Pancreatic cancer
Palliative Care

Snežana Bošnjak

Institute for Oncology and Radiology of Serbia
Dept. Supportive Oncology & Pall Care
ESO & ESMO Faculty
Symptom management: key points

- Cause & pathophysiology
- Comprehensive assessment
- Management
  - Treat the cause & exacerbating factors
    "treat the treatable / correct the correctable"
  - Pathophysiology-based therapy
  - Alleviate symptom-related distress
Pancreatic Cancer: Palliative Care Guidelines

- Cancer Pain (ESMO, 2018)
- Nausea and vomiting (MASCC / ESMO, 2016)
- Anorexia & cachexia
- Malnutrition (ESPEN, 2016)
- Constipation (ESMO, 2018)
- Depression (Grassi et al., Annals Oncol 29: 101–111, 2018)
- Delirium (ESMO, 2018)
- Venous thromboembolism (ESMO, 2011)
- Patient-Clinician Communication (ASCO, 2017)
Cancer Pain: Assessment

- Routine screening of pain (NRS) and other symptoms (ESAS)
- Evaluate:
  - Cancer & its Dx & Tx: the cause of pain
  - Pain: intensity & mechanism & its treatment
  - Patient: clinical situation, comorbidities, pain-related distress
- Formulate personalized pain Tx plan

Mercadante S, Portenoy RK. Pain 2016; 157:2657-2633
Hui D, Bruera E. J Clin Oncol 2014; 32: 1640-1646
Personalized Pain Treatment Plan

• Treat the underlying cause of pain
  - Anti-cancer treatment
  - Interventions that target exacerbating factors

• Releive pain
  - Physical (patophysiology-based Tx)
  - Pain-related distress (psychosocial, spiritual)

• Pharmacological & non-pharmacological Tx

• Multidisciplinary approach & team work

Mercadante S, Portenoy RK. Pain 2016; 157:2657-2633
Hui D, Bruera E. J Clin Oncol 2014; 32: 1640-1646
ESMO Guidelines

1-3

Paracetamol
NSAIDs

(Weak) OPIOID ± NSAIDs
Paracetamol

4-6

OPIOID ± NSAIDs
Paracetamol

Co-analgesics (NeP, bone pain, visceral pain)
Medications to prevent & treat adverse effects
The Usefulness of Weak Opioids

- Codeine (or tramadol) compared with low dose morphine (Mo: 5 mg, Q4h) for moderate pain (4-6/10)
- Morphine:
  - Significantly higher clinically meaningful (≥30%) and highly meaningful (≥50%) pain relief
  - Earlier onset of analgesic effect and less need for rotation
- Comparable good tolerability

Weak opioids: ESMO 2018

• As an alternative to weak opioids low doses of strong opioids could be an option but is not included in the WHO guidance (II, C)

• There is no evidence of increase in adverse effects from the use of low-dose strong opioids instead of the standard step 2 approach with weak opioids (II, C)

Strong opioids

- Oral first-line opioids: morphine, oxycodone, hydromorphone
- TD alternatives to oral opioids (Fen, Bu)
- Methadone: an alternative strong opioid with non-opioid mechanism of action
- Tapentadol: opioid & non-opioid (SNRI)

Meracadante S, Bruera E. JPSM 2018;55:998-1003
Opioids: routes of administration

- The least invasive route is preferred:
  - Oral: first choice (IR, SR formulations)
  - Transdermal

- The s.c route: the first choice for patients unable to receive opioids by oral or t.d. route

- The i.v. Infusion: when s.c. administration is contraindicated

- Titration with an i.v. opioid: when rapid pain control is needed

- Topical: morphine mouthwash (oral mucositis)

- Intramuscular: NOT recommended

Opioids: individual dose titration

- The starting dose: driven by safety, not by the intensity of pain

  - Equivalent to 20-30 mg of PO morphine / 24h (opioid-naive patients, eGFR > 60 ml/min)

- Dose titration: gradual escalation of the starting dose, until pain is relieved or unmanageable adverse effects occur

- The minimal clinically meaningful increase: 30-50% / total 24 h dose

Opioid dosing: oral opioids

- Regular “around the clock” analgesia w/ short-acting (IR) or long acting (SR) oral formulations
- “Rescue” doses: IR oral formulations prescribed “as required” for pain that is uncontrolled w/ regular ATC regimen
- Adjust regular dose to take into account the total amount of rescue doses

Breakthrough (episodic) pain

Predictable (incident)

**Timing** a painful activity after regular or pre-emptive administration of an oral opioid

Unpredictable (spontaneous):

- Transmucosal fentanyl formulations (oral, buccal, sublingual and intranasal) have a role in unpredictable and rapid-onset BTcP
- Morphine i.v as an alternative if available

Opioids: individual tailoring

- Favorable balance btw analgesia and AEs
- Fentanyl and buprenorphine (t.d. or i.v.) are the safest opioids in patients with eGFR <30 mL/min
- Liver failure (morphine, hydromorphone)
- Alcohol / drug abuse: methadone, buprenorphine
- Coexisting symptoms will determine the choice of an opioid
- Methadone superior to TD fentanyl for cancer pain with neuropathic component

Opioids: adverse effects

Prevent:
• Individual tailoring / dose titration
• Laxatives, antiemetics
• New formulations (oxycodone + naloxon)

Treat:
• Reduce the dose, if the pain is stable
• Medications for Tx of adverse effects
• Switching to another opioid / administration route

Pancreatic cancer: neuropathic pain

- Celiac Plexus Block & CP Neurolysis
- Analgesics (opioids: ? methadone)
- Coanalgesics
  - Corticosteroids (for decompression)
  - Analgesic antidepressants & anticonvulsants
Neuropathic pain (ESMO 2018)

• Cancer related NP can be treated using opioid combination therapies and carefully dosed adjuvants, when opioid alone provide insufficient pain relief (II, B)

• Gabapentin, pregabalin, duloxetine and TCA (doses ≤75 mg/day) are strongly recommended as single-agents for NP first line Tx

Assessment & Tx of cancer-related NP

Clinical exam, pain drawings

Criterion 1:
Neuroanatomical plausible pain distribution

Anamnesis

Criterion 2:
Suggestive history of a relevant lesion or disease

Diagnosis test:
CT, MRI, neurophysiology

Criterion 4:
Confirmation of the lesion by a diagnostic test

Not likely NP: criterion 1 or 2 not fulfilled

Possible NP: criteria 1 and 2

Probable NP: criteria 1, 2 and 3 or criteria 1, 2 and 4

Definite NP: criteria 1, 2, 3 and 4

Opioids [IL 3]

Opioid combination therapies and adjuvants [IL 8]

- Gabapentin
- Pregabalin
- Duloxetine
- TCA

Nausea and vomiting in advanced cancer

2016 Updated MASCC/ESMO consensus recommendations: Management of nausea and vomiting in advanced cancer

Declan Walsh¹,²,³ • Mellar Davies⁴ • Carla Ripamonti⁵ • Eduardo Bruera⁶ • Andrew Davies⁷ • Alex Menzies⁸
Nausea and vomiting: advanced cancer

- **Systemic**: metabolic, medications, infection, anxiety
  - Hypercalcemia, hyponatremia, liver, renal failure
  - Opioids, NSAIDs, antibiotics

- **Above neck**
  - Intracranial: tumor, metastases, meninges, increased ICP
  - Vestibular
  - Migraine

- **Below neck**
  - Gastric outlet / duodenal, bowel obstruction
  - Gastroparesis, hepatomegaly, ascites, constipation
  - Mucosa: infection, inflammation, irritation
  - Motility: compression, obstruction, constipation, fecal impaction

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Roila F. et al., Annals of Oncology 2016; 27 (Supplement 5): v119–v133
EPEC-O curriculum
Nausea and vomiting: advanced cancer

- Metabolic
- Medications
- Microbes: infection
- Mental: anxiety
- Masses & Metastases
- Motility (GI)
- Mucosa
- Movement
- Myocardial
Nausea and vomiting-advanced cancer
MASCC / ESMO recommendations

Bowel obstruction (BO)
Gastric outlet / duodenal: Endoscopic duodenal stenting
Octreotide + an antiemetic (haloperidol preferred)
Corticosteroids for decompression

Advanced cancer-unspecified cause:
Metoclopramide is the drug of choice
Haloperidol, levomepromazine, olanzapin: alternatives

Opioid-induced nausea and vomiting: no Rec can be made

Cachexia

- Loss of appetite / an aversion to food
- Reduced food intake
- Non-volitional weight loss
- Muscle wasting
- Fatigue, reduced physical performance
- Psychosocial distress (patient / family)
- Impacts QoL, treatment tolerance, survival

Hui D. J Oncol Pract 2016: 12: 1172-1173
Cachexia: Inflammatory Malnutrition
The Global Leadership Initiative on Malnutrition (GLIM)

- **Etiologic**
  - Reduced food intake / assimilation
  - Chronic disease with systemic inflammation

- **Fenotypic criteria**
  - Non-volitional weight loss
  - Low BMI
  - The loss of skeletal muscle (with/without the loss of fat)

Adaptirano od Jensen GD et al. J Parenter Enteral Nutr 2018;0:1–9
Symptoms / conditions interfering with food intake

- Loss of apetite, anorexia
- Early satiety, nausea, vomiting
- Changed taste / smell of food
- Difficulties with chewing / swallowing
- Mucositis, xerostomy, infection
- Gastroparesis, constipation, bowel obstruction diarrhoea
- Pain, including abdominal pain
- Anxiety, depression

Jensen GD et al. J Parenter Enteral Nutr 2018;0:1–9
Patient With Cancer

Disease-specific product LMF

\[ \Delta \text{Proinflammatory cytokines} \]
\[ \text{IL-6, IL-1, TNF-\alpha} \]
\[ \Delta \text{APP} \]

Corticosteroids
MABp1
IP1510
ALD518

Endocrine abnormalities

\[ \Delta \text{Ghrelin} \]
\[ \Delta \text{Leptin} \]
\[ \Delta \text{GH} \]
\[ \Delta \text{Testosterone} \]
\[ \Delta \text{Insulin resistance} \]
\[ \Delta \text{CRF} \]

Anamorelin

Enobosarm

Neural
Sympathetic activation
Vagal dysfunction

\[ \Delta \text{Fat} \]
\[ \downarrow \text{Lipogenesis} \]
\[ \uparrow \text{Lipolysis} \]

\[ \downarrow \text{Muscle} \]
\[ \downarrow \text{Myosin production} \]
\[ \uparrow \text{Proteolysis} \]

Ruxolitinib
Bimagrumab
Trevogrumab

Megesterol

Cancer Cachexia:
International Consensus Definition

“Multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment”.

Stages of Cancer Cachexia

- **Precachexia**
  - Weight loss ≤5%
  - Anorexia and metabolic change

- **Cachexia**
  - Weight loss >5% or BMI <20 and weight loss >2%
  - Sarcopenia and weight loss >2%
  - Often reduced food intake/systemic inflammation

- **Refractory cachexia**
  - Variable degree of cachexia
  - Cancer disease both procatabolic and not responsive to anticancer treatment
  - Low performance score
  - <3 months expected survival

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Cancer Cachexia: strategy

• Malnutrition screening & assessment

• Treatment

✓ Treat the cause (anti-cancer Tx)
✓ Adress Sx & conditions which interfere w/ food intake
✓ Target disbalance btw catabolism and anabolism
✓ Provide energy and nutrients (dietary advice / nutrition support)
✓ Physical therapy: physical exercise
✓ Psychosocial support & education for patients / families

J. Arends: ESMO annual meeting 2018 presentation  www.ESMO.org
## Cancer Cachexia: Strategy

<table>
<thead>
<tr>
<th>Anticancer treatment</th>
<th>Consensus Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megestrol acetate</td>
<td>Stimulate appetite + increase weight, but not muscle mass (VTE risk!)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Anorexia (3-4 wks) w/ additional benefit on other Sx</td>
</tr>
<tr>
<td>Prokinetics: metoclopramide</td>
<td>Nausea, vomiting, early satiety</td>
</tr>
<tr>
<td>Oral nutritional supplements</td>
<td>YES</td>
</tr>
<tr>
<td>Enteral / Parenteral nutrition</td>
<td>If on anti-cancer Tx or longer survival is expected</td>
</tr>
<tr>
<td>Pharmaco-nutrients</td>
<td>Supplements enriched in N-3 fatty acids + protein: potential benefit</td>
</tr>
</tbody>
</table>

### References

ESPEN Guideline

ESPEN guidelines on nutrition in cancer patients

Jann Arends a, Patrick Bachmann b, Vickie Baracos c, Nicole Barthelemy d, Hartmut Bertz a, Federico Bozzetti e, Ken Fearon f, Elisabeth Hütterer g, Elizabeth Isenring h, Stein Kaasa i, Zeljko Krznaric j, Barry Laird k, Maria Larsson l, Alessandro Laviano m, Stefan Mühlbach n, Maurizio Muscaritoli m, Line Oldervoll i, o, Paola Ravasco p, Tora Solheim q, r, Florian Strasser s, Marian de van der Schueren t, u, Jean-Charles Preiser v,*
Cancer Related Fatigue

Dexametahsone 4 mg BID better than placebo for cancer fatigue at day 8 and 15

CONCLUSION

The integration of the tumor-directed and the patient-directed approach in oncology