GUIDELINES ON PERIPHERAL NEUROPATHY

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Benign paroxysmal positional vertigo
PERIPHERAL NEUROTOXICITY
Chemotherapy induces polyneuropathy (CIPN)

- 30-40% of patients receiving cancer treatment suffer from chronic CIPN
- depends on chemotherapeutic agent, dose administered and therapy schedule

Individual risk factors:
  - age
  - preexisting neuropathy
  - genetically determined factors

<table>
<thead>
<tr>
<th>CIPN Incidence</th>
<th>Cisplatin</th>
<th>Oxaliplatin</th>
<th>Vincristin</th>
<th>Paclitaxel</th>
<th>Bortezomib</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 - 68%</td>
<td>68 - 92%</td>
<td>41 - 91%</td>
<td>57 - 82%</td>
<td>36 - 64%</td>
<td>36 - 64%</td>
</tr>
<tr>
<td>7 - 21%</td>
<td>12 - 39%</td>
<td>- 30%</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

*CTCAE Common terminology criteria for Adverse Events

Park, Goldstein et al. 2013, Staff, Grisold et al. 2017
FIGURE 1. Depiction of the Typical “Glove-and-Stocking” Distribution of Chemotherapy-Induced Peripheral Neuropathy (CIPN) Symptoms With Putative Targets for CIPN Toxicity in the Peripheral Nervous System Depicted From the Dorsal Root Ganglion to Axon and Axonal Components (Myelin, Microtubules, Mitochondria, Ion Channels, and Vascular Network) and the Distal Nerve Terminals.
## CIPN – CLINICAL SIGNS

### Sensory

<table>
<thead>
<tr>
<th>Damage of</th>
<th>Examples</th>
<th>Minus Symptoms</th>
<th>Plus Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large fibres</td>
<td>Cisplatin</td>
<td>Decreased <strong>vibration sense</strong></td>
<td>tingling</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased <strong>proprioception</strong></td>
<td>pins &amp; needles</td>
</tr>
<tr>
<td>Small fibres</td>
<td>vinca alcaloids</td>
<td>Decreased <strong>pain and temperature</strong> sensation</td>
<td>permanent burning, lancinating pain jabbing pain</td>
</tr>
<tr>
<td></td>
<td>taxans</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>thalidomide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>bortezomib</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Remember: Only „plus symptoms may be pharmacologically treated“

Small fibres: C (Heat), Aδ (Cold), both pain fibres form Tractus spinothalamicus anterior

Finnerup, Attal et al. 2015
## CIPN – CLINICAL SIGNS

### Motor

<table>
<thead>
<tr>
<th>Minus Symptoms</th>
<th>Plus Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>(distal) Weakness</td>
<td>Fasciculations</td>
</tr>
<tr>
<td>Hypo- to areflexia</td>
<td>Cramps</td>
</tr>
<tr>
<td>Atrophy</td>
<td></td>
</tr>
<tr>
<td>Deformity, e.g. pes cavus</td>
<td></td>
</tr>
</tbody>
</table>

*Fig. 3. The neurotic form of muscular atrophy. Feet and legs (not thighs) involved.*
## CIPN – CLINICAL SYMPTOMS

### Autonomic

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Vincristin, Bortezomib, Thalidomide</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>Bortezomib</td>
</tr>
<tr>
<td>Reduced heart rate variability</td>
<td>Many…</td>
</tr>
<tr>
<td>Disturbance of bladder</td>
<td></td>
</tr>
<tr>
<td>Delayed gastric emptying</td>
<td>Bortezomib</td>
</tr>
</tbody>
</table>
CIPN – CLINICAL EXAMINATION

Sensory
- Asking for positive symptoms (burning, tingling, shooting)?
- Numbness in hand and feet?
- Evoked pain? Pin prick hyperalgesia?
  - Cold induced hyperalgesia
  - Dynamic: moving on skin
- Proprioception sense

Sensory ataxia?

- Cotton applicator
- Toothpick
- Ice pack
- Cotton applicator
- Tuning fork

Romberg, walking on line or blind
CIPN – CLINICAL EXAMINATION

Motor

- Ankle jerks reduced?
- Walking on heels and toes

- Atrophy of small foot and hand muscles (Extensor digitorum brevis)

Figure 1: Normal extensor digitorum brevis in a healthy individual
CIPN – NEUROPHYSIOLOGY (1)

Reduction of sensible nerve action potential amplitude (SNAP) = Axonal damage
But pitfalls: Stimulation artefacts, edema

Kandula, Farrar et al. 2017
Electromyography may verify

- Axonal damage in motor fibres
- Denervation

EMG is not needed in typical CIPN patients
### CIPN – CLINICAL CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Pain</th>
<th>Sensory</th>
<th>Motor</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>(+)</td>
<td>+++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>+++*</td>
<td>+++</td>
<td>+</td>
<td>*90 % acute hyperexcitability: dysaesthesia, cramps, fasciculations</td>
</tr>
<tr>
<td>Vincristin</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>foot drop, wrist extensors at high doses</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>Acute musculoskeletal pain syndrom 60 %</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Ixabepilone</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Thalidomide</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Brentuximab Vedotin</td>
<td>(+)</td>
<td>++</td>
<td>++</td>
<td></td>
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</table>

+++ frequently (> 20 %), ++ occasionally (10-20 %), + rare (< 10 %)

Miltenburg and Boogerd 2014
### Contents of the EORTC QLQ-CIPN20

**Sensory scale (9 items)**
- Tingling
- Numbness
- Pain
- Instability when walking or standing
- Distinguishing temperature
- Hearing

**Motor scale (8 items)**
- Cramps
- Writing
- Manipulating small objects
- Weakness

**Autonomic scale (3 items)**
- Vision
- Dizziness after changing position
- Erection disorder
Guidelines on peripheral neuropathy
ANTICANCER THERAPY-INDUCED PERIPHERAL AND CENTRAL NEUROTOXICITY
ESMO/EONS/EANO Clinical Practice Guidelines for diagnosis, prevention, treatment and follow-up

To be published in 2019

https://www.esmo.org/Guidelines/Supportive-and-Palliative-Care
CIPN - PREVENTION

No prevention method nor agent have been identified

- Acetylcystein
- Amifostin
- Amitryptilin
- Carbamazepine
- Gluthatione (GSH)
- Vitamin E
- Nimodipine
- Calcium and Magnesium

Dose modification of chemotherapy as only preventive strategy (lowering dose, adaption of schedules)

Hershman, et al. 2014, Jordan et al. 2017
# NON PHARMACOLOGICAL INTERVENTION

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Comments</th>
<th>LOE/GOR</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acupuncture</td>
<td>(n = 48), outcome of electroacupuncture was worse than with sham acupuncture</td>
<td>II, E</td>
<td>Greenlee H, Breast Cancer R Treat 2016</td>
</tr>
<tr>
<td>Cryotherapy with e.g. frozen socks and gloves</td>
<td>Most evidence available for taxane therapy</td>
<td>II, B</td>
<td>Hanai A, J Natl Cancer Inst. 2018;110:141.</td>
</tr>
<tr>
<td>Compression therapy using surgical gloves</td>
<td>(n = 42), in the study additional drugs such as duloxetine were allowed</td>
<td>II, C</td>
<td>Tsuyuki S 2016</td>
</tr>
<tr>
<td>Exercise</td>
<td>Many early reports suggest a possible protective effect of exercise on CIPN</td>
<td>II, B</td>
<td>Kleckner IR, Support Care Cancer. 2018;26(4):1019</td>
</tr>
</tbody>
</table>
Non-pharmacological prevention of CIPN

CRYOTHERAPY
Cryotherapy
Cryotherapy - Prevention

- 36 Breast cancer patients
- Paclitaxel (cumulative dose 960 mg/m²)
- **Primary Endpoint:** Incidence of CIPN (Tactile-Sensory Deficits on the monofilament test)
  - Reduced objective and subjective symptoms of CIPN

Cryotherapy - Prevention

Patient Compliance ?!
MECHANISMS BASED PHARMACOLOGICAL TREATMENT OF NEUROPATHIC PAIN
CIPN TREATMENT – CONSIDER DRUG TREATMENT

You never treat only the nerve damage, but the patient.

Neuropathic pain may be aggravated by sleep disturbance, anxiety and depression.

There is central sensitisation of pain.

Lee, Jung et al. 2018
CIPN – PHYSICAL EXERCISE

Physical treatment is effective and should be focused on exercise of
• Distal motor skills
• Power and endurance of activity
• Body coordination and balance

Kleckner, Kamen et al. 2018
CIPN - TREATMENT

Physical exercises with a moderate level of evidence

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<tr>
<td>Physical exercise</td>
<td>Several strategies are available: eg. supervised medical exercise (sensorimotor function, endurance, strength of flexibility), self-management interventions (eg. EXCAP©®)</td>
<td>II, B</td>
<td>Kleckner 2018, Jordan 2017</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>mostly uncontrolled or underpowered studies</td>
<td>II, C</td>
<td>Franconi G, plement Altern Med 2013; Bao Euro J Cancer 2018</td>
</tr>
<tr>
<td>Scrambler therapy</td>
<td>Non-invasive cutaneous electrostimulation.</td>
<td>III, C</td>
<td>Pachman, D SCC 2015, Loprinzi ASCO 2018</td>
</tr>
<tr>
<td>Neurofeedback</td>
<td>pilot study in 71 cancer survivors, potential benefit for electroencephalogram (EEG)-based neurofeedback</td>
<td>II, C</td>
<td>Prinsloo S, J Pain Symptom Manage 2018</td>
</tr>
<tr>
<td>Self guided online cognitive</td>
<td>Proactive Self-Management Program for Effects of Cancer Treatment, pilot RCT (n = 60), greater improvements in “worst” pain than usual care</td>
<td>II, C</td>
<td>Knoerl 2018</td>
</tr>
<tr>
<td>Spinal cord stimulation</td>
<td>small number case series, only in truly refractory pain due to CIPN, invasive and expensive procedure: electrode insertion into the dorsal re-entry zone of spinal cord and pulse generator implantation under the skin</td>
<td>V, C</td>
<td>Majithia, N Oncology Journal 2016</td>
</tr>
</tbody>
</table>

**EXCAP©®**: Exercise for Cancer Patients, RCT randomized controlled trial
CIPN TREATMENT

Medical treatment: Duloxetine (recommendation grade 2 B)

- Dosing: 30 mg/d for one week, then 60 mg/d (120 mg possible)

According to treatment of neuropathic pain try to get relief of „plus-symptoms“ with membrane stabilising agents like

- Gabapentin/ Pregabalin
- Tricyclic antidepressants (Amitryptiline)

Local therapies:

- Topical baclofen, amitryptiline, ketamine (BAK)
- Topical low concentration menthol
- Capsaicin 8 %

Cavaletti and Marmiroli 2018
THERAPY OF CIPN: DULOXETIN

- Cross over, Phase III, n = 231, platinum derivates and taxanes
- Primary end product: Reduction of neuropathic pain (BPI)
- week 1: Duloxetin 30 mg, week 2: Duloxetin 60 mg

![Graph showing pain reduction results for Duloxetin and Placebo](image)

- Duloxetin (n=87) vs Placebo (n=94)
- Pain reduction ('any')
- 59% for Duloxetin vs 38% for Placebo
- Δ21% improvement

Remarkable Placebo effect

Smith EM., JAMA 2013
### PRACTICAL ASPECTS: RISK ASSESSMENT OF FALLING

Tofthagen 2012, 13*, expert opinion

<table>
<thead>
<tr>
<th>Risk assessment of falling, particularly in elderly patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Observe patients at the clinical setting e.g. walking pattern (gait) when entering a room.</td>
</tr>
<tr>
<td>• Use visual input to compensate for loss of lower extremity sensation in navigating changing terrain</td>
</tr>
<tr>
<td>• Patient reports losing balance</td>
</tr>
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</table>

Coasting phenomenon: worsening of symptoms after cessation of therapy, may last up to 3 months

Partial recovery with residual deficits in most pts. Drugs persisting in nerve axons after finishing therapy (paclitaxel) lead to ongoing toxicity

Improvement in neurophysiology is usually poor.

different grading scales for evaluation limit evaluation

sensory ganglion after ixapebilone

(Wozniak, Vornov et al. 2018)

Staff, Grisold et al. 2017
TAKE HOME MESSAGES

• CIPN is a dose limiting side effect in cancer therapies
• Diagnoses of CIPN can mostly be established in clinical examination
• No prevention is available at at the moment
• Duloxetin shows efficacy (moderate evidence)
• Diagnosis and treatment of CIPN should include functional parameters (anxiety, depression, sleep)
• Only „plus“ symptoms of sensory neuropathy can be treated
• Spectrum of central toxicity has widened and includes immune mediated processes in new cancer therapy agents