Preventing and managing neurotoxicity by oncologists and neurologists

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Long-term side effects of systemic anticancer treatment

- More patients can be cured from malignant disease
- More long-term survivors
- Late side effects of anticancer treatment become more relevant

- Classical side effects of systemic anticancer treatment are manageable
  - Haematotoxicity with growth factors
  - Nausea/vomiting with 5-HT$_3$-antagonists
  - Nephrotoxicity by hydration
What makes the nervous system peculiar compared to other organs?
Areas of neurotoxicity

Neurotoxicity

Central nervous system
- brain
- spinal cord

Peripheral nervous system
- sensory
- autonomic
- motor
- Neuromuscular junction
- muscle
CNS-Neurotoxicity

**Acute**

- **Cytarabine**-related acute cerebellar syndrome
  - Purkinje cell death

- **Ifosfamide**-related metabolic encephalopathy

- Posterior reversible encephalopathy syndrome (PRES)

- **SMART** syndrome
  - Stroke-like migraine attacks after RT

**Chronic** (long-term survivors)

- Toxic **leukencephalopathy**
  - Radiotherapy (esp. WBRT)
  - High-dose methotrexate
  - Intrathecal and intraventricular Ctx

- „**Chemobrain“** , „**Chemo-fog““

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1 Dworkin et al., 1985
2 Sweiss et al., 2008
3 Fischer et al., 2017
4 Armstrong et al., 2014
1 Rimkus et al., 2014
2 Magge et al., 2015
3 Wang et al., 2015
# PNS-Neurotoxicity

## Acute
- Docetaxel-induced myalgia/arthralgia syndrome
  - musculoskeletal pain syndrome
- Oxaliplatin-induced neurotoxicity
  - cold intolerance, throat dyscomforth, cramps

## Chronic (long-term survivors)
- Sensory polyneuropathy
  - pain, ataxia, decreased dexterity
- Autonomic neuropathy
  - constipation, nausea, sexual dysfunction
- Cranial nerve neuropathy
  - dd: leptomeningeal disease
  - Vinca alkaloides

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1 Seguin et al., 2017
2 Avan et al., 2015
1 Magge et al., 2015
Questions addressed by the oncologist

- What is the etiology of the neurological symptoms?
- Has the neurological diagnosis any impact on my treatment strategy?
Considerations of the neurologist

- No pre-treatment neurological examination available
  - ...as usual..!

1. **Is there any direct association with the underlying malignancy?**
   - i.e. infiltration or metastasis

2. **Is there any indirect association with the malignancy?**
   - Paraneoplastic syndrome (vary rare !!!)
   - Infections, co-morbidities, vascular risk factors, pre-treatments

3. **Is there any association with current systemic treatment?**
Case reports

- 52 year old male
  - Esophageal cancer
  - 20 kg weight loss in 12 weeks
  - Neoadjuvant Ctx
    - Cisplatin, docetaxel, cetuximab
  - Bilateral foot drop syndrome

- 52 year old female
  - Metastatic breast cancer
  - 5 kg weight loss in 8 weeks
  - Chemotherapy
    - 8 cycle docetaxel
  - Bilateral burning feet syndrome
Chemotherapy-induced polyneuropathy (CIPN)

- **CIPN is a serious side effect of modern cancer treatment**

- 30-40% of cancer survivors suffer from CIPN \(^1,2,3\)

- Oxaliplatin-based CTx: 80% after two years \(^4\)

- **Acute toxicity (functional)**

- **Chronic toxicity (structural)**
CIPN – clinical presentation

**Type of polyneuropathy**

- Distal-symmetric
- Mostly lengths dependent
- Glove and stocking distribution
- Axonal-sensory

- Loss of vibration sense
- Loss of ankle jerks

**Negative symptoms**

- Numbness
- Gaint disturbance
- Trophic dysfunction
- Vegetative dysfunction

**Positive symptoms**

- Neuropathic pain
- Burning and tingeling
## Culprits of CIPN

<table>
<thead>
<tr>
<th>Drug group</th>
<th>1\textsuperscript{st} generation</th>
<th>2\textsuperscript{nd} generation</th>
<th>Mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platin compounds</td>
<td>Cisplatin</td>
<td>Carboplatin, Oxaliplatin</td>
<td>DNA-damage</td>
</tr>
<tr>
<td>Taxanes</td>
<td>Paclitaxel, Nab-paclitaxel</td>
<td>Docetaxel</td>
<td>Microtubuli stabilisation</td>
</tr>
<tr>
<td>Vinca alkaloides</td>
<td>Vincristine</td>
<td>Vinblastine, Vindesine</td>
<td>Mitotic spindel derangement</td>
</tr>
<tr>
<td>Proteasome inhibitors</td>
<td>Bortezomib</td>
<td>Carfilzomib</td>
<td>Reduced misfolded protein breakdown</td>
</tr>
<tr>
<td>Epothelione</td>
<td>Ixabepilone</td>
<td>-</td>
<td>Microtubuli stabilisation</td>
</tr>
<tr>
<td>Immun-modulators</td>
<td>Thalidomide</td>
<td>Lenalidomide</td>
<td>Anti-angiogenetic</td>
</tr>
</tbody>
</table>

- 1\textsuperscript{st} generation drugs are more neurotoxic than 2\textsuperscript{nd} generation drugs
CIPN - clinical consequences

- Cancer therapy is hampered by
  - Dose reduction
  - Treatment delay („stop and go“ strategy)
  - Treatment cessation
- Less effective cancer treatment!
- Less quality of life!
CIPN: risk factors (patient/drugs)

**Pre-existing diseases** Chaudry et al., 2003
- Alcoholic or diabetic polyneuropathy
- Pre-existing immunneuropathy
- Hereditary polyneuropathy

**Type of malignancy**
- Multiple myeloma, amyloidosis
- SCLC with paraneoplastic anti-Hu syndrome

**Prior exposure to neurotoxic agents**
- Recurrent disease, x-line therapy
- Secondary malignancy

**Age** Akerley et al., 2003
- Older patients carry a higher risk
- More comorbidities

**Cachexia** Hundsberger et al., 2014
- Systemic inflammation
- Catabolic state

**Drug-related factors**
- Type of drug
- Cumulative dose
- Dose intensity
- Combination therapies
- Route of administration
How do chemotherapeutic agents designed to destroy proliferative cells damage post-mitotic cells?

**Target: Dorsal root ganglion**

- DNA alkylation
- Apoptosis

- mtDNA alkylation
- Oxidative stress

- Disruption of axonal transport
  - Secondary „dying back PNP“
Coasting-phenomenon

- Increased neuropathic symptoms despite treatment cessation
  - 2-3 months after chemotherapy has stopped

- Problem: **Interference with second line chemotherapy**

- **Typically associated with platinium compounds**
  - Sublethal damage of dorsal root ganglia
  - Secondary apoptosis long after Ctx has stopped
Identification of risk factors before (!) application of chemotherapy is key in primary prevention of CIPN!
Prevention of CIPN by dose intensity and route of administration: Bortezomib in multiple myeloma

<table>
<thead>
<tr>
<th>Bortezomib ¹</th>
<th>2 x week</th>
<th>1 x week</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNP °1-4</td>
<td>46%</td>
<td>27%</td>
</tr>
<tr>
<td>Treatment cessation</td>
<td>15%</td>
<td>5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bortezomib ²</th>
<th>i.v.</th>
<th>s.c.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNP °1-4</td>
<td>53%</td>
<td>38%</td>
</tr>
<tr>
<td>PNP &gt;/= °2</td>
<td>41%</td>
<td>24%</td>
</tr>
<tr>
<td>PNP &gt;/= °3</td>
<td>16%</td>
<td>6%</td>
</tr>
</tbody>
</table>

¹Bringhen et al.; 2010
²Moreau et al.; 2011
CIPN – symptomatic treatment

- **Nortriptylin** (RCT, 100mg/d; 8 Wochen) Hammack 2002
- **Amitriptylin** (RCT, 50 mg/d; 8 Wochen) Kautio 2008
- **Gabapentin** (RCT, 2700 mg/d; 6 Wochen) Rao 2007
- **Lamotrigin** (RCT, 300 mg/d; 10 Wochen) Rao 2008
- **Topical gel** (RCT, 4 Wochen) NO6CA/Barton2011
  - Baclofen, Ketamin, Amitriptyline
- **Duloxetine** (RCT, 60 mg; 4 Wochen) Smith 2013
Case reports

**Compression neuropathy due to weight loss**

No consequences for treatment!

- 20 kg weight loss in 12 weeks
- Neoadjuvant Ctx
  - Cisplatin, docetaxel, cetuximab
- Bilateral foot drop syndrome

**CIPN**

Consequences for treatment!
- Dose modification
- Stop and go!
- Cessation

- Chemotherapy
  - 8 cycle docetaxel
- Bilateral burning feet syndrome
Learning points - CIPN

- CIPN is frequent and potentially dose-limiting
- No medical prevention available
- Drug-related factors can lower the risk of CIPN
  - Dosing, timing, route, intensity
- Watch out for risk factors!
Summary

· Prevention
  · take a good history

· Co-operation and shared care
  · challenge the neurologist to see the patient together with you!

· Use your own skills
  · knowledge of neuroanatomy
  · perform a good clinical and neurological examination