
5. ASO-Expertenworkshop
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Rottach-Egern

*„Strategien bei Chemotherapie-induzierter
Polyneuropathie“*

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Strategien bei Chemotherapie-induzierter Polyneuropathie

Relevanz

CIPN häufiger CTX-Dosis-limitierender Faktor

neurotoxische Kombinationen en vogue

Chemoprotektion ermöglicht CTX-Dosis-Eskalation

CIPN schränkt insbesondere bei Persistenz Lebensqualität ein

Strategien bei Chemotherapie-induzierter Polyneuropathie

Voraussetzungen

- Reliable Erfassung der CIPN (vorwiegend klinisch)
 - Elektrophysiologische Charakterisierung
 - (keine etablierte Methode zur Frühdiagnose)
 - Differentialdiagnostische Abgrenzung der CIPN
 - Klärung des pathophysiologischen Mechanismus
 - Therapie auf der Grundlage adäquater klinischer Studien
 - Neuroprotektion ohne Beeinträchtigung des anti-Tumor-Effektes
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Strategien bei Chemotherapie-induzierter Polyneuropathie

Pathomorphologische Klassifikation

- Neuronopathie
 - sensibel (Ganglionopathie)
 - motorisch
 - häufig irreversibel (neuronale Apoptosis)
 - Periphere Neuropathie (im allgemeinen sensomotorisch)
 - Myelinopathie
 - Axonopathie (dying-back type).
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Strategien bei Chemotherapie-induzierter Polyneuropathie

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**
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Grading scales

Scale	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
WHO [32]	None	Paresthesias and/or decreased tendon reflexes	Severe paresthesias and/or mild weakness	Intolerable paresthesias and/or motor loss	Paralysis
ECOG [35]	None	Decreased deep tendon reflexes, mild paresthesias, mild constipation	Absent deep tendon reflexes, severe constipation, mild weakness	Disabling sensory loss, severe peripheral neuropathic pain, obstipation, severe weakness, bladder dysfunction	Respiratory dysfunction secondary to weakness, obstipation requiring surgery, paralysis confining patient to bed/wheelchair
NCIC-CTC sensory neuropathy [38]	None	Loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Objective sensory loss or paresthesia interfering with function but not interfering with activities of daily living	Sensory loss or paresthesia interfering with activities of daily living	Permanent sensory loss that interferes with function
NCIC-CTC motor neuropathy [38]	None	Subjective weakness but no objective findings	Mild objective weakness interfering with function but not interfering with activities of daily living	Objective weakness interfering with activities of daily living	Paralysis
Ajani sensory neuropathy [1]	None	Paresthesia, decreased deep tendon reflexes	Mild objective abnormality, absence of deep tendon reflexes, mild to moderate functional abnormality	Severe paresthesia, moderate objective abnormality, severe functional abnormality	Complete sensory loss, loss of function
Ajani motor neuropathy [1]	None	Mild or transient muscle weakness	Persistent moderate weakness but ambulatory	Unable to ambulate	Complete paralysis

Total Neuropathy Score (TNS)

Parameter	Score				
	0	1	2	3	4
Sensory symptoms	none	limited to fingers or toes	extend to ankle or wrist	extend to knee or elbow	above knees or elbows, or functionally disabling
Motor symptoms	none	slight difficulty	moderate difficulty	require help/assistance	paralysis
Autonomic symptoms (n)	0	1	2	3	4 or 5
Pin sensibility	normal	reduced in fingers/toes	reduced up to wrist/ankle	reduced up to elbow/knee	reduced to above elbow/knee
Vibration sensibility	normal	reduced in fingers/toes	reduced up to wrist/ankle	reduced up to elbow/knee	reduced to above elbow/knee
Strength	normal	mild weakness	moderate weakness	severe weakness	paralysis
Tendon reflexes	normal	ankle reflex reduced	ankle reflex absent	ankle reflex absent, others reduced	all reflexes absent
Vibration sensation QST	normal to 125% ULN	126 - 150% ULN	151 – 200% ULN	201 – 300% ULN	>300% ULN
Sural nerve SAP	normal/reduced to <5% LLN	76 – 95% LLN	51 – 75% LLN	26 – 50% LLN	0 – 25% LLN
Peroneal nerve CMAP	normal/reduced to <5% LLN	76 – 95% LLN	51 – 75% LLN	26 – 50% LLN	0 – 25% LLN

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

Neuroprotektion bei Platin-Derivat-assoziiierter CIPN

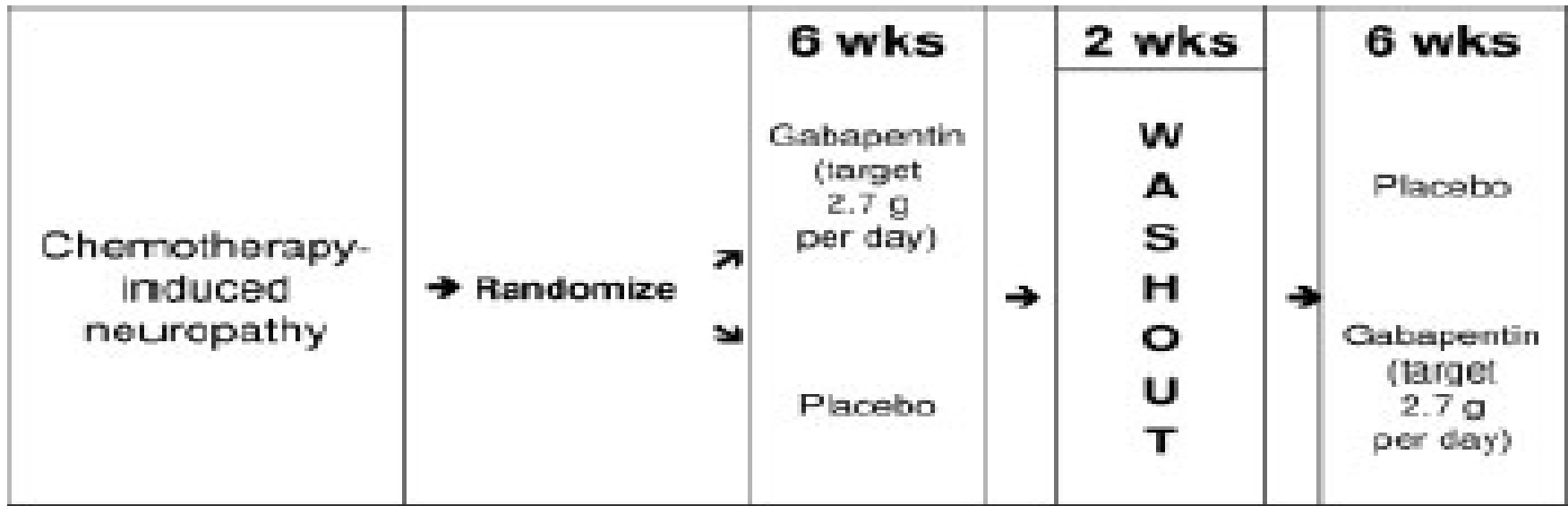
Autoren	Chemotherapie	Prophylaxe	Design	N	Outcome
Kemp et al. 1996	Cisplatin / Cyclophosphamid	Amifostin 910 mg/m ² i.v.	RD C	242	Signifikanter Effekt auf PNP-Inzidenz und -Schweregrad
Cascinu et al. 2002	Oxaliplatin-basiert	Glutathion 1500 mg/m ² i.v.	RD DB PC	52	Signifikanter Effekt auf Suralis-SNAP- Amplitude und mittlere Latenz
Pace et al. 2003	Cisplatin	Vitamin E 300 mg/d p.o. bis 3 Monate nach Chemotherapie	RD C	27	PNP-Inzidenz 30,7 % vs. 85,7 %
Lin et al. 2006	Oxaliplatin-basiert	N-Acetylcystein 1200 mg p.o.	RD PC	14	Neurotox. Grad 2-4 signifikant reduziert
Wang et al. 2007	Oxaliplatin-basiert	Glutamin 2x 15 g / d p.o. über 7 d	RD C	86	Neuropathie Grad 3-4 signifikant reduziert

Neuroprotektion

bei Paclitaxel-assoziiierter CIPN

Autoren	Chemotherapie	Prophylaxe	Design	N	Outcome
Hilpert et al. 2005	Paclitaxel/ Carboplatin	Amifostin 740 mg/m ² i.v.	RD DB PC	72	Signifikanter Effekt auf sensible Neuropathie gemäß NCI-CTC und Vibrationsschwelle
De Vos et al. 2005	Paclitaxel/ Carboplatin	Amifostin 740 mg/m ² i.v.	RD C	90	Neurotox Grad 2 2% vs. 12%
Argyriou et al. 2005	Paclitaxel/ Cisplatin	Vitamin E 600 mg/d p.o.	RD C	31	PNP-Inzidenz 25,0% vs.73,3%

Gabapentin in the Management of Chemotherapy-induced Peripheral Neuropathy

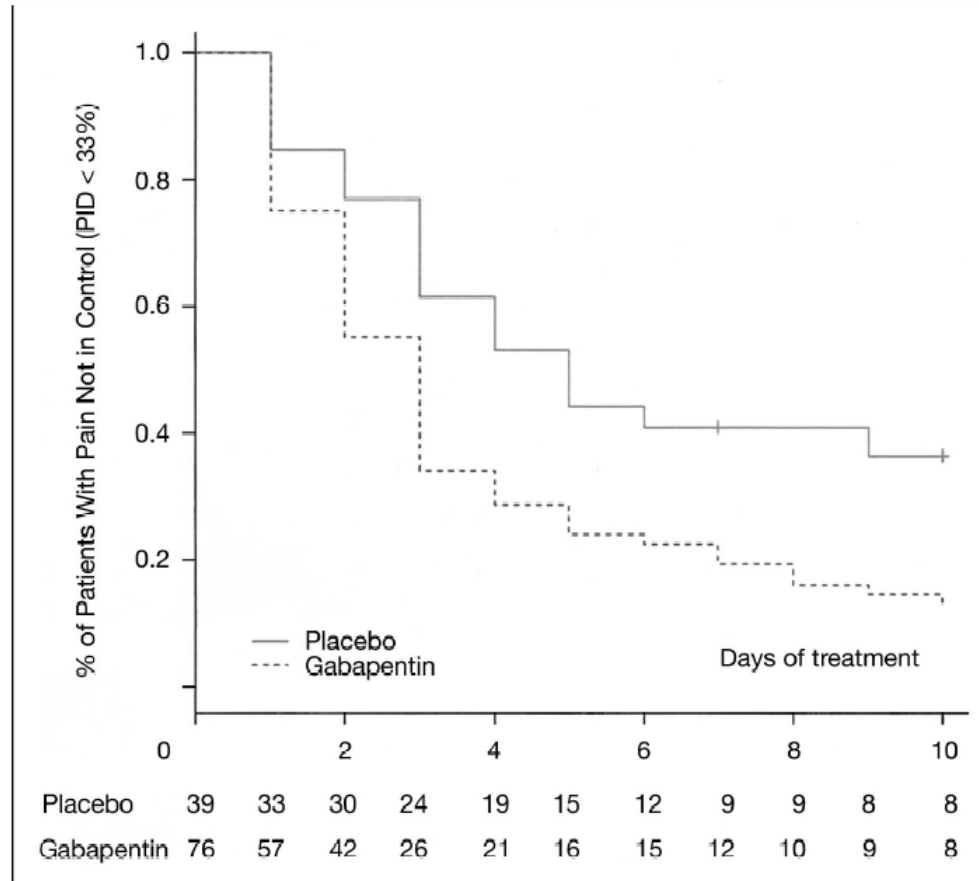


This trial failed to demonstrate any benefit to using gabapentin to treat symptoms caused by CIPN.

Gabapentin for Neuropathic Cancer Pain: A Randomized Controlled Trial

	Gabapentin (n = 80)		Placebo (n = 41)	
	No. of Patients	%	No. of Patients	%
Peripheral nerve syndromes				
Due to paraspinal mass	1	1.2	0	0
Due to chest wall mass	8	10.0	2	4.8
Due to retroperitoneal mass	1	1.2	0	0
Due to soft tissue or bony tumor	1	1.2	0	0
Radiculopathy or cauda equina syndrome				
Due to vertebral lesion	11	13.7	5	12.2
Due to leptomeningeal metastases	0	0	0	0
Due to intraspinal neoplasm	0	0	0	0
Plexopathy				
Brachial plexopathy	23	28.7	10	24.4
Lumbosacral plexopathy	18	22.5	8	19.5
Sacral plexopathy	7	8.7	6	14.6
Cervical plexopathy	2	2.5	2	4.8
Cranial neuropathy				
Due to base of skull tumor	1	1.2	1	2.4
Due to leptomeningeal metastases	0	0	0	0
Due to bony or soft tissue cranial tumor	4	5.0	3	7.3
Perineal pain and tenesmus due to presacral tumor mass	6	7.5	6	14.6

Gabapentin for Neuropathic Cancer Pain: A Randomized Controlled Trial



Neuropathischer Schmerz

Medikamentöse Therapie

Pharmakon		Dosis (mg/d)	Evidenz-Level
NSAID			
	Paracetamol	1500 – 3000	↑ PNP
Antidepressiva			
	Amitriptylin	50 – 75	↑↑ PZN, PNP
	Venlafaxin	75 – 150	↑↑ PNP
	Duloxetin	60	↑ PNP
Antiepileptika			
	Gabapentin	1200 – 2400	↑↑ PZN, PNP
			↑ CANC
	Pregabalin	150 – 300	↑↑ PZN, PNP
	Carbamazepin	600 – 1200	↑ PNP
	Lamotrigin	100 – 200	↑ PNP, RM
Opioide			
	Tramadol ret.	100 – 400	↑↑ PZN, PNP
	Morphin ret.	20 – 200	↑ PZN, PHAN
	Oxycodon	20 – 160	↑↑ PNP
Lokalanästhetika			
	Lidocain (topische Therapie)	5 %	↑↑ PZN

Strategien bei Chemotherapie-induzierter Polyneuropathie

Take-Home-Message

- Der Total Neuropathy Score (TNS) stellt in der kombinierten Version (klinisch und neurophysiologisch) wie auch in der klinischen Version ein validiertes Instrument zur quantitativen Erfassung der Chemotherapie-induzierten peripheren Neurotoxizität dar.
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Strategien bei Chemotherapie-induzierter Polyneuropathie

Take-Home-Message

- Modifikation der Chemotherapie
 - Dosisintensität reduzieren
 - Kombination neurotoxischer Pharmaka vermeiden
 - Risikofaktoren identifizieren
 - Einsatz chemoprotektiver Substanzen
 - Glutathion zur CIPN-Prävention bei Oxaliplatin-basierter Chemotherapie
 - Symptomatische Therapie neuropathischer Schmerzen und Parästhesien
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Strategien bei Chemotherapie-induzierter Polyneuropathie

Take-Home-Message

- Gabapentin erwies sich schmerztherapeutisch bei der carcinomatösen Plexopathie als wirksam, bei Chemotherapie-induzierter peripherer Neuropathie (CIPN) jedoch als unwirksam.
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