Palliative Care in Terminal Stage Liver CancerTitle

Dr Ben S Clark MRCP MRCPsych
Consultant in Palliative Medicine

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

General Medical Council

LACPD -Leadership Alliance for the Care of Dying People

Imperial College Healthcare NHS
NHS Trust

RECOGNISE the possibility that the person may die within the hours to days.

Sensitively **COMMUNICATE** information

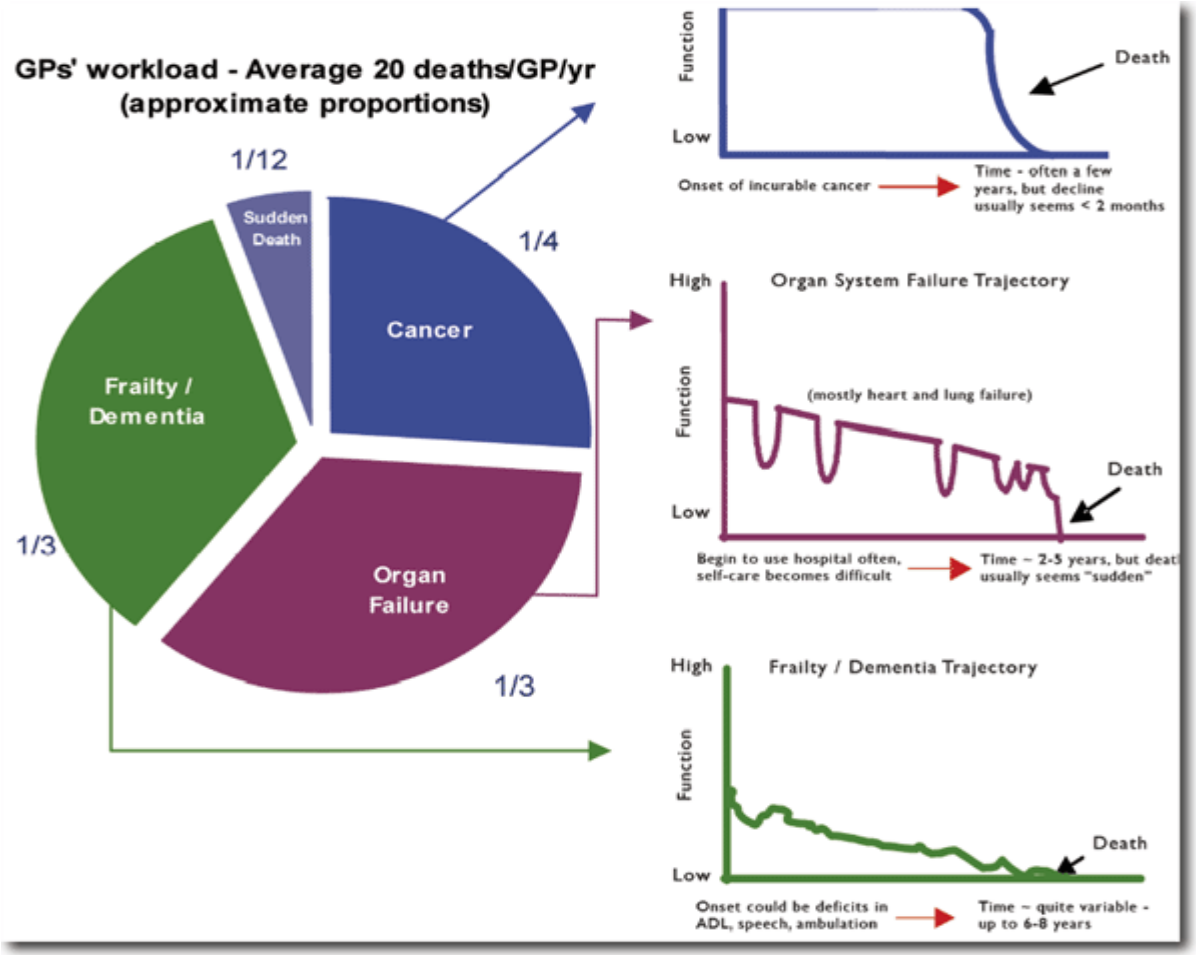
INVOLVE the people important to the patient

SUPPPORT the dying patient

PLAN AND DO

develop an individualised care plan.

Identifying the 'Palliative' Patient[1]



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

[1] Prognostic Indicator Guidance (PIG) 4th Edition Oct 2011 © The Gold Standards Framework Centre In End of Life Care CIC, Thomas.K et al

3 steps for earlier identification[1]

① Ask the surprise question[2]:

- *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

[3] Glare P, Sinclair CT (2008). Palliative medicine review: prognostication. *J Palliat Med;11;84-103*

Specific indicators 1 - Cancer[1,3]

- 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

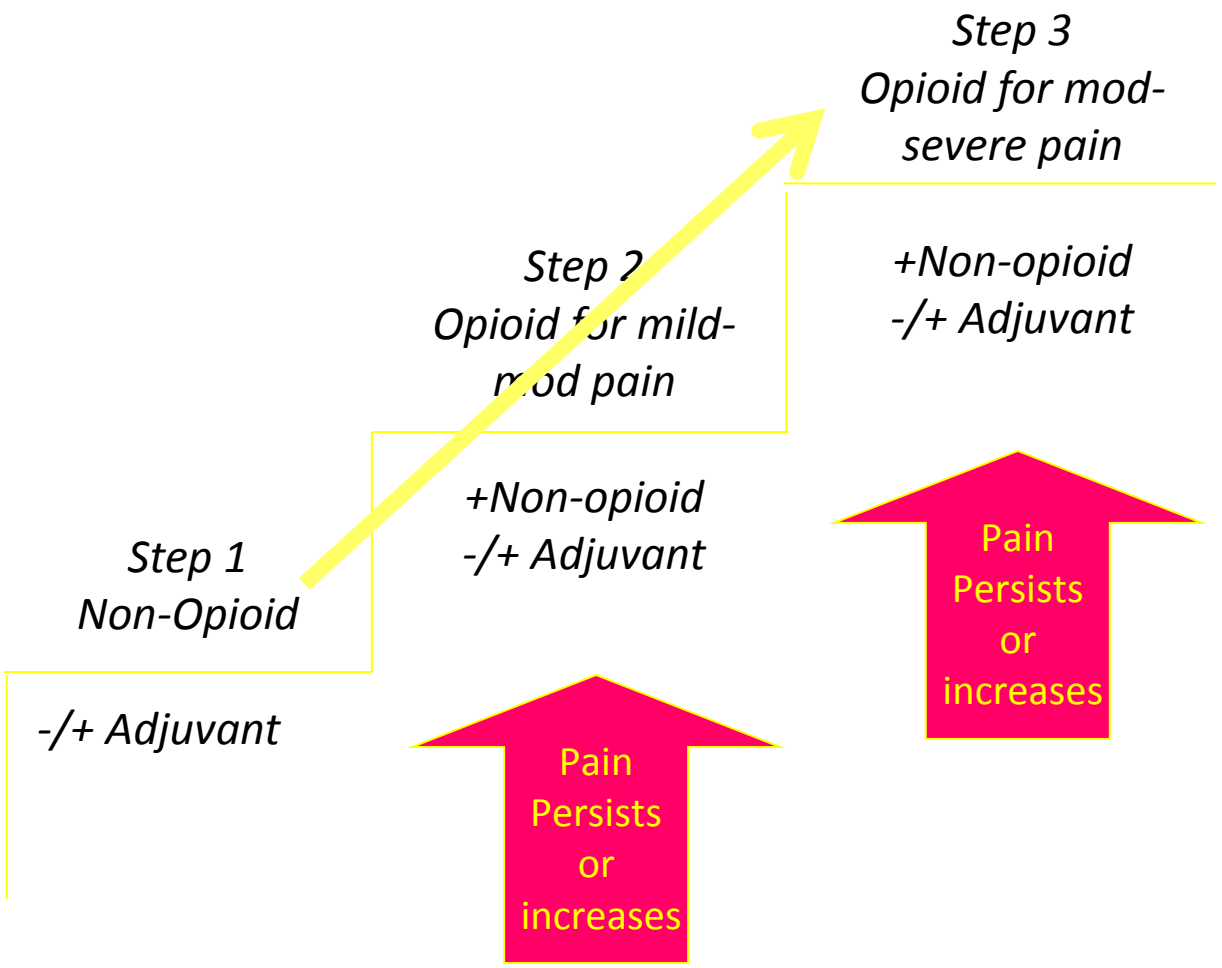
- Abdominal pain most common symptom (2/3 patients)
  - Either from cancer or cancer-treatment
- Cancer-related symptoms:
  - Fatigue
  - Cachexia
  - Dyspnoea
  - Vomiting
- Symptoms related to decompensated cirrhosis:
  - Ascites
  - Variceal bleeding
  - Oedema
  - Encephalopathy

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



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

[4]NICE 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[4,5]

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

Therefore:

- Tramadol 50mg ≈ Morphine SO_4 5mg p.o.
- Tramadol 100mg ≈ Morphine SO_4 10mg p.o.
- Codeine 60mg > Morphine SO_4 5mg p.o.
- Codeine 60mg q.d.s. > MST 10mg b.d.

[5]Twycross R, Wilcock A (Eds, 2012). Palliative Care Formulary 4th Ed.

Morphine[4,5]

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

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

- **<u>Halve oral Morphine dose if giving s/c</u>**
  - e.g. Morphine SO_4 5mg p.o. = 2.5mg s/c

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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[4,5]

- Approx 1.5-2x as potent as Morphine, therefore:
  - Morphine SO_4 5mg p.o. ≈ 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 mot significantly altered
- Appears to be safe in advanced liver disease, at least for short-term

Buprenorphine[4,5]

- Sublingual and Transdermal preparations
- SL and TD – *approx* 70-100x as potent as oral Morphine
- As a guide, over 24hrs:
  - Butrans 20mcg/hr patch ≈ oral Morphine SO_4 30mg/24hrs
  - Transtec 35mcg/hr patch ≈ oral Morphine SO_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

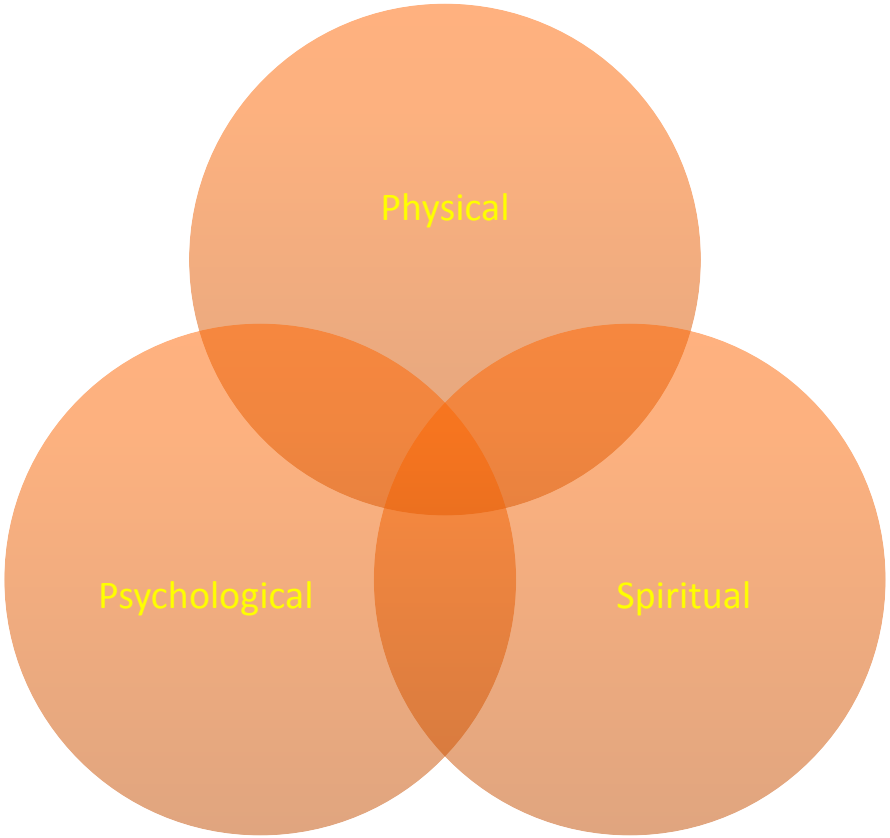
Depression

- “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)
- Mirtazipine

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



If in doubt…

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