# MANAGEMENT OF NEUROPATHY

# DUE TO CANCER THERAPHY

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# WHAT İS NEUROPATHY

- Neuropathy or periferal neuropathy is define as condition arising from the demage and dysfunction of the peripheral nerves
  - Motor
  - Sensory
  - Autonomic nerves

- The major anotomic demarcation peripheral nervous system include
  - Nerve root
  - Plexus
  - Peripheral nerves

# WHAT İS NEUROPATHY

- Neuropathy is most common in people over age 55
- Prevalence is %3-4
- All level of the peripheral nervous system may be affected
- There are more than 100 known types

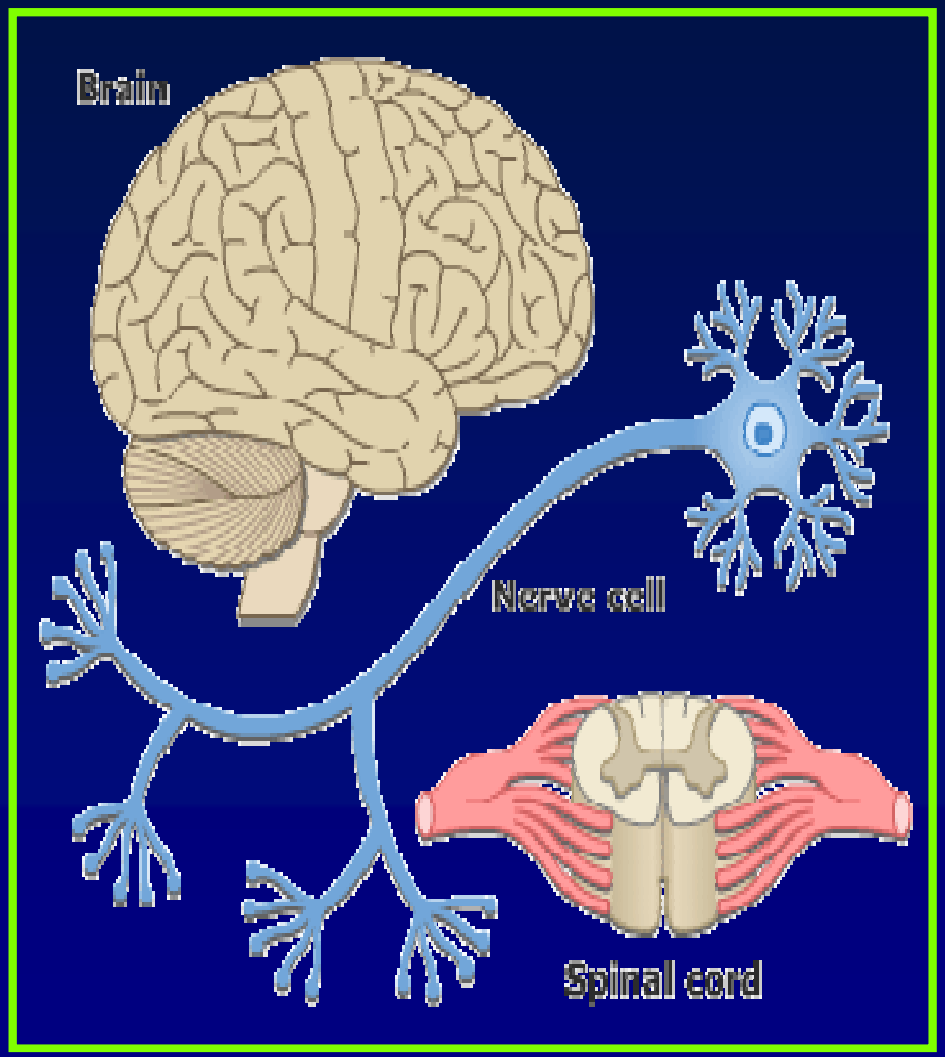
# WHAT İS NEUROPATHY

- About a third of cases are caused by diabets
- A third of cases are caused unknown
- Chemotherapy induced neuropathy can be variable, but often ranges from 30-40% of patients received chemotherapy
- CINP is a major dose limiting side effect of many chemotherapy agents

# Incidence increases with:

- Duration of infusion (longer infusion: increased chance)
- Previous exposure to neurotoxic drugs
- Combination chemotherapies (in which more than one neurotoxic drug is given)
- Co-morbidities

# Pathophysiology of CIPN




- The Peripheral Nervous System (PNS) communicates signals between the central nervous system (CNS) and the periphery of the body
- The peripheral nerves originate from the spinal cord

## Sensory nerves

- Pain
- Touch
- Temperature
- Position
- Vibration

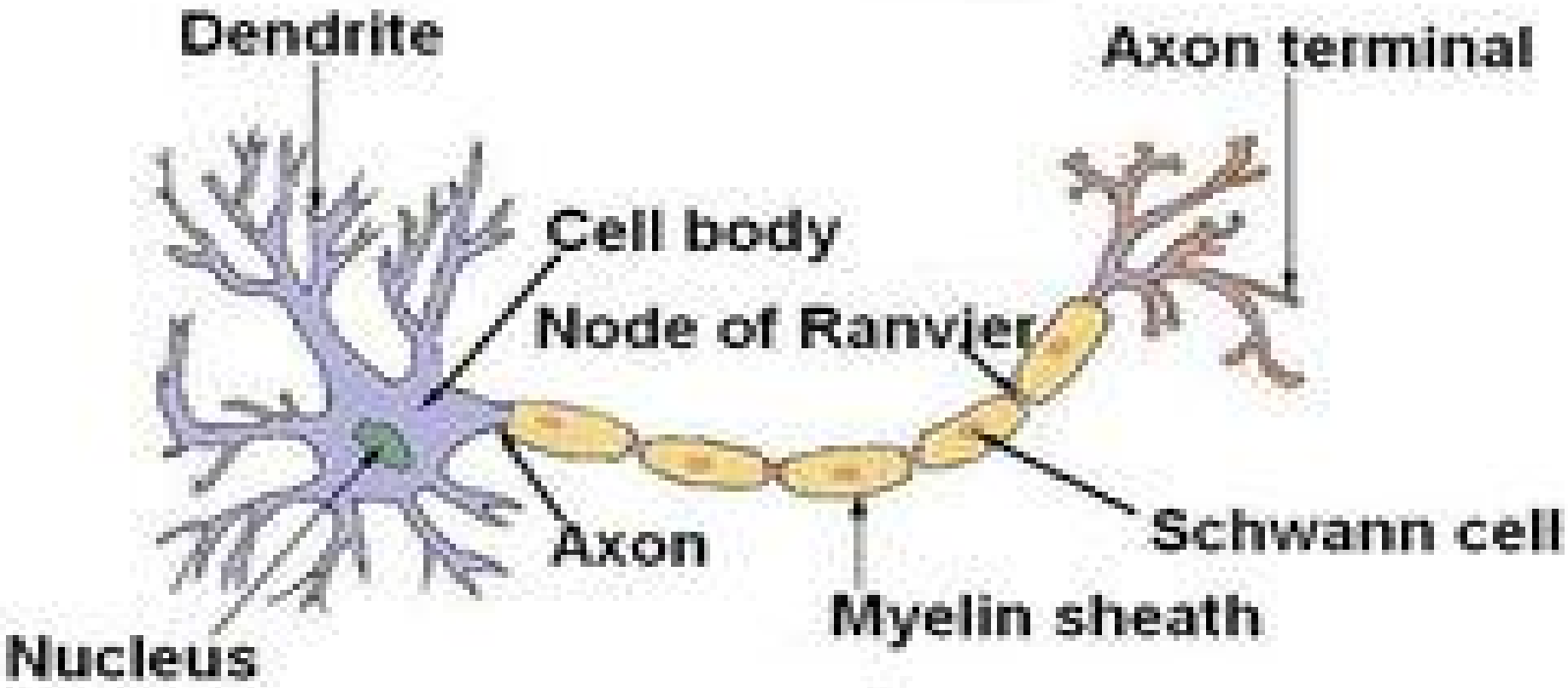
## Motor nerves

- Voluntary movement
- Muscle tone
- Coordination

## Autonomic nerves

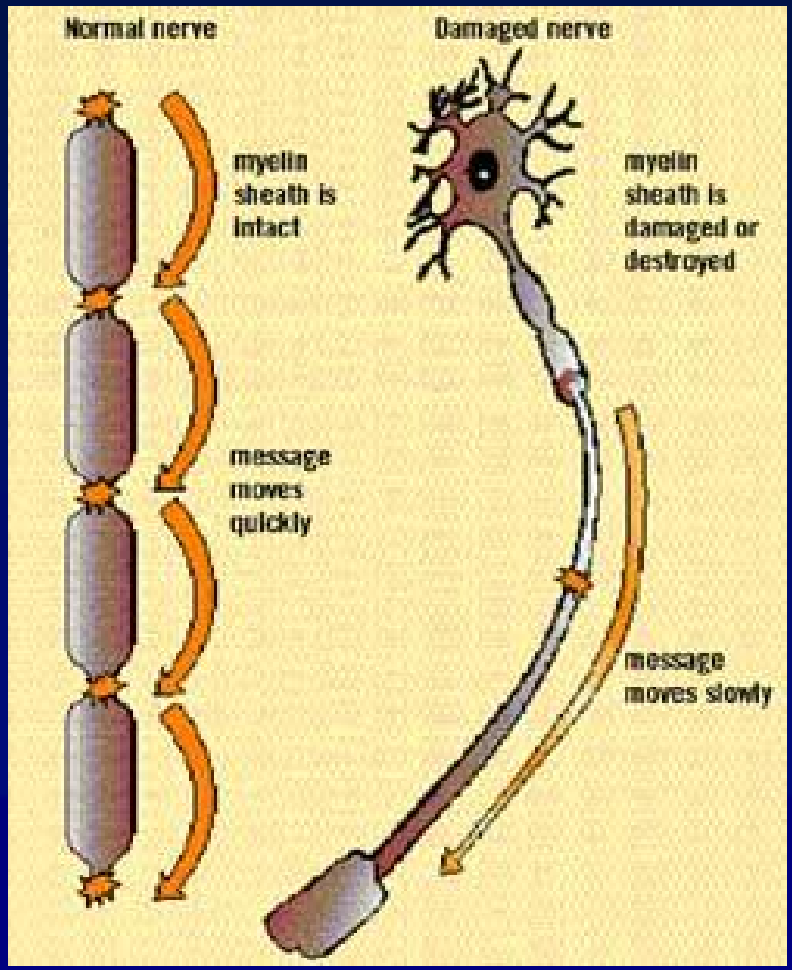
- Intestinal motility
- Blood pressure
- Involuntary muscle movements

# Structure of a Typical Neuron



# Pathophysiology (continued)

- Pathogenesis of CIPN is not completely understood
- Peripheral neuropathy results from damage to the
  - Axon,
  - Myelin sheath or
  - Cell body



# Pathophysiology (continued)

- İn contrast to the blood brain barrier CNS, DRG and peripheral axons lack an efficient neurovascular barrier
- Which allows the facile diffusion of large moleculer weight compounds in the DRG and axon filaments
- İn addition to capillary fenestrationsin the vascular supply to the DRG and axons
- This absence of a vascular barrier may an important role in CIPN devolopment

# Pathophysiology (continued)

- CIPN is usually **symmetrical**
- Begins in **distal** end of longest axons
- CIPN usually progresses from toes to feet to ankles to lower legs **(stocking distribution)**
- Upper extremity damage usually comes later
- Moves from fingertips to fingers to hands **(glove distribution)**

# Nerve Growth Factor

- Axons regenerate if toxic agent **removed**
- **Nerve Growth Factor** (NGF) plays role in neuron repair
- NGF is usually reduced after neurotoxic chemotherapy
- Animal studies show if given NGF, some neuropathy and neural structural changes were prevented or reversed
- Exact mechanism not well understood

# Chemotherapeutic Agents Known to Cause Neuropathy

- Platinum-based agents
  - Cisplatin
  - Carboplatin
  - Oxaliplatin
- Vinca alkaloids
  - Vincristine
  - Vinblastine
- Taxanes
  - Paclitaxel
  - Docetaxel
- Epothilones
  - Ixebepalone
- Others
  - Bortezomib
  - Thalidomide
  - Lenolidamide

# Methotrexate (Central toxicity)

## Acut toxicity

- Than 3 g/m$^2$ development of acute encephalopathy
- Characterized primarily by somnolence, confusion, and seizures
- Although the pathogenesis of this syndrome is unknown, folinic acid (leucovorin) diminished these metabolic effects

## Subacute Toxicity

- Develops weeks after methotrexate administration
- Most frequently received cranial radiation
- Completely reversible in weeks, and steroid treatment may accelerate recovery.

## Chronic Neurotoxicity

- Known as leukoencephalopathy.
- Develops months to years after methotrexate (IV or IT)
- Cranial radiation and younger patients higher risk for leukoencephalopathy
- Clinically, progressive loss of cognitive function may progress to profound dementia, coma, or death.
- No treatment is known, and the neurologic deficits generally are irreversible.

# Ifosfamide (Central toxicity)

- The most common manifestation with ifosfamide is encephalopathy.
- Severe ifosfamide-induced encephalopathy has been reported in children and adults.
- Symptoms usually begins within hours
- Confusion, hallucinations, and aphasia are the most common initial signs.
- Progression to coma generally is rapid. EEG shows severe slowing with delta wave activity and can display evidence of seizure activity.
- Persistent mental status changes in some patients 10 weeks after treatment.
- A recent study of 60 patients ifosfamide neurotoxicity to be 26%
- Riks factors include
  - Low serum albumin concentration,
  - High serum creatinine, pelvic cancer and
  - Previous treatment with cisplatin
- These abnormalities resolved over several days.

# Cisplatin / Carboplatin:

- Affects 57-92% of patients undergoing chemotherapy
- DRG neuropathy and axonal swelling and loss
- Progress from sensory, to motor and (rare) autonomic symptoms
- Can occur later in treatment course
- Causes loss of sense of position, vibration and paresthesias
- 66% of patients have full recovery
- Some patients can take two years for recovery to occur

# Oxaliplatin

- Alters neuron excitability axon conduction
- Causes sensory neuropathy of large fibers
- 80% of patients develop
- 40% of those who develop have resolution of symptoms in 6-8 months
- Can cause acute neuropathy (30-60 min after infusion)
- May be associated with calcium chelation by oxalate released from the drug, adversely affecting ion channels and synaptic transmission
    - Cramps/spasms in hands and feet
    - by cold weather
    - Causes sensation of loss of breath, jaw tightness

# Paclitaxel and Docetaxel

- Risk depends on dosing & use with other neurotoxic agents
- Disrupt axonal transport via microtubule damage
- Paclitaxel causes CIPN in 60% of patients
- Docetaxsel causes CIPN in about 49% of patients
- Affect small fibers, causes axonal injury, and demyelinization
- Altered vibratory, sense loss of deep tendon reflexes, paresthesias
- Causes progressive neurological dysfunction

# Vincristine, Etoposide, Vinorelbine & Vinblastine:

- Risk depends on dosing & use with other neurotoxic agents
- Greatest potential for CIPN is Vincristine: Occurs in about 57% of patients
- Degenerates the peripheral nerve fibers
- Affects small and large fibers
- Causes most commonly:
  - motor and sensory disruption;
  - can cause autonomic effects
- Paresthesisas, then progresses to muscle cramping/weakness, constipation, bladder dysfunction, altered heart rate

# Thalidomide / Bertazomib

- Thalidomide oral immunomodulator agent used in the treatment for patients with multiple myelome
- CIPN is a common potentially severe side effect
- Thalidomide caused distal axonal degeneration without demyelination, incidance 30%
- Bertazomib also used for the treatment MM
- Bertazomib is reversibl inh. of proteasome
- Tocity is predominantly sensory and motor involvement,
- Incidance 37%

# Antineoplastic Agents Known to Induce Neuropathy

| Drug | Incidence % | Onset dose | Recovery |
|---|---|---|---|
| Cisplatin | 28-100 | 300mg/m$^2$ | months |
| Carboplatin | 6-42 | 800-1600mg/m$^2$ | months |
| Oxaliplatin | | | |
| Acute | 85-95 | any | with in a week |
| Chronic | 10-18(severe) | 750-850mg/m$^2$ | months |
| Vinca alkaloids | 30-47 | 4-10mg | months |
| Paclitaxel | 57-83 | 100-300mg/m$^2$ | months |
| Docetaxel | 11-64 | 75-100mg/m$^2$ | months |
| Thalidomide | 28-83 | 20gr | 1 year |
| Bortezomib | 31-55 | 1.3mg/m$^2$ | months |

# Signs and Symptoms of CIPN

- Symptoms that patients may experience depend on
  - Length of infusion,
  - Dose
  - Co-morbidities
  - Other neurotoxic drugs

- Symptoms are divided into
  - Sensory
  - Motor
  - Autonomic symptoms,

# Sensory Symptoms include:

- Paresthesia:
  - feeling of warmth,
  - burning, tingling,
  - cold, pinprick sensation,
  - numbness
- Hyperesthesia:
  - increased sensitivity to sensory stimulus,
  - not painful, but can cause cramping, usually worse at night
- Hypoesthesia:
  - Decreased feeling sensations
- Hyporeflexia:
  - Decreased deep tendon reflexes

# Sensory Symptoms include:

- Dysesthesia:
  - Abnormal sensation in skin
  - Feels like electric sensation,
  - Tingling, prickling of the skin
- Diminished/absent
  - Vibration sensation
  - Cutaneous sensation
  - Feeling object as sharp or dull
- Pain:
  - Can be burning, shooting, sharp
- Numbness/tingling

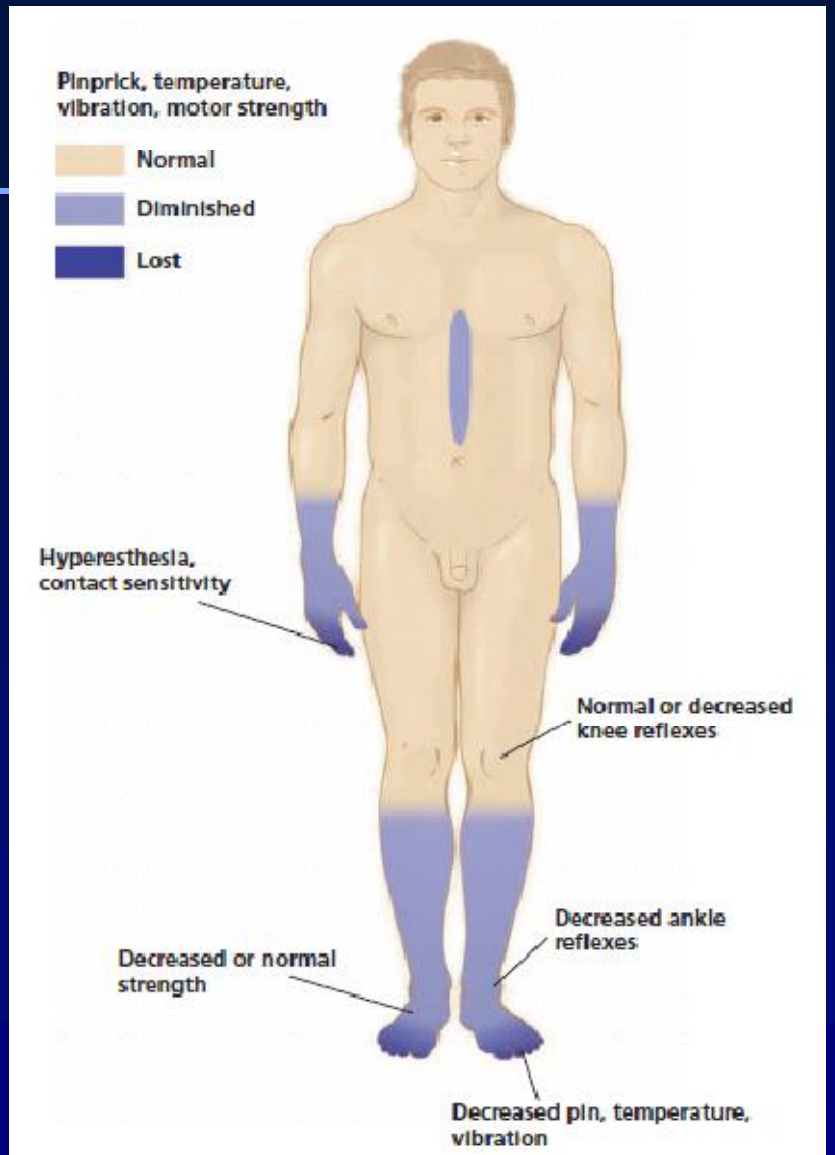



Figure 1 Symptoms of chemotherapy-induced peripheral neuropathy.
Adapted from: Simpson DA, Tagliati M, Gonzales-Duarte A, Mongello S. Neurologic manifestations. In: Mildvan D, ed. International Atlas of AIDS, 4th edition. Hoboken, NJ: Current Medicine Group LLC; 2007; with permission.

# Motor Symptoms İnclude:

- Weakness
- Gait disturbance
- Balance disturbance
- Difficulty with fine motor skills
  - Writing,
  - Buttoning
  - Clothing,
  - Sewing

# Autonomic symptoms include:

- Constipation
- Urinary retention
- Sexual dysfunction (erectile dysfunction in men)
- Blood pressure changes

# Assessment of CIPN

- **Baseline** neurological assessment is key

- Must assess
  - All motor,
  - Sensory, and
  - Autonomic function not only before start of treatment, but during and after as well

# Assessment of CIPN

NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Effects) assesses from Grades 1-4 of Sensory and Motor function:

- Grade I: Asymptomatic
- Grade II: Some sensory alteration or weakness
- Grade III: Interfering with activities of daily living
- Grade IV: Life threatening and disabling (paralysis)

# Grading Scales for Neuropathy

| Scale | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| NCI-CTCAE<br>▪Sensory<br>▪Motor | No symptoms, loss of DTR | Paresthesia, ADL ok | Paresthesia, ADL interference | Disabling |
| ECOG<br>▪Sensory<br>▪Motor | Mild Paresthesia<br>Loss DTR | Sensory loss<br>Paresthesia<br>Weakness | Severe sensory and motor loss with function | Paralysis |
| WHO | Paresthesia<br>Decreased DTR | Severe paresthesia<br>Weakness | Intolerable | Paralysis |

Postma TJ. Annals Oncol 9:739-744, 1998

## Patients at risk for developing CIPN

- Some conditions or co-morbidities make patients more prone to developing CIPN complication than other patients

- The following is a list of other factors that, if present in a patient undergoing chemotherapy with a neurotoxic drug, may put them more at risk for developing CIPN

- It’s essential to assess for risk factors to determine who will need close monitoring during treatment!

# Patients at risk for developing CIPN

- Endocrine diseases include:
  - Diabetes mellitus (Can causes small fiber injury)
  - Hypothyroidism
- Infectious diseases include:
  - HIV/AIDS
  - Lyme disease
  - Herpes zoster
- Hereditary diseases include:
  - Charcot-Marie-Tooth syndrome (Causes large fiber injury)
  - Freidreich's ataxia

# Patients at risk for developing CIPN

- Nutritional diseases include:
  - Alcoholism
  - Vitamin B12 deficiency (causes large fiber injury)
  - Thiamine deficiency
  - Vitamin E deficiency
  - Folate deficiency
- Crohn's disease

# Patients at risk for developing CIPN

- Connective tissue diseases:
  - Rheumatoid arthritis
  - Lupus
- Metal neuropathy:
  - Mercury
  - Gold
  - Thallium
- Other:
  - Amyloidosis
  - Ischemic lesions, Atherosclerotic heart disease
  - Sarcoidosis
  - Biliary cirhosis
  - Uremia
  - Vasculitis

# Patients at risk for developing CIPN

## Medications Including

- Colchicine
- Isoniazid
- Hydralazine
- Metronidazole
- Lithium
- Phenytoin
- Cimetadine
- Amiodarone
- Pyridoxine
- Amitriptyline

# Treatment of CIPN

- PREVENTİON MANAGEMENT

- SYMPTOM MANAGEMENT

# PREVENTİON

- Many agents have been proposed for preventing neuropathy caused by antineoplastic drugs
- Most of these drugs might minimize neuropathy are based on limited preclinical data
- A few have been evaluated in randomized controlled trials
- Most have been assessed during platinum based chemotherapy

# Vitamin E:

- Protects against cell damage such as numbness, tingling, burning, and pain in periphery caused by Cisplatin and other chemotherapy drugs
- Studies show those who received Vitamin E supplementation during and after chemotherapy reported less CIPN
- Possibly a relationship between Cisplatin neurotoxicity and Vitamin E deficiency
- Vitamin E receiving 300-400mg/d
- There are small randomized trails
  - 47 patiens **à** (31% versus 86% p: 0.01)
  - 32 patients **à** (25% versus 73% p:0.026)

# Calcium/Magnesium infusions:

- Oxalate, found in Oxaliplatin, binds to Calcium and Magnesium
- This may deplete these essential elements and be responsible for the neurotoxicity of Oxaliplatin
- Retrospective trail 161 patients **à** 20% versus 45% (p:0.003)
- Two Prospective trail: 1 gr Ca-Mg before Oxa inf
  - N0C7 study **à** reduction in CİPN incidence
  - CONCEPT trail was early terminated worse tumour-related outcomes
- Prospective randomized controlled trials are imperative

# Amifostine:

- Chemoprotectant
- Detoxifies chemotherapy drugs
- Facilitates DNA repair of cells
- Does not interfere with chemotherapy effectiveness
- In lab animals, shows sparing of nerve fibers
- In some human trials, it seems ineffective in preventing or reducing paclitaxel and cisplatin induced PN
- Needs more research with other chemotherapy drugs

# Glutathione and N-acetylcysteine

- May hamper initial accumulation of platinum agents in peripheral nerve cells
- Two small randomised trails suggest that glutathione was benefical for prevention cispaltin and oxliplatin induced neuropathy
- Another trail addition of glutathion to cisplatin reduced toxicity and allowed more cycle of treatment to be administered
- N-acetylcysteine an antioxidant drug which increases whole blood concentrations of glutathione, demonsrated a suggestion of benefit in preventig CIPN in patients receiving oxaliplatin

# Glutamine:

- Amino acid, may have neuroprotecive properties
- Upregulates NGF
- In studies, those who take it for Paclitaxel preventive CIPN showed less weakness, loss of vibratory sensation, and toe numbness versus control group
- 86 patients receive Oxaliplatin **à** 30mg / 7d, gr III-IV neuropathy ( 5% v 18% p:0.005)
- There are needed larger randomised trial before recommended routine practice

# Antiepileptic agents (Carbamazepine,Oxcarbazepine)

- Carbamazepine an antiepileptic agent that inhibibits sodium channel activity has been suggested to have a role in perventing oxaliplatin neuropathy
- Nonetheless, results of a pilot trial (n:12) testing carbammazepin for this indication were not supportive
- Oxcarbazzepine a ketanalogue of carbamazepine
- Small randomised trial suggest may protect aganist oxaliplatin induced neuropathy
- A larger randomized trial is needed to confirm these results.

# Acetyl-L-carnitine **and** Xaliproden**:**

- Acetyl-L-carnitine tested in presence of preexisting Taxol or Cisplatin-induced CIPN
  - Very small studies have been performed, but look promising
- Xaliproden Oral neuroprotecive drug, NGF analog
  - Incidence of Grade 3-4 CIPN was 39% less in patients who received oxaliplatin versus placebo
  - A phase III trial is ongoing

# Agents for Prevention CIPN (positive findings randomised controlled trials)

| | | | |
|---|---|---|---|
| **Vitamin E** | **n** | **CIPN%** | |
| Pace 2003 | 47 | 31 | 86 p<0.001 |
| Argyriou 2005 | 40 | 25 | 73 p<0.019 |
| Argyriou 2006 | 35 | 21 | 66 p<0.026 |
| Pace 2007 | 81 | CIPP score lower in the vitamin E group p<0.05 | |
| **Calcium/magnesium** | | | |
| Nikcevich 2008 | 104 | 28 | 51 p<0.02 |
| **Glutamine** | | | |
| Wang 2007 | 86 | 12 | 32 P<0.04 |
| **Glutation** | | | |
| Cascinu 2002 | 52 | | P<0.04 |
| Smyth 1997 | 152 | 31 | 75 p<0.03 |
| Cassınu 1995 | 50 | 17 | 84 p<0.0001 |
| **N-acetylcysteine** | | | |
| Lin 2006 | 14 | 5/7 | 0/7 p<0.05 |
| **Oxcarbazepine** | | | |
| Argyriou 2006 | 40 | 31 | 75 P< 0.03 |
| **Xaliproden** | | | |
| Cassidy 2006 | 649 | 11 | 17 |

# Agents for Prevention CIPN

## Negative Findings Randomised Controlled Trials

- Amifostine
- Nimodipine
- Org 2766 (Adrenocorticotrophic hormone analogue)
- rhuLIF (Recombinant human leukaemia inhibitory factor)

## Ongoing Phase III Radomized Controlled Trials

- Vitamin B12/B6 (essential for nerve function)
- Acetyl-L- carnitine (oxidation of free fatty acids/nerve)
- Alpha lipoic asid (antioxidant)

# Symtomatic Treatment of CIPN

- Aim to relieve the symptoms of CIPN
- This a problem in all patients with PN regardles of aetiology
- Majority of trials symptomatic neuropathies especially those related diabetes mellitus
- Most agents tried have been
  - Anticonvulsants or antidepressants
- Unfortunately when these data are extrapolated to CIPN
- May be due to different qualities and pathophysiologies of toxic CIPN and other aetiologies

# Sysmtomatic Treatment of CIPN
## Randomised Controlled Trials

| | Patients | Findings |
|---|---|---|
| **Nortriptyline** | | |
| Hammack 2002 | 57 | no CIPN benefit observed |
| **Amitriptyline** | | |
| Kautio 2008 | 44 | no CIPN benefit observed |
| **Gabapentin** | | |
| Rao 2007 | 115 | no CIPN benefit observed |
| **Lamotrigine** (anticonv) | | |
| Rao 2008 | 131 | no CIPN benefit observed |

# Agents for Pain Management in Neuropaty

| | Dose |
|---|---|
| Duloxetine (antidep) | 30-120mg/d |
| Gabapentin | 300-3600mg/d |
| 5% lidocaine patch | 3 patch/d |
| Opioid (Oxycodona Morphine,methadone) | 5-15mg / every 4h |
| Pregabalin | 50-200mg/every 8h |
| Tramadol | 50-400mg/d |
| TAD (amitryl,nortryl,desipmn) | 10-150mg/d |

# Paclitaxel Acute Pain Syndrome

- These symptom begin 1-3 days after drug administration
- Generally self limited, often resolving within 7 days
- Pain described in large axial muscular and joint regions
- Neorologic and musculoskeletal examinaton is normal
- Pain syndrome distinct from paclitaxel assosiated peripheral neuropathy
- Commonly treated with
  - NSAİD
  - Acetaminophen
  - Opioid

# Summary

- Neuropathy or periferal neuropathy is define as condition arising from the demage and dysfunction of the peripheral nerves
- Chemotherapy induced neuropathy can be variable, but often ranges from 30-40% of patients received chemotherapy
- Pathogenesis of neuropathy is not completely understood
- This absence of a vascular barrier may an important role in CIPN devolopment

# Summary

- Some conditions or co-morbidities effect developing CIPN
- CIPN is full recovery generaly of patients
- Some patients can take two years for recovery to occur
- Treatment of CINP is prevention and symptom management
- Symptom teratment is not effected