

Preventing and managing neurotoxicity by oncologists and neurologists

Thomas Hundsberger

Department of Neurology and
Department of Haematology/Oncology

Cantonal hospital St. Gallen
Switzerland



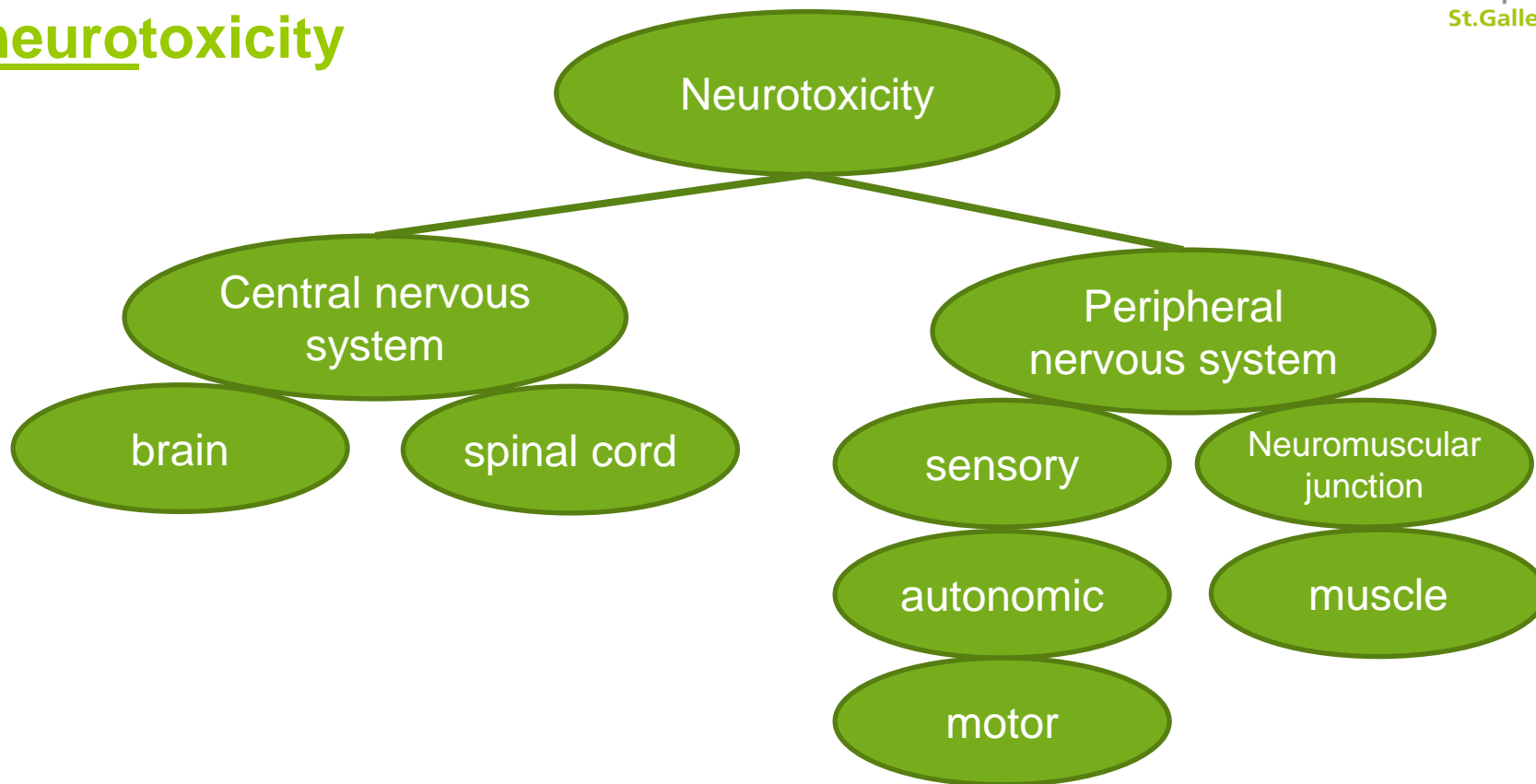
Long-term side effects of systemic anticancer treatment

- 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-HT₃-antagonists
 - Nephrotoxicity by hydration

What makes the nervous system peculiar
compared to other organs ?

Areas of neurotoxicity

Kantonsspital
St.Gallen



CNS-Neurotoxicity



Acute

- **Cytarabine**-related acute cerebellar syndrome
 - Purkinje cell death ¹
- **Ifosphamide**-related metabolic encephalopathy ²
- Posterior reversible encephalopathy syndrome (**PRES**) ³
- **SMART** syndrome ⁴
 - Stroke-like migraine attacks after RT

¹ Dworkin et al., 1985

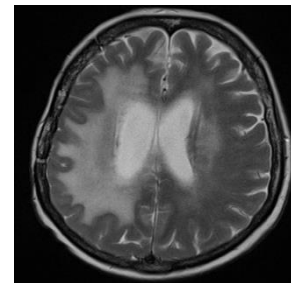
² Sweiss et al., 2008

³ Fischer et al., 2017

⁴ Armstrong et al., 2014

Chronic (long-term survivors)

- Toxic **leukencephalopathy** ¹
 - Radiotherapy (esp. WBRT)
 - High-dose methotrexate ²
 - Intrathecal and intraventricular Ctx
- „**Chemobrain**“ ³, „**Chemo-fog**“



¹ Rimkus et al., 2014

² Magge et al., 2015

³ Wang et al., 2015

PNS-Neurotoxicity

Acute

- Docetaxel-induced myalgia/arthralgia syndrome ¹
 - musculoskeletal pain syndrome
- Oxaliplatin-induced neurotoxicity ²
 - cold intolerance, throat discomfort, cramps

Chronic (long-term survivors)

- Sensory polyneuropathy
 - pain, ataxia, decreased dexterity
- Autonomic neuropathy ¹
 - constipation, nausea, sexual dysfunction
- Cranial nerve neuropathy ¹
 - dd: leptomenigeal disease
 - Vinca alkaloides

¹ Seguin et al., 2017

² Avan et al., 2015

Questions addressed by the oncologist

Kantonsspital
St.Gallen



quick

fast

immediate

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

Sure?

Serious?

Never heard of it?

Considerations of the neurologist

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

A large blue arrow pointing from the right towards the text 'Shared care !'.

Shared care !

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 femal**
- Metastatic breast cancer
- 5 kg weight loss in 8 weeks
- Chemotherapy
 - 8 cycle docetaxel
- Bilateral burning feet syndrome

Chemotherapy-induced polyneuropathy (CIPN)

Kantonsspital
St.Gallen



- **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)**

common

**impacts
quality of survival**

**only
partially reversible**

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
- Gait disturbance
- Trophic dysfunction
- Vegetative dysfunction

- **Positive symptoms**

- Neuropathic pain
- Burning and tingeling

Culprits of CIPN

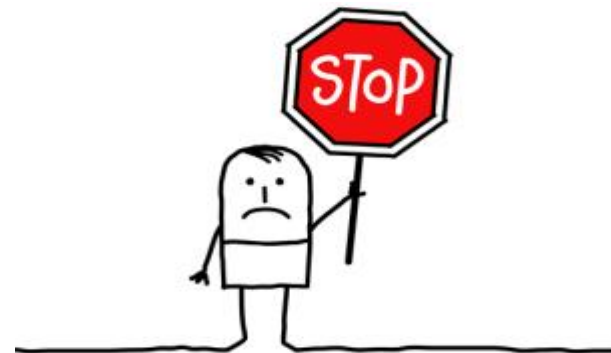


Drug group	1 st generation	2 nd generation	Mode of action
Platin compounds	Cisplatin	Carboplatin, Oxaliplatin	DNA-damage
Taxanes	Paclitaxel, Nab-paclitaxel	Docetaxel	Microtubuli stabilisation
Vinca alkaloides	Vincristine	Vinblastine Vindesine	Mitotic spindle derangement
Proteasome inhibitors	Bortezomib	Carfilzomib	Reduced misfolded protein breakdown
Epothelione	Ixabepilone	-	Microtubuli stabilisation
Immun-modulators	Thalidomide	Lenalidomide	Anti-angiogenetic

- 1st generation drugs are more neurotoxic than 2nd 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

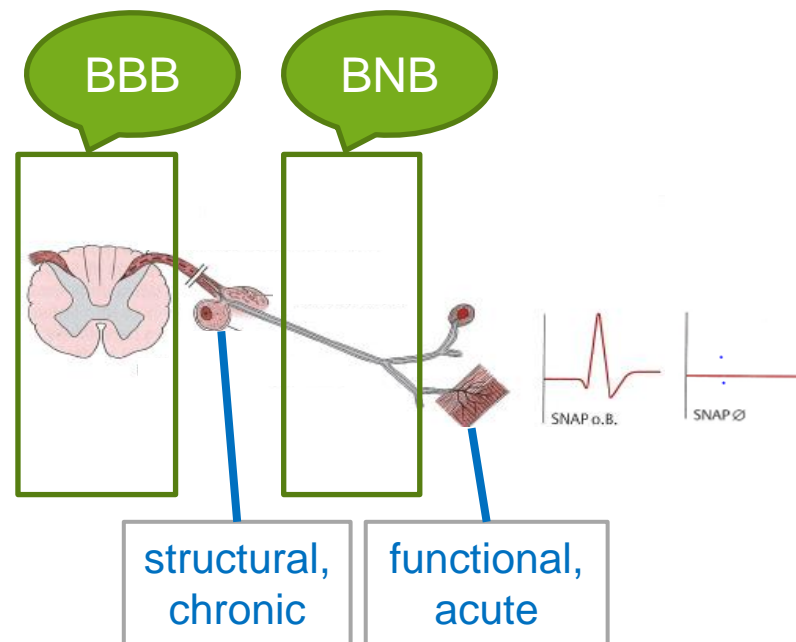
Drug-related factors

- 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

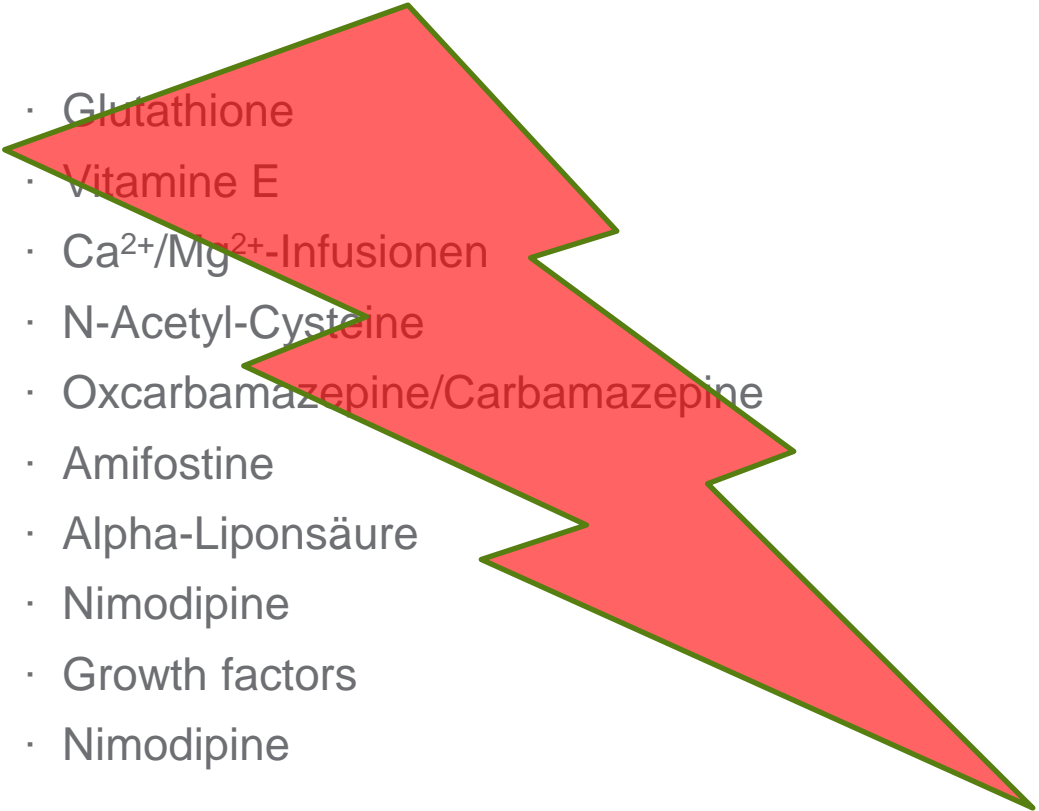
- DNA alkylation
 - Apoptosis
- mtDNA alkylation
 - Oxidative stress
- Disruption of axonal transport
 - Secondary „dying back PNP“



Coasting-phenomenon

- Increased neuropathic symptoms despite treatment cessation
 - 2-3 months after chemotherapy has stopped
- Problem: **Interference with second line chemotherapy**
- **Typically associated with platinum compounds**
 - Sublethal damage of dorsal root ganglia
 - Secondary apoptosis long after Ctx has stopped

CIPN - prevention

- 
- A large red lightning bolt with a green outline, pointing downwards and to the right, partially obscuring the list of prevention methods.
- Glutathione
 - Vitamine E
 - $\text{Ca}^{2+}/\text{Mg}^{2+}$ -Infusionen
 - N-Acetyl-Cysteine
 - Oxcarbamazepine/Carbamazepine
 - Amifostine
 - Alpha-Liponsäure
 - Nimodipine
 - Growth factors
 - Nimodipine

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

Kantonsspital
St.Gallen



Bortezomib ¹	2 x week	1 x week
PNP °1-4	46%	27%
Treatment cessation	15%	5%

Bortezomib ²	i.v.	s.c.
PNP °1-4	53%	38%
PNP >/= °2	41%	24%
PNP >/= °3	16%	6%

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