  - Hold, then go back to dose that **didn't** cause the side effects

*Per ASCO, NCCN, ONS, MASCC, ESMO

Basch E, JCO 2011
Navari RM, ASCO 2012, #9064

As for the other GI symptoms…

- Diarrhea, bloating, gassy, profound weight loss
  - Loose stools, break apart in bowl, may float
  - Cramping, some urgency, maybe accidents
- These are all signs of
  Pancreatic Exocrine Insufficiency (PEI)

What is PEI?

- Inadequate delivery of critical digestive enzymes into the small intestine to help with food breakdown and absorption
  - Tumor in situ blocks the pancreatic duct(s)
  - Fibrosis occurs after radiation, surgery
  - **Lipase** – breaks down fats and facilitates *vitamin A, D, E & K*
- ***You're flushing the fats you eat right down the toilet!***
- Persistent low-grade cramping, gas, floating or loose stools
  - Rarely recognized in clinical practice even by experienced MDs
- **No need** for any testing to diagnosis & treat (in pancreas ca)
  - A low vitamin D level is a clue

Halloran CM, 2011
Dominguez-Munoz JE, 2011

How do we treat PEI?

- Empiric pancreatic enzyme replacement
  - Creon (lipase 12,000 IU) or ZenPep (10,000 IU)
  - Normal fat diet (not low-fat)
- Take lipase to mimic natural secretion
  - 40-65,000 IU with each meal (3-6 tabs!)
  - Snacks: 20-25,000 IU (2-3 tabs)
- Never take on an empty stomach
  - Stomach acid inactivates/cooks the lipase enzyme
  - Mixing with the whole meal can be critical

Whitcomb DC, 2010

Refractory Symptoms

1. Be sure you are taking the enzymes correctly
2. Increase the # of pills (higher doses of lipase)
   - 72,000 IU/meal & 36,000 IU/snack
3. Start twice daily acid suppression
   - PPI (e.g. omeprazole) or H2-blocker (e.g. Pepcid)

Trials have show patients can regain weight significantly

- Improve nutritional status
- *Can* be tracked with vitD levels but not necessary if gaining weight

Whitcomb DC, 2010
Dominguez-Munoz JE, 2011

Reminder about Connie

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Connie's Pain Story

- Upon meeting her, I:
  - Changed her Norco to morphine-IR 15 mg every 4 as needed to avoid exceeding the Tylenol ceiling every day
  - Added a slow-release morphine every 12 hours (MSContin) on a schedule to prevent pain
  - Referred immediately to anesthesia for celiac plexus nerve block, performed about 8 days later
- Connie had a dramatic improvement in her pain
  - Able to stop her slow-release morphine 1 week later
  - Only needed 1-2 tabs of fast-acting morphine per day
  - Relief lasted the full 6 months duration until she was able to go to surgery

Connie's Bowel Challenges

- For the nausea & weight loss - I started olanzapine 5 mg
  - She quickly developed a hearty appetite
- We treated her rope-like, floating stools as presumed PEI
  - Creon 5 tablets with meals: 60,000 IU
  - Noted 21 lbs weight gain & improved stools until….
- Underwent Whipple, followed by fecal urgency on her usual dose of Creon
  - I added Protonix twice daily on an empty stomach
  - **Then better mixing** of Creon with food throughout the meal
  - < 3 stools daily long term

Case #2: "Bob"

- A 67 y.o. man with advanced pancreas cancer
  - I met as a palliative care consultant
  - About to start gemcitabine/abraxane
- Increasing belly distension – "7 months pregnant"
- Early satiety, poor appetite, sluggish bowel
- Since diagnosis, lost his sense of purpose in life
  - Stopped doing going to church or seeing friends
  - Stopped calling his adult children regularly

Bob's Challenges

- Ascites
  - Belly swelling as fluid builds around intestines
- Gastroparesis
  - "Stagnant stomach" or sluggish bowel
- Depression
- Whether to integrate a Palliative Care Team into his care

Ascites

- Fluid leaked around the intestines due to:
  - Carcinomatosis (tumor deposits on outside of bowel)
  - Causes nausea, constipation, "I get full easily"
- Solutions
  - Usually diuretics are unhelpful & dehydrate
  - An effective chemotherapy regimen
  - Easy 1-time drainage called paracentesis (<5L)
  - If ongoing, an indwelling catheter can be placed so that patients can do their own drainage for comfort whenever, usually at home
    - Vastly improved QOL and symptoms

Fleming ND, 2009
Courtney A, 2008

Gastroparesis

- Slow transit of food & medicine out of stomach
  - >50% of patients with pancreas cancer
  - Results in nausea, reflux of acid or food hrs later
- Disrupted nerve impulses along the intestine
  - From concomitant Diabetes Mellitus, or surgery
- Choice of nausea med would be metoclopramide (Reglan) over Compazine (prochlorperazine)
  - Additionally, low dose erythromycin can be helpful

Depression

- The "evil humors" change the brain
  - Majority of pts meet criteria for depression **before** they even have a diagnosis of cancer
  - Up to 75% incidence for pancreas cancer patients
  - Increased risk of suicide (>10x)
    - Highest for men in 4-6 weeks after a Whipple
- All patients are screened and treated if willing
  - Benefits of antidepressants are significant
  - Experienced counselor, works w existential concerns

What is Palliative Medicine?

- New discipline dedicated to the relief of suffering
  - Physical, emotional and existential challenges
  - Improve quality of life for patients and families
    - Add a layer of support and expertise
- Prior skeptics now overwhelmed by the evidence
  - Temel NEJM 2010: Pts receiving chemo at MGH for stage 4 lung ca lived 3 months **longer with better QOL** if they had palliative care from diagnosis vs standard care
- ASCO Position: Integration into Standard Oncology Care

J. Temel, NEJM 2010.
https://www.asco.org/practice-guidelines/cancer-care-initiatives/palliative-care-oncology

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Bob's Recent Palliative Visit

- 4 cycles into gem/nab-paclitaxel (Abraxane) doing well
  - Dramatic reduction in CA19-9 – obviously responding
- Abdominal catheter in, his wife is draining at home
  - Was 3x—now only 1x weekly with much less output
- Vast improvement in nausea with an appetite finally!
  - On Reglan and olanzapine
- Engaging with a therapist
  - Planning 1-on-1 ice fishing trips with each of his sons
  - Focusing on gratitude, life review and legacy building
- Reinstated poker night – now at his house weekly w friends

Acknowledge Family & Caregivers

- Pancreas cancer causes enormous stress – under-recognized by the health care team
  - Financial
  - Physical
  - Family
  - Burnout
- Resources are extensive through Patient Central at the Pancreatic Cancer Action Network so I encourage everyone to call and get connected

In Conclusion

- There may be many challenges with pancreas cancer but there is hope of genuine healing
- Hopefully these pearls will be useful
- With or without a palliative care team, aggressive supportive care results in better quality of life for all team members
- Thank you for your time and attention

Questions?