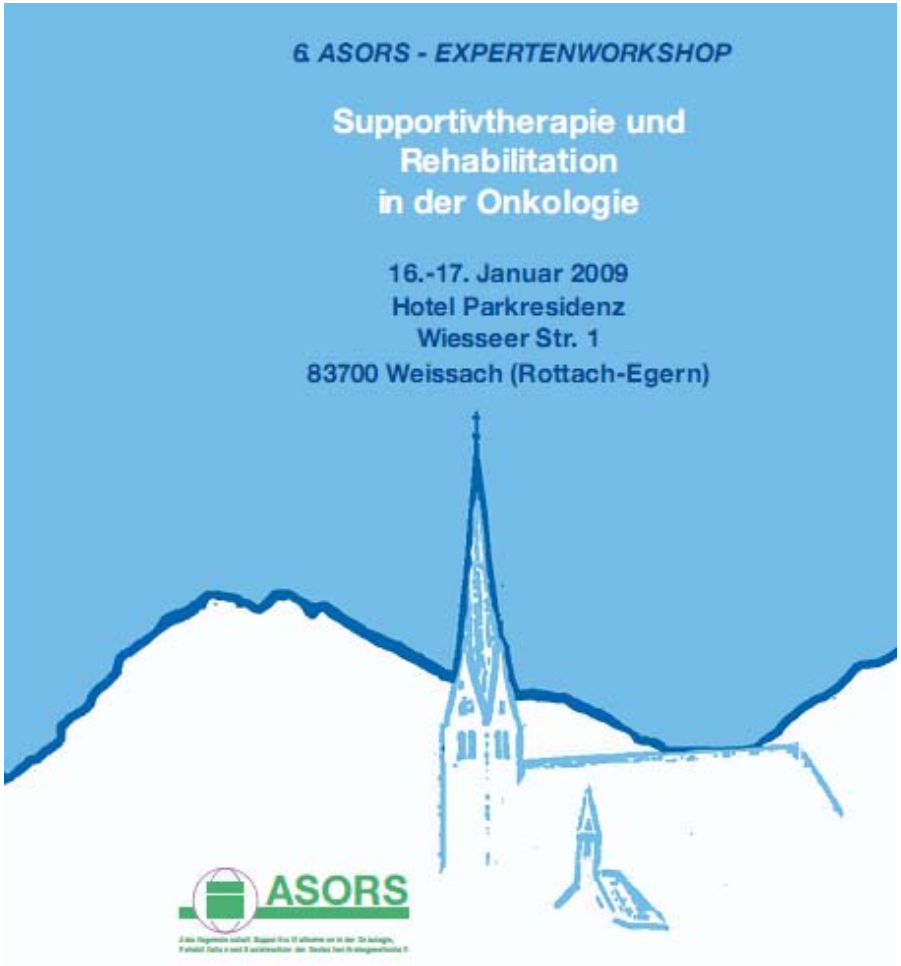
Neurotoxicity



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Classification

Chemotherapy-induced peripheral neurotoxicity (CIPN)

- a common dose-limiting toxicity of platinum compounds, taxanes and vinca alkaloids

Chemotherapy-induced central neurotoxicity (CICN)

- changes in cognitive function (“chemo-brain”) are a common complaint

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CIPN - Clinical presentation

- **Large fiber neuropathy**
  - **loss of vibration sense**
  - **loss of proprioception**
  - **loss of reflexes**
  - **muscle weakness**
- **Small fiber neuropathy**
  - **burning/lancinating pain**
  - **cutaneous hyperaesthesia**
  - **loss of pain and temperature senses**
  - **autonomic dysfunction**

Prevention of CIPN

- Usually dependent on dose intensity and cumulative dose
- Impairs functional capacity
- Sometimes persisting after efficient tumor therapy
- May progress after cessation of chemotherapy (“coasting”)
- Heterogeneity in the mechanism of nerve injury
- Wide variation in the resultant symptoms
- Identification of risk factors
- Reproducible and easy-to-use measurement scales

Neurotoxicity

Neuroprotectants

Acetyl-L-carnitine
Amifostine
$ACTH_{4-9}$
Alpha-lipoic acid
Vitamin E
Glutamine
Glutathione
Diethyldithiocarbamate
Erythropoietin
Calcium gluconate / Magnesium sulfate

General use of these agents cannot be recommended because of either inadequate positive or sufficient negative clinical trial data

Neurotoxicity

Platinum drugs

- This review identified 16 randomized controlled trials of five different potential neuroprotective therapies (amifostine, glutathione, Org 2766, diethyldithiocarbamate, vitamin E) including a total of 1,420 participants.
- Meta-analysis was possible for only a small number of measures in very few trials.
- The data from the trials were insufficient to conclude that any of the neuroprotective agents tested prevent or limit the neurotoxicity of platinum drugs.

Albers J et al. Cochrane review 2007

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Acetyl-L-carnitine

- present throughout the central and peripheral nervous system
- essential role in the oxidation of free fatty acids
- effective and well-tolerated in patients with diabetic neuropathy
- preliminary results on the effect of ALC in patients with paclitaxel and/or cisplatin-induced neuropathy

Important issues

- Neurotoxicity of combination chemotherapy
- Pre-existing neuropathy as a risk factor for CIPN
- Predictors of neurotoxicity
- Advanced age as a risk factor

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CICN

Potential underlying mechanisms include effects on

- blood-brain barrier permeability
- efficiency of cellular efflux pumps
- DNA damage
- telomere shortening
- alteration of cytokine regulation
- defects in neural repair
- oxidative stress

Kannarkat G et al. Curr Opin Neurol 2007

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Neurotoxicity

5-Fluorouracil

- acute neurotoxicity
  diffuse encephalopathy
  cerebellar syndrome
  dose-related and generally self-limiting
  DPD deficiency type (dihydropyrimidine dehydrogenase)
  5-FU catabolite type (fluoroacetate causing a transient hyperammonemia)

- incidence of 5-FU-induced encephalopathy in patients undergoing HD-5-FU chemotherapy 5.7 %

- prevalence of DPD gene variant 1 % in the general population but 25 % in affected patients

Kim, Y-A et al. Jpn J Clin Oncol 2006

Neurotoxicity

Cytarabine

- CNS prophylaxis in 31 patients with de novo ALL
- 5 patients experiencing a severe neurologic event (seizures, pseudotumor cerebri, coma, cauda equina syndrome) after i. th. liposomal cystarabine and hyper-CVAD
- drug exposure approximately 40 times longer compared with standard cytarabine
- incidence of grade 3-4 neurotoxicity 16 vs < 1 %

Jabbour E et al. Blood 2007

Neurotoxicity

take home message

Prevention of CIPN / CICN

- **Modification of drug regimens based on individual drug toxicity and pharmacokinetic characteristics**
- **To maintain efficacy while minimizing toxicity**
- **Supportive and symptomatic treatment is the mainstay of current management**
- **Pharmacogenetic approaches**

Neurotoxicity

take home message

Neuroprotection

- **lower incidence and severity of CX-induced neurotoxicity**
- **no interference with antitumor activity**
- **dose-escalation of chemotherapeutic agents**
- **transfer of preclinical data to the clinical setting**
- **randomized placebo-controlled clinical trials**