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ESMO Minimum Clinical Recommendations for the management of cancer pain

Incidence of pain

- Over 80% of cancer patients with advanced metastatic disease suffer pain caused mostly by direct tumor infiltration. Pain undermines quality of life considerably and is a clinically important indicator of tumor progression. Cancer pain may be acute or chronic and should be addressed accordingly. Approximately 20% of pain in cancer patients may be attributed to the effects of surgery, radiotherapy, or chemotherapy.

Assessment and management

- All patients should be evaluated for the presence of pain at every visit. Pain severity is best assessed by patient self-report and may be aided by visual analogue scales (VAS). The extent of diagnostic investigation must be appropriate to the patient's general status and the goals of care. Pain should already be managed during the diagnostic evaluation.
- Most cancer patients can attain satisfactory relief of pain through an approach that incorporates primary anti-tumor treatments, systemic analgesic therapy, and other non-invasive techniques such as psychological or rehabilitative interventions. Step-wise escalation of analgesic therapy should usually follow the 'pain ladder' as described by the WHO.

Treatment of mild pain (WHO level I analgesics)

- Mild pain is treated with non-opioid analgesic such as acetaminophen/paracetamol or a non-steroidal anti-inflammatory drug (NSAID) (Table 1).
- Selective COX-2 inhibitors might be an alternative for patients with gastric intolerance of other NSAID. However, there are unsettled toxicity issues and lacking solid data regarding the efficacy of COX-2 inhibitors for cancer pain.

Treatment of moderate pain (WHO level II analgesics)

- Weak opioids may be used for moderate pain persisting despite the use of adequate doses of non-opioid analgesics. Low doses of morphine or its equivalents are a reasonable alternative, especially if progressive pain is to be expected. Weak opioids may be combined with ongoing use of a non-steroidal anti-inflammatory agent but not with WHO level III analgesics (Table 2).

Treatment of severe pain (WHO level III analgesics)

- Morphine is most commonly used. Oral administration is the preferred route. If given parenterally, the equivalent dose is 1/3 of the oral medication. Hydromorphone or oxycodone, in both normal release and modified release formulations for oral administration are effective alternatives to oral morphine. Methadone is an alternative but may be more complicated to use because of pronounced inter-individual differences in its plasma half-life and duration of action. Transdermal fentanyl is best reserved for patients whose opioid requirements are stable at a level corresponding to $\geq$60 mg/day of morphine. Strong opioids may be combined with ongoing use of a level I agent (Table 3).

Scheduling and titration

- Opioid doses should be titrated to effect as rapidly as possible. All patients should receive around the clock dosing with provision of a 'breakthrough dose' to manage transient exacerbations of pain. The 'breakthrough dose' is usually equivalent to at least 10% of the total daily dose. If more than four 'breakthrough doses' are necessary, the baseline opioid treatment with slow release formulation has to be adapted.

Management of opioid side effects

- Many patients develop adverse effects such as constipation, nausea, vomiting and central nervous system toxicity (drowsiness, cognitive impairment, confusion, hallucinations, and myoclonic jerks).
- In some cases a reduction in opioid dose may alleviate refractory side effects. This may be achieved by using a co-analgesic or an alternative approach such as a nerve block or radiotherapy. Other strategies include the continued use of anti-emetics for nausea, laxatives for constipation, major tranquillizers for confusion, and psychostimulants for drowsiness. Alternatively, switching to another opioid agonist and/or another route may allow titration to adequate analgesia without the same disabling effects. Naloxone is a short-acting opioid antagonist for intravenous use able to revert symptoms of accidental severe opioid overdose.

Radiotherapy

- Radiotherapy has specific and critical efficacy in the relief of pain caused by bone metastases, tumors compressing neural structures, and cerebral metastases. It is essential for managing radicular pain.

Table 1. Selected non-opioid analgesics (WHO level I)

Substance	Widely available forms and strengths	Time to onset (minutes)	Caution	Maximal daily dose
Acetaminophene (Paracetamol)	Tablets, suppositories 500–1000 mg	15–30	Hepatotoxicity	4–6×1000 mg
Acetylsalycic acid	Tablets 500–1000 mg	15–30	GI toxicity, allergy, platelet inhibition	3×1000 mg
Ibuprofen	Tablets 200–400–600 mg Tablets 800 mg retarded, topic gels	15–30 ≈ 120	GI & renal toxicity	4×600 mg, 3×800 mg retarded
Ketoprofen	Tablets 25–50–75 mg	≈30	GI & renal toxicity	4×75 mg
Diclofenac			GI & renal toxicity	
Mefenamic acid	Capsules 250–500 mg	≈ 30	GI & renal toxicity	4×500 mg
Naproxen	Tablets 250–375–500 mg	≈ 30	GI & renal toxicity	2×500 mg

Table 2. Comparison of selected weak opioids (WHO level II)

Substance	Widely available forms and strengths	Relative effectiveness compared to oral morphine	Duration of effectiveness(hours)	Maximal daily dose	Starting dose without pretreatment
Dihydrocodein	Modified release tablets 60–90–120 mg	0.17	12	240 mg	60–120 mg
Tramadol	Drops 100 mg/ml, capsules 50 mg	0.1–0.2	2–4	400 mg	50–100 mg
	Modified release tablets 100–150–200 mg	0.1–0.2	12	400 mg	50–100 mg

Table 3. Comparison of selected strong opioids (WHO level III: may be combined with level I medication)

Substance route	Relative effectiveness compared to oral morphine	Maximal daily dose	Starting dose without pretreatment
Morphine sulfate oral	1	[a]	20–40 mg
Morphine parenteral	3	[a]	5–10 mg
Oxycodone oral	2	[a]	20 mg
Fentanyl intravenous	7.5	[a]	8 mg
Fentanyl transdermal	∼4[b]	[a]	25 μg/h
Buprenorphine oral	75	4 mg	0.4 mg
Buprenorphine intravenous	100	3 mg	0.3–0.6 mg
Buprenorphine transdermal	∼1.7[b]	140 μg/h	17.5–35 μg/h
Methadone oral	4–*8*–12[d]	[a]	10 mg
Nicomorphine oral	1	20 mg	5 mg
Nicomorphine intravenous	3	20 mg	5 mg

[a]No upper limit: The maximal dose depends from tachyphylaxis.
[b]Calculated with conversion from mg/day to μg/h.
[c]Not usually used as first opioid (the 25 μg/h dose corresponds to 60–120 mg of oral morphine sulfate daily).
[d]Factor 4 for daily morphine doses <90 mg, 8 for doses 90–300 mg, and 12 for >300 mg.

Surgery and other interventions

- Surgery may have a specific and critical efficacy in the relief of pain caused by impending or evident fractures. Surgery or other interventional approaches may be necessary to control pain caused by obstruction of hollow organs.

Treatment of resistant and neuropathic pain

- Some patients, whose pain remains inadequately relieved, may benefit from invasive anesthetic or neurosurgical treatments and, occasionally, sedation may be considered for patients with refractory pain at the end of life. Subanesthetic doses of ketamine, an NMDA antagonist, may be tried in intractable pain.
- Neuropathic pain caused either by tumor infiltration or due to paraneoplastic or treatment-induced polyneuropathy often responds poorly to analgesic opioids. Combination with co-analgesics as listed below may improve pain control. Long lasting and neuropathic pain may cause psychological problems that should be specifically addressed.

Co-analgesic medication

- Non-opioid and opioid analgesics may be combined with anti-depressive or neuroleptic psychoactive drugs or anti-

Table 4. Selected co-analgesics

Substance	Widely available forms & strengths	Activity	Sedation	Range of daily doses
Amitryptiline	Tablets 25–50 mg	Antidepressive	+ + +	50–200 mg
Clomipramine	Tablets 10–75 mg	Antidepressive	(+)	50–200 mg
Nortriptyline	Tablets 10–25 mg	Antidepressive	+	50–225 mg
Fluoxetin	Tablets 20 mg	Antidepressive	+	20–80 mg
Haloperidol	Drops, tablets, vials	Neuroleptic	+	3–20 mg
Chlorpromazin	Drops, tablets, suppositories, vials	Neuroleptic	+ +	25–200 mg
Carbamazepine	Tablets 200–400 mg	Antiepileptic	+	400–1600 mg
Gabapentin	Tablets 200–300–400–800 mg	Antiepileptic	+	900–3600 mg

epileptic drugs in case of neuropathic pain. Steroids should be considered in case of nerve compression. There is insufficient evidence to justify the general use of bisphosphonates for bone pain relief (Table 4).

Literature

1. Zech DF, Grond S, Lynch J et al. Validation of World Health Organization guidelines for cancer pain relief: a 10 year prospective study. Pain 1995; 63: 65–76.

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