Palliative Care in Terminal Stage Liver Cancer

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Learning Objectives

• 5 Priorities of Care of the Dying
• Identification of Terminal Stage
• Pain control
• Opioid prescribing in hepatic disease
• Management of other physical symptoms
• Psychological support
• Role of holistic care in Terminal illness
Terminal stage liver cancer

- Hepatocellular carcinoma 5th most common malignancy, worldwide
- Approx 1,000,000 deaths per year globally
- Africa & Asia
- 15-20% present at end or terminal stage
- Median survival = 3-4 months
- 1 year survival = 11%
Kumar, M & Panda, D (2016).

- Consensus statement:
  - “Patients [with] end stage or terminal HCC have a poor survival and should receive palliative support including management of pain, nutrition and psychological support. In general, they should not be considered for participating in clinical trials [Level of evidence 2b, Grade of recommendation B].”
Priorities for Care of the Dying Person

When it is thought that a person may die within the next few days or hours...

• 1. This possibility is recognised and communicated clearly, decisions made and actions taken in accordance with the person’s needs and wishes, and these are regularly reviewed and decisions revised accordingly.
• 2. Sensitive communication takes place between staff and the dying person, and those identified as important to them.
• 3. the dying person, and those identified as important to them, are involved in decisions about treatment and care to the extent that the dying person wants.
• 4. the needs of families and others identified as important to the dying person are actively explored, respected and met as far as possible.
• 5. an individual plan of care, which includes food and drink, symptom control and psychological, social and spiritual support, is agreed, co-ordinated and delivered with compassion.
5 priorities of care for the dying

- **RECOGNISE** the possibility that the person may die within the hours to days.
- Sensitively **COMMUNICATE** information
- **INVOLVE** the people important to the patient
- **SUPPPOORT** the dying patient
- **PLAN AND DO** develop an individualised care plan.
Identifying the ‘Palliative’ Patient

- 8 Frailty / co-morbidity / Dementia
- 5-6 (single) organ failure
- 5 Cancer
- 1-2 sudden unexpected deaths

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3 steps for earlier identification

① Ask the surprise question:

- would you be surprised if the patient were to die in next months, weeks or days?

② Does the patient have general indicators of decline?

③ Does the patient have any Specific Clinical Indicators heralding deterioration?

The ‘Surprise question’: Lynn J 2005 Altarum Institute Center for Elder Care and Advanced Illness
General Indicators$^1$, $^3$

- Decreasing activity – functional performance status declining (e.g. Barthel score) limited self-care, in bed or chair 50% of day) and increasing dependence in ADLs
- Co-morbidity = biggest indicator of mortality and morbidity
- General physical decline and increasing need for support
- Unstable, deteriorating complex symptom burden
- Decreasing response to treatments, decreasing reversibility
- Progressive weight loss (>10%) in past six months
- Repeated unplanned/crisis admissions
- Sentinel Event e.g. serious fall, transfer to nursing home
- Serum albumen <25g/l

Specific indicators 1 - Cancer¹,³

• Metastatic cancer

• The single most important predictive factor in cancer is performance status and functional ability’
  – if patients are spending more than 50% of their time in bed/lying down, prognosis is estimated to be about 3 months or less.

• More exact predictors for cancer patients are available e.g. PiPS (UK validated Prognosis in Palliative care Study). PPI, PPS etc.
Physical Symptoms in advanced HCC

• Abdominal pain most common symptom (2/3 patients)
  – Either from cancer or cancer-treatment
• Cancer-related symptoms:
  – Fatigue
  – Cachexia
  – Dyspnoea
  – Vomiting
• Symptoms related to decompensated cirrhosis:
  – Ascites
  – Variceal bleeding
  – Oedema
  – Encephalopathy
Psychological Symptoms in advanced HCC

• Mod-Severe Depression
• Psychological distress
  – Third highest reported level of distress among different types of cancer
PAIN MANAGEMENT IN TERMINAL STAGE HCC
WORLD HEALTH ORGANISATIONS
ANALGESIC LADDER

Step 1
Non-Opioid
-/+ Adjuvant

Step 2
Opioid for mild-mod pain
+Non-opioid
-/+ Adjuvant

Step 3
Opioid for mod-severe pain
+Non-opioid
-/+ Adjuvant

Pain Persists or increases

Pain Persists or increases
Pharmacokinetic issues in cirrhosis

- Worsening liver function in advanced cirrhosis and/or HCC increases risk of adverse effects
- Paracetamol may be safe
- NSAIDs to be avoided (risk of bleeding)
- COX-2 inhibitors generally avoided (cardiovascular risks, and limited experience to guide safe use)
- Opioids may be used, but with caution:
  - Metabolized by oxidation and/or glucuronidation
  - Clearance depends on protein binding, hepatic blood flow, hepatic enzyme capacity
Paracetamol

- Doses up to 4g per day appear to be safe
- Usual recommendation in cirrhosis/advanced liver disease: limit intake to 2g/day
4NICE Clinical Guideline 140: Safe & effective prescribing of strong opioids for pain in palliative care of adults

1. Morphine
2. Oxycodone
3. Fentanyl
4. Buprenorphine
Morphine\textsuperscript{4,5}

- Approx. 10x as potent as Tramadol or Codeine when given orally

Therefore:

- Tramadol 50mg $\approx$ Morphine SO$_4$ 5mg p.o.
- Tramadol 100mg $\approx$ Morphine SO$_4$ 10mg p.o.
- Codeine 60mg $>$ Morphine SO$_4$ 5mg p.o.
- Codeine 60mg q.d.s. $>$ MST 10mg b.d.

\textsuperscript{5}Twycross R, Wilcock A (Eds, 2012). Palliative Care Formulary 4\textsuperscript{th} Ed.
Morphine$^{4,5}$

- Oral or parenteral (i.e. subcutaneous)
- Oral: Immediate release or sustained release

- Oral bioavailability of Morphine means need to dose reduce when converting to s/c
  - s/c Morphine approx. 2x as potent

- Halve oral Morphine dose if giving s/c
  - e.g. Morphine SO$_4$ 5mg p.o. = 2.5mg s/c

$^5$Twycross R, Wilcock A (Eds, 2012). Palliative Care Formulary 4$^{th}$ Ed.
Morphine

• Increased bioavailability in advanced liver disease
  – Reduced first-pass metabolism
• Metabolism: rapid glucuronidation in the liver
  – Usually preserved despite diminished liver function
• Clearance delayed by 35-60% in patients with cirrhosis
• NB metabolites hydrophilic and will accumulate in renal failure
Morphine

• Prescribing advice in advanced liver disease:
  – With caution
  – Reduce starting dose if using orally (e.g. Morphine sulphate MR 5mg b.d.)
  – Increased interval of PRN administration (4hrly, rather than 1-2hrly)
  – Avoid if concomitant renal impairment (increased risk of opioid toxicity)
Oxycodone\textsuperscript{4,5}

- Approx 1.5-2x as potent as Morphine, therefore:
  - Morphine SO\textsubscript{4} 5mg p.o. \(\approx\) Oxycodone 2.5mg p.o.

- Metabolized in the liver to noroxycodone and oxymorphone
  - Safer than Morphine or Diamorphine in renal impairment

- In mild-moderate hepatic dysfunction peak plasma concentrations of Oxycodone 50% greater
Oxycodone

• Oral or parenteral (i.e. subcutaneous)
• Oral: Immediate release or sustained release

• Oral bioavailability of Oxycodone means need to dose reduce when converting to s/c
  – s/c Oxycodone approx. 2x as potent
• Halve oral Oxycodone dose if giving s/c
  – e.g. Oxycodone HCl 2.5mg p.o. = 1.25mg s/c
Oxycodone

• Prescribing advice in advanced liver disease:
  – With caution
  – Reduce starting dose if using orally
  – Increased interval of PRN administration (4hrly, rather than 1-2hrly)
  – Monitor for worsening renal impairment (some risk of opioid toxicity)
Fentanyl$^{4,5}$

- Approx 100x as potent as oral Morphine
- As a guide, over 24hrs:
  - Fentanyl 25mcg/hr patch ≈ oral Morphine SO$_4$ 60-90mg/24hrs
- Lipid soluble
- V low oral bioavailability, therefore parenteral use only
- Converted by hepatic hydroxylation and dealkylation to inactive and nontoxic metabolites
  - Pharmacokinetics unchanged in cirrhosis
Fentanyl

• Transdermal patches or s/c use known to be safe in renal failure
  – also sublingual, buccal and nasal preparations*
    • Quick onset of action and short half-life make Fentanyl relatively well-suited for incident/breakthrough cancer pain
    • *transmucosal Fentanyl products should be used only in adults on a regular strong opioid for on-going cancer pain for ≥1 week

• Injection volumes can limit doses when given s/c
Methadone

• Long-acting opioid
• In mild-moderate cirrhosis: pharmacokinetic profiles unchanged
• In severe cirrhosis:
  – half-life can be mildly prolonged
  – Drug behaviour not significantly altered
• Appears to be safe in advanced liver disease, at least for short-term
Buprenorphine\textsuperscript{4,5}

- Sublingual and Transdermal preparations
- SL and TD – \textit{approx} 70-100x as potent as oral Morphine
- As a guide, over 24hrs:
  - Butrans 20mcg/hr patch ≈ oral Morphine SO\textsubscript{4} 30mg/24hrs
  - Transtec 35mcg/hr patch ≈ oral Morphine SO\textsubscript{4} 80mg/24hrs
- Extensive first-pass metabolism: 15% oral bioavailability
- Inactive metabolites: also safe in renal failure
- Least likely to cause opioid-induced hyperalgesia
OTHER PHYSICAL SYMPTOMS
Corticosteroids

• Anorexia, fatigue, nausea
• Pain relief – esp liver capsule pain
• Dexamethasone:
  – long half-life
  – Low mineralocorticoid effects
  – Limited evidence, but usual dose 1-2mg daily
  – Risk of proximal myopathy, psychomimetic effects
  – NB alkaline: not compatible in CSCI
Anorexia-Cachexia

• Megestrol Acetate (dose range 160-1600mg/day)
Nutrition management

• Weight loss, muscle wasting and under-nutrition common problems
  – Associated with poorer clinical outcomes
• Limited evidence: only a few RCTs on nutritional intervention
• 1 trial of PN and 5 trials of oral supplements
• Current data not compelling to support use of PN or supplements in HCC patients
Fatigue management

• Needs holistic assessment:
  – Pain and other physical symptoms
  – Anaemia
  – Emotional distress
  – Sleep
  – Functional status and deconditioning

• Often non-pharmacological approaches preferable (and more effective),
  – e.g. aerobic exercise or activity pacing

• Anti-depressants if Depression

• Methylphenidate?
Ascites

- Exudates v Transudates
- Diuretics only of benefit in Exudates
- Paracentesis
- PleurX or other permanent drainage system
Nausea & Vomiting

• Multiple possible causes
• Treatment should be directed to underlying cause:
  – Gastroparesis – Metoclopramide
  – Nausea from deranged liver/renal function – Haloperidol (low dose)
  – Nausea/vomiting from chemotherapy or radiotherapy – 5-HT3 antagonist (Ondansetron)
Pruritis

• Can be severe
• Mild symptoms will respond to non-pharmacological interventions: warm baths, emollients, creams
  – Can try 1-2% menthol in aqueous
• Mod-severe pruritis (e.g. due to bile salt accumulation):
  – Cholestyramine
  – Rifampicin
  – Naltrexone
Constipation

- Try to avoid, esp if underlying liver cirrhosis
- Lactulose
- Movicol, etc largely unhelpful
- For opioid-induced constipation:
  - Senna
  - +/- Sodium Docusate
PSYCHOLOGICAL SYMPTOMS
Depression

• “depression” vs. “Depression”
  – Importance of proper assessment
• Large range of anti-depressants
• In terminal HCC or advanced liver disease: caution with SSRIs (esp if still using alcohol)
• Mirtazapine
Anxiety

• Caution with benzodiazepines in cirrhosis
• Non-pharmacological approaches often preferred
  – Supportive care, counselling
  – CBT
• If benzodiazepines are needed:
  – Low doses
  – Lorazepam, Oxazepam (and possibly Temazepam) preferred
    • Primary elimination by glucuronidation (selectively spared in liver disease)
Holistic Model

- Physical
- Psychological
- Spiritual
If in doubt...

... call Palliative Care for advice!
5 priorities of care for the dying

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