Management of cancer pain: ESMO Clinical Recommendations

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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), numerical rated scales (NRS) and verbal rated scales (VRS). 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 analgesics such as acetaminophen/paracetamol or a non-steroidal anti-inflammatory drug (NSAID). When NSAIDS are used over a prolonged period gastroprotection is recommended (Table 1).

treatment of moderate pain (WHO level II analgesics)
Traditionally, patients with moderate pain have been treated with a combination product containing acetaminophen, aspirin or a NSAID plus an opioid for moderate pain such as codeine, dihydrocodeine, tramadol or propoxyphene or a strong opioid at low doses such as morphine or oxycodone. The doses of these combination products can be increased until their maximum dose is attained (e.g. 4000 mg acetaminophen and 240 codeine). Recent years have witnessed the proliferation of new opioid formulations that may improve the convenience of drug administration for patients with moderate pain. These include controlled release formulations of codeine, dihydrocodeine and tramadol in dosages appropriate for moderate pain. Additional options include low doses of buprenorphine.

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. Transdermal fentanyl is best reserved for patients whose opioid requirements are stable. It is usually the treatment of choice for patients who are unable to swallow, patients with poor tolerance to morphine and patients with poor compliance. Methadone is an alternative but may be more complicated to use because of marked inter-individual differences in its plasma half-life and duration of action. Methadone use should be initiated by physicians with experience and expertise in its use. Worries regarding an inferior equipotency ratio of buprenorphine to oral morphine or of a ceiling effect and partial antagonistic effects of buprenorphine as compared to fentanyl have not been substantiated by newer publications. Strong opioids may be combined with ongoing use of a level I agent.

Patients presenting with severe pain that need urgent relief should be treated with parenteral opioids, usually administered by the intravenous or subcutaneous route. Intramuscular
injections are themselves painful and have no pharmacokinetic advantage.

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 ~10% of the total daily dose. If more than four ‘breakthrough doses’ per day are necessary, the baseline opioid treatment with a 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. However, since some of the side effects may be caused by accumulation of toxic metabolites, switching to another opioid agonist and/or another route may allow

<table>
<thead>
<tr>
<th>Substance</th>
<th>Widesly available forms and strengths</th>
<th>Time to onset (min)</th>
<th>Caution</th>
<th>Maximal daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophene</td>
<td>Tablets, suppositories 500–1000 mg</td>
<td>15–30</td>
<td>Hepatotoxicity</td>
<td>4–6 x 1000 mg</td>
</tr>
<tr>
<td>(paracetamol)</td>
<td>Tablets 500–1000 mg</td>
<td>15–30</td>
<td>GL toxicity, allergy, platelet inhibition</td>
<td>3 x 1000 mg</td>
</tr>
<tr>
<td>Acetylsalicyc acid</td>
<td>Tablets 200–400–600 mg, tablets 800 mg retarded, topic gels</td>
<td>15–30–120</td>
<td>GL and renal toxicity</td>
<td>4 x 600 mg, 3 x 800 mg retarded</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Tablets 25–75 mg, tablets 100–150–200 mg retarded</td>
<td>~30</td>
<td>GL and renal toxicity</td>
<td>4 x 75 mg, 2 x 200 mg</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Tablets 25–50–75 mg, tablets 100 mg retarded</td>
<td>30–120</td>
<td>GL and renal toxicity</td>
<td>4 x 50 mg, 2 x 100 mg</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Capsules 250–500 mg</td>
<td>~30</td>
<td>GI and renal toxicity</td>
<td>4 x 500 mg</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>Tablets 250–375–500 mg</td>
<td>~30</td>
<td>GI and renal toxicity</td>
<td>2 x 500 mg</td>
</tr>
</tbody>
</table>

GI, gastrointestinal; WHO, World Health Organization.

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

Table 2. Comparison of selected opioids for mild to moderate pain (WHO level II)

Table 3. Comparison of selected opioids for moderate to severe pain (WHO level III: may be combined with level I medication)

WHO, World Health Organization.

*aThe maximal dose depends from tachyphylaxis.

*bCalculated with conversion from mg/day to µg/h.

*cNot usually used as first opioid (the 12 µg/h dose corresponds to 30–60 mg of oral morphine sulfate daily).

*dFactor 4 for daily morphine doses <90 mg, factor 8 for doses 90–300 mg, and 12 for >300 mg
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.

**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. Limited evidence supports the use of subanesthetic doses of ketamine, an NMDA antagonist, in intractable pain.

Neuropathic pain caused either by tumor infiltration or due to paraneoplastic or treatment-induced polyneuropathy may not be adequately controlled by opioids alone. Combination with co-analgesics as listed in Table 4 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 antidepressive or neuroleptic psychoactive drugs or anti-epileptic drugs in case of neuropathic pain. Steroids should be considered in case of nerve compression. There is sufficient evidence for use of bisphosphonates for refractory bone pain but not for general use as first line therapy of bone pain.

**note**

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

**literature**


Table 4. Selected co-analgesics

<table>
<thead>
<tr>
<th>Substance</th>
<th>Widely available forms and strengths</th>
<th>Activity</th>
<th>Sedation</th>
<th>Range of daily doses (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitryptiline</td>
<td>Tablets 25–50 mg</td>
<td>Antidepressive</td>
<td>+++</td>
<td>50–200</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Tablets 10–75 mg</td>
<td>Antidepressive</td>
<td>(+)</td>
<td>50–200</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Tablets 10–25 mg</td>
<td>Antidepressive</td>
<td>+</td>
<td>50–225</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Tablets 20 mg</td>
<td>Antidepressive</td>
<td>+</td>
<td>20–80</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Drops, tablets, vials</td>
<td>Neuroleptic</td>
<td>+</td>
<td>25–200</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Drops, tablets, suppositories, vials</td>
<td>Neuroleptic</td>
<td>++</td>
<td>100–1600</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Tablets 200–400 mg</td>
<td>Antiepileptic</td>
<td>+</td>
<td>900–3600</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Tablets 200–300–400–800 mg</td>
<td>Antiepileptic</td>
<td>+</td>
<td>10–15mg</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Tablets 25–50–75–100–150–200–300 mg</td>
<td>Antiepileptic</td>
<td>+</td>
<td>15–600</td>
</tr>
</tbody>
</table>