Multidisciplinary pain management in patients with cancer

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Chair Comprehensive Center of Excellence in Pain Practice, EPP – WIP (2014)
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Motivators / Disclosures of Kris Vissers

• Full time chair- and professorship at the Radboudumc University Nijmegen Medical Center, the Netherlands
• Member of national taskforces for chronic pain and palliative care of the ministry of health
• Immediate Past President of WIP
• President of Dutch IASP Chapter: PA!N

• No industry payed relationships
• No honoraria for lecturing

• Only independent research grants from KWF, ZonMw, NWO, EU-FP7, H2020, Medtronic, Grunenthal
Overview of this Refresher Course

• Historical perspectives on oncological pain treatment
• Pain is an important symptom in oncological states
• Cancer pain is not systematically evaluated
• Cancer pain & Quality of life
• High Evidence that Cancer pain treatment is effective
• Cancer Pain Management is complex!
• Minimal invasive procedures for cancer pain
Historical perspectives on oncological pain treatment
A special thank you to
Dame Cicely Saunders

You matter because you are you,

And you matter to the end of your life.

We do all we can

Not only to help you die peacefully,

But also to live

Until you die.
Pain: important symptom in oncological states
Pain: important symptom in oncological states

- Pain is most prominent symptom in oncological states
- Present in
  - 30 – 40 % of cases on diagnosis
  - 40 – 70 % of cases during treatment
  - 70 – 90 % of cases in terminal (supportive) care
- Also present in survivors!
Early in the course of the disease!
Most prevalent symptom in primary care!

**FIG. 1.** Symptom burden across PPS trajectory.
Prevalence of cancer pain

1a: anticancer treatment (> 6 m), curative
1b: anticancer treatment (< 6 m), curative
2: palliative anticancer therapy
3: treatment no longer possible

M. Van den beuken, Pain, 2007
Prevalence of cancer pain per tumor

M. Van den beuken, Pain, 2007
The WHO three step ladder:

<table>
<thead>
<tr>
<th></th>
<th>1a (n = 374) n (%)</th>
<th>1b (n = 375) n (%)</th>
<th>2 (n = 559) n (%)</th>
<th>3 (n = 75) n (%)</th>
<th>Total (n = 1383) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PMT(^b)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insufficient</td>
<td>154 (41)</td>
<td>183 (48)</td>
<td>226 (40)</td>
<td>18 (24)</td>
<td>581 (42)</td>
</tr>
<tr>
<td><strong>Medication(^c)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO 1</td>
<td>48 (13)</td>
<td>42 (11)</td>
<td>79 (14)</td>
<td>33 (44)</td>
<td>202 (15)</td>
</tr>
<tr>
<td>WHO 2</td>
<td>9 (2)</td>
<td>16 (4)</td>
<td>39 (7)</td>
<td>14 (19)</td>
<td>78 (6)</td>
</tr>
<tr>
<td>WHO 3</td>
<td>9 (2)</td>
<td>11 (3)</td>
<td>41 (7)</td>
<td>34 (45)</td>
<td>95 (7)</td>
</tr>
<tr>
<td>Co-analgesics</td>
<td>19 (5)</td>
<td>23 (6)</td>
<td>35 (6)</td>
<td>18 (24)</td>
<td>95 (7)</td>
</tr>
</tbody>
</table>
Cancer pain is not systematically evaluated!
Pain is not Systematically Registered in Dutch Medical Oncology Outpatients

Nienke D. te Boveldt, MSc*; Myrrha J.F.J. Vernooij-Dassen, PhD†,‡; Anne Jansen, BSc*; Kris C.P. Vissers, MD, PhD, FIPP*; Yvonne Engels, PhD*

*Anaesthesiology, Pain and Palliative Medicine Department, Radboud University Nijmegen Medical Centre (RUNMC), Nijmegen; †IQ Healthcare Department, Department of Primary and Community Care, Radboud University Nijmegen Medical Centre (RUNMC), Nijmegen; ‡Kalaroma Foundation, Beek-Ubbergen, The Netherlands
Pain registration in 6 oncological outpatient departments

Figure 2. Pain registration by hospital. See additional file. (□) No pain registration. (■) Registration of a nonspecific symptom description. (▲) Registration of pain or its absence. *Chi-square test significant at $P < 0.05$ (two-sided); F, academic medical center vs. A to E, nonacademic medical center ($P = 0.00$).

Figure 3. Pain registration by consultation. See additional file. (□) No pain registration. (■) Registration of a nonspecific symptom description. (▲) Registration of pain or its absence. *Chi-square test significant at $P < 0.05$ (two-sided); Difference between consultations $P = 0.01$. 

teBoveldt N & Vissers K, Pain Practice 2014 

Radboudumc
Cancer pain & Quality of life!
Pain prevalence in ambulatory oncological patients:

Pain and Its Interference with Daily Activities in Medical Oncology Outpatients

Nienke te Boveldt, MSc¹, Myrra Vernooij-Dassen, PhD², Nathalie Burger, BSc¹, Michiel IJsseldijk, BSc¹, Kris Vissers, MD, PhD¹, and Yvonne Engels, PhD¹

Background: Pain prevalence at various stages of cancer ranges from 27% to 60% for outpatients. Yet, how pain is managed in this patient group is poorly understood.

Objectives: The primary objective was to assess pain prevalence and intensity, and its interference with daily activities, in medical oncology outpatients. The secondary objectives were the adequacy of analgesic pain treatment and to identify independent predictors for moderate to severe pain.
1a Patients without pain (NRS 0) (N=260)

1b Patients with mild pain (NRS 1-4) (N=84)

1c Patients with moderate pain (NRS 5-6) (N=42)**

1d Patients with severe pain (NRS 7-10) (N=40)

No interference (0)
A little interference (1-4)
Quite a bit interference (5-6)
Very much interference (7-10)

Note: Pain intensity categories used were adapted from the Dutch guideline: Pain in patients with cancer (28).
*Includes households. ** Data was missing on one patient (Patient was excluded from figures). NRS = Numeric Rating Scale

Fig. 1. Pain related interference with daily activities of patients with cancer by pain intensity category (%)
Analgesic pain treatment in relation to pain severity:

![Bar chart showing analgesic treatment in relation to pain severity](image)

- No pain: 86%
  - No analgesic: 9%
  - Non-opioid: 2%
  - Weak opioid: 3%
  - Strong opioid: 3%
- Mild pain: 50%
  - No analgesic: 14%
  - Non-opioid: 7%
  - Weak opioid: 12%
  - Strong opioid: 6%
- Moderate pain: 46%
  - No analgesic: 8%
  - Non-opioid: 35%
  - Weak opioid: 19%
  - Strong opioid: 6%
- Severe pain: 38%
  - No analgesic: 12%
  - Non-opioid: 29%
  - Weak opioid: 38%
  - Strong opioid: 38%

*Fig. 2. Analgesic pain treatment in relation to pain severity.*

Note: Analgesic pain treatment categories adapted from WHO categories.
What is quality of life?

Medical progress retunes a lot of diseases from terminal to chronic diseases.

Improving the quality of life of this prolongation of life seems to be much more difficult.
High Evidence cancer pain treatment is effective!
Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer

Early Palliative Care for patients with metastatic non-small-lung cancer

Hads and Patient Health Questionnaire

Kaplan-Meier curve

Temel, August 2010, NEJM
Can we prove that palliative care is useful?

Palliative Care — A Shifting Paradigm
Amy S. Kelley, M.D., M.S.H.S., and Diane E. Meier, M.D.

Despite the increasing availability of palliative care services in U.S. hospitals and the body of evidence showing the great distress to patients caused by symptoms of the illness, the burdens on family caregivers, and the overuse of costly, ineffective therapies during advanced chronic illness, the use of palliative care services by physicians for their patients remains low. Physicians tend to perceive palliative care as the alternative to life-prolonging or curative care — what we do when there is nothing more that we can do — rather than as a simultaneously delivered adjunct to disease-focused treatment.
Cancer Pain Management is complex!
Different populations of patients with cancer

Cancer disease trajectory

- Remission
- Cure
- Survivorship
- Relapse
- Chronic pain in survivors

Treatment related pain
Unrelated pain
Metastatic Disease pain
End of life pain

Adapted from Ahmedsai S, Pain Medicine, 2012
Different populations of patients with cancer

Screening
Evaluation
Self empowerment
Telemedicine

Remission
 Cure
survivorship
relapse

Chronic pain in survivors

Pain specialist – nurse (specialist)

Cancer disease trajectory

Treatment related pain
Unrelated pain
Metastatic Disease pain
End of life pain
The consequences of implementing suboptimal treatment are far-reaching; therefore, effective treatment methods are in a great demand.

The face of cancer pain management has changed in considerable ways, and **interventional procedures** have become an integral part of providing multimodal analgesia in cancer pain treatment.

The previous WHO pain treatment algorithm has been modified to include **interventional pain treatment** modalities that can be opioid sparing.
Management of cancer pain

Increasing pain

WHO step I: peripheral analgesics
- Role of co-analgesics
- Opioid induced neurotoxicity

WHO step II: Weak opioids
- Side effects

WHO step III: Strong opioids

Interventional pain management
Pain Specialists need more integrated expertise!

- Targeted (immuno) therapy dramatically changed oncological care!

- Not only are the responses to the combination of these approaches under evaluation; but is also of great interest to find the appropriate dose, timing and best sequence of them in order to achieve successful results. Not to forget that the intensification of the response might lead to higher toxicity.
Complications of Treatment

The role of drug-drug interactions in prostate cancer treatment: Focus on abiraterone acetate/prednisone and enzalutamide

Abiraterone metabolism: CYP3A4
- CYP450 isoforms inhibited by abiraterone: 1A2, 2C8, 2D6, 2C9, 2C19
- CYP substrates at risk of abiraterone-DDIs:
  + Analgesics (e.g., hydrocodone, codeine)
  + Antidepressants (e.g., venlafaxine)
  + Cardiovascular drugs (e.g., metoprolol)
  + Antidiabetics (pioglitazone)
  + Lipid-lowering drug (atorvastatin)

Enzalutamide metabolism: CYP2C8
- CYP450 isoforms induced by enzalutamide: 3A4, 2D6, 2C9, 2C19
- CYP substrates at risk of enzalutamide-DDIs:
  + Immunosuppressants (e.g., sirolimus)
  + HIV antivirals (e.g., atazanavir)
  + Anticoagulants (e.g., rivaroxaban)
  + Antiplatelet drugs (e.g., clopidogrel)
  + CNS drugs (fentanyl, pimozide, midazolam)

Drug concentration

Inhibition of drug metabolism

No DDI

Induction of drug metabolism

Time
Sparse to no knowledge about:

- Interactions between different oncological and pain / palliative care treatments

- Interactions between all these treatments and effect on metabolisation, toxicological effect, Cytochroom p-450, glycoproteins

- Responses of different tumor diagnosis and pharmacological profiles (PK and dynamic) of analgesics

- Interaction between multidimensional treatments and quality of life

Westdorp & Vissers, JPSM, 2018
### Integrated Expertise – oncological pain treatment

**Table 2 (continued)**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>CYPs (main pathways in bold)</th>
<th>Active metabolite</th>
<th>DDIs ABI-P</th>
<th>DDIs ENZA</th>
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<tbody>
<tr>
<td>Inflammation and pain</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylsalicylic acid [144]</td>
<td>2C9</td>
<td>No</td>
<td></td>
<td></td>
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<tr>
<td>Buprenorphine [145]</td>
<td>3A4</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codeine [62]</td>
<td>2D6, 3A4, 2D7</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Etoricoxib [146]</td>
<td>3A4, 2C9, 2D6</td>
<td>No</td>
<td></td>
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<tr>
<td>Fentanyl [105]</td>
<td>3A4</td>
<td>No</td>
<td></td>
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<tr>
<td>Hydrocodone [58]</td>
<td>2D6</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibuprofen [8]</td>
<td>2C9</td>
<td>No</td>
<td></td>
<td></td>
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<tr>
<td>Meloxicam [147]</td>
<td>2C9, 3A4</td>
<td>No</td>
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<tr>
<td>Methadone [148]</td>
<td>3A4, 2B6, 2C19, 2C9, 2D6</td>
<td>No</td>
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<tr>
<td>Morphine [59]</td>
<td>2D6 (minor)</td>
<td>No</td>
<td></td>
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<tr>
<td>Nimesulide [149]</td>
<td>1A2, 2C9</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Oxycodone [150]</td>
<td>2D6, 3A4</td>
<td>Yes</td>
<td></td>
<td></td>
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<tr>
<td>Paracetamol [151]</td>
<td>2E1, 3A4 (production of toxic metabolite NAPQI)</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Enzalutamide treatment =
  Do not give: fentanyl – methadone – oxycodone - paracetamol

Higher metabolism = inductor
Integrated management for cancer pain
Standards for the management of cancer-related pain across Europe

• 10 standards formulated by an EFIC taskforce are aimed:
  
• To improve cancer pain management
• Reduce variation in practice across Europe
• Promotion of the quality of care of patients
• Reduce unnecessary suffering

Grade definitions of recommendations & evidence:
1A strong: high quality
1B strong: moderate quality
1C: strong: low quality
2A: weak: high quality
2B: weak: moderate quality
2C: weak: low quality
EFIC Taskforce recommendations using grade

• Patients with a history of cancer should be routinely screened for pain at every engagement with a health care professional (1B)

• Patients identified with cancer-related pain should receive a pain assessment when seen by a healthcare professional, which at a minimum classifies the cause of pain based on proposed ICD-11 taxonomy and establishes the intensity and impact on quality of life of any pain that they report (1B)

• A multimodal pain management plan should be agreed with the patient that explains the causes of their pain and its likely prognosis, the need for further investigations, the multimodal treatment options and includes the patient’s preferences and goals of treatment (1C)
EFIC Taskforce recommendations using grade

• **Patients should receive tailored multimodal treatment** which reduces the pain and its impact on daily living and that may include a combination of medicines, non-pharmacological treatments, oncological interventions, physical rehabilitation and psychosocial or spiritual support *(1A)*

• **Support and advice for self-management should be provided** *(1A)*

• **The pain management plan should be reviewed regularly** to assess outcomes and plan longer-term care *(1B)*

• **Patients should be referred for more specialist advice and treatment** if pain is not improving or if they are experiencing intolerable side-effects *(1C)*
EFIC Taskforce recommendations using grade

• Healthcare professionals who treat patients with cancer should receive ongoing education and training in order to undertake basic pain assessment, initiate basic management, and learn about correctly referring for more specialist support (1C)

• Regular review of service outcomes for all patients with cancer pain should be in place (1C)

• Each Efic Chapter should have national evidence or consensus based guidelines in place for cancer-related pain (1C)
Minimal invasive procedures for cancer pain
EVIDENCE-BASED MEDICINE
Evidence-Based Interventional Pain Medicine According to Clinical Diagnoses

23. Pain in Patients with Cancer

Kris C. P. Vissers, MD, PhD, FIPP*; Kees Besse, MD, FIPP*; Michel Wagemans, MD, PhD†; Wouter Zuurmond, MD, PhD‡; Maurice J.M.M. Giezeman, MD, PhD§; Arno Lataster, MSc¶; Nagy Mekhail, MD, PhD, FIPP**; Allen W. Burton, MD, FIPP††; Maarten van Kleef, MD, PhD, FIPP‡‡; Frank Huygen, MD, PhD, FIPP§§
Early initiation of intrathecal pain management in patients with recurrent vulvar carcinoma and refractory pain:

• Recurrent vulvar carcinoma tends to spread locally before widespread metastases occur and like most incurable cancers, pain control is often the most difficult issue.

• Early initiation of preventive ITC placement with external pump

• Resulted in:
  • Optimal pain control hence transfer possible to home situation
  • Clinical observation of
    • Spontaneous wound repair
    • Delayed metastasis

S.E. Poulino, T.C. Besse, K.C.P. Vissers,
World Congress on gynecological oncology, 1014
Conclusions: Take home messages

• Pain is highly prevalent in patients with cancer
• Patients don`t report spontaneously about their pain
• Medical specialists don`t explore or measure pain
• Multi-/interdisciplinaire approach should be offered
• Interventional pain management is unknown for medical oncologists
• Early initiation of pain management improves general outcome:
  move forward towards the oncologist
Recommendations on cancer pain: how to start?

- Introduce a multidimensional diagnosis and treatment program for cancer pain
- Standardize, register and deliver accreditation to best practices
- Install follow-up programs measuring outcome
- Introduce special education & training programs for professionals
- Repeat prospective trials (survivors versus non survivors)
- Improve your databanking & ICT monitoring tools

Vissers et all: National Taskforce on the future on Pain in the Netherlands
SAVE THE DATE!

August 4-8, 2020  Amsterdam, the Netherlands