NCI Symptom Management and Quality of Life Steering Committee Clinical Trials Planning Meeting on Chemotherapy Induced Peripheral Neuropathy

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Topics

- Introductory comments
- A picture of the problem
- Prevention of CIPN-story for a sample study
- Summary statements
- Discussion

Chemotherapy-Induced Peripheral Neuropathy

- Major oncologic problem
- Common chemotherapy dose limiting toxicity
- Affects life quality
- Promising preliminary results regarding effective prevention and treatment of this problem

Meeting Data

- March 23, 2009
- Approximately 100 participants
- Thought-provoking presentations/discussion
- Report provided
- Informal reviews/remarks

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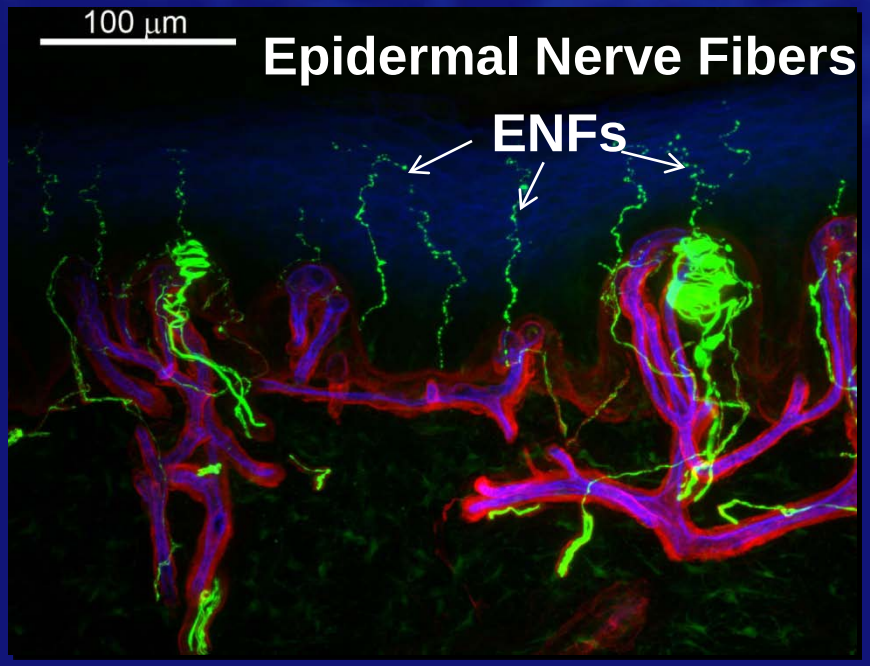
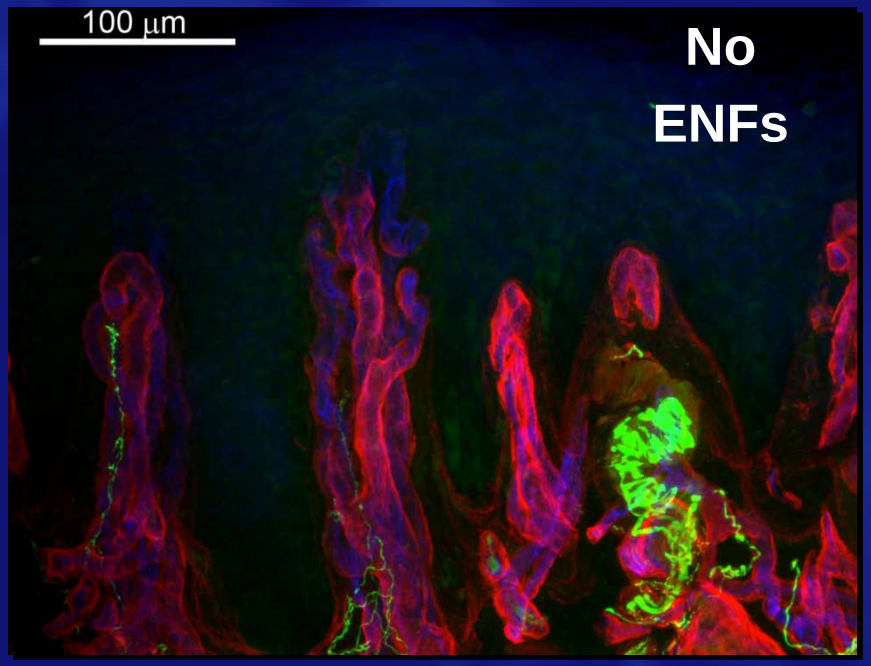
Abnormal Innervation following Chemotherapy



Normal palm

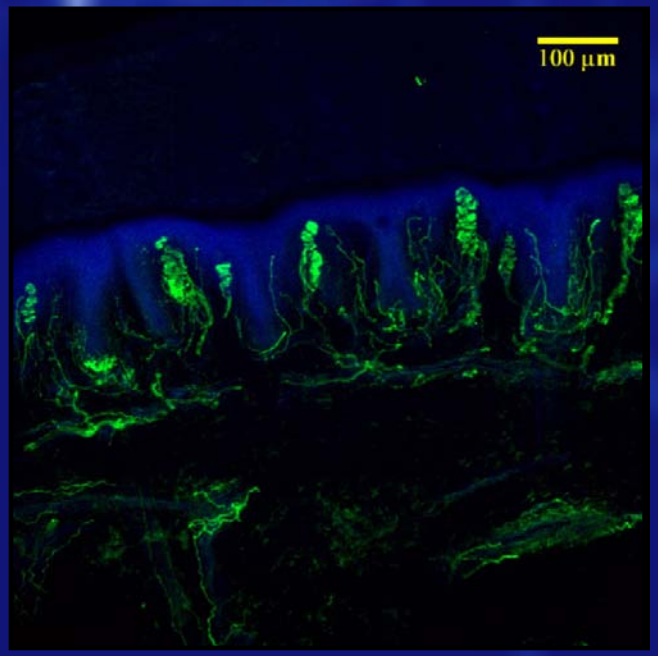
20x magnification



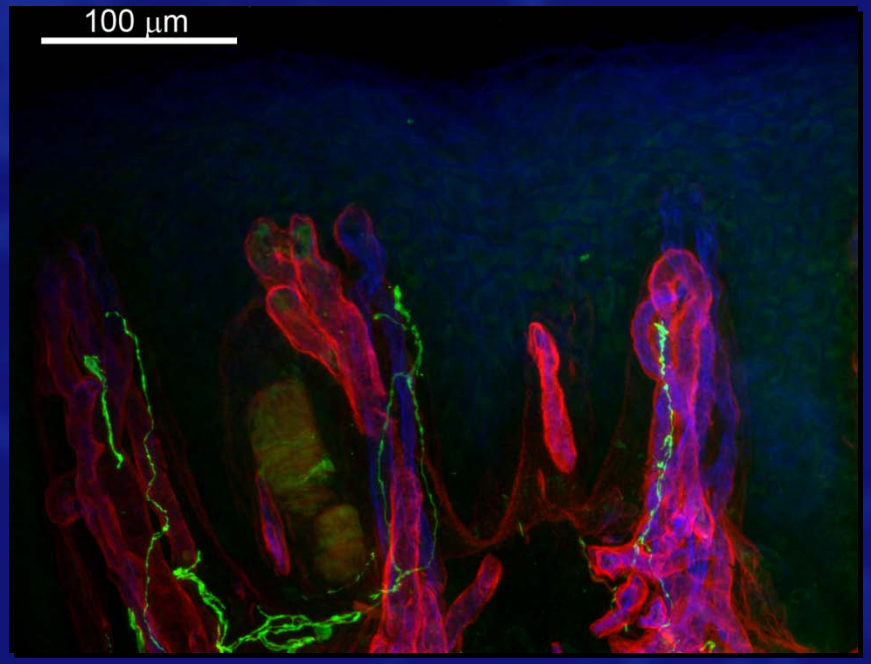
Site A

20x magnification

Meissner's Corpuscles from finger tip



Normal Meissner's Corpuscles



Abnormal Meissner's Corpuscles

Nolano M, Provitera V, et al. Ann Neurol 2003; 54 : 197-205

Measurement issues

- Multiple proposed tools
- Work is needed to fine tune means to delineate the fine aspects of CIPN
  - Different symptoms
  - Differences between drugs

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Intravenous Calcium and Magnesium for Oxaliplatin-Induced Sensory Neurotoxicity (N04C7)

DA Nikcevich, A Grothey, JA Sloan, JW Kugler, PT Silberstein, T Dentchev, DB Wender, PJ Novotny, HE Windschitl, CL Loprinzi

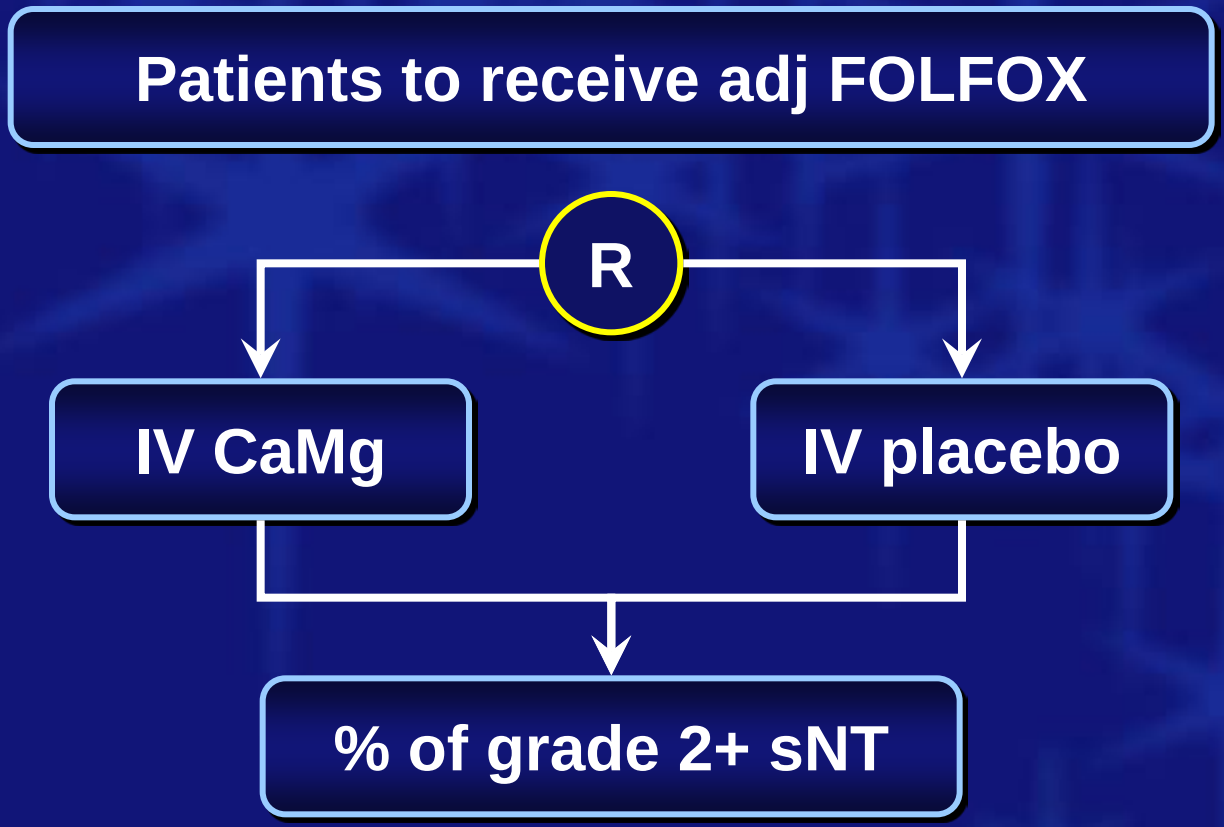
For the North Central Cancer Treatment Group

J Clin Oncol 2008; May 20 suppl (abstract 4009)

Background

- It was proposed that CaMg would stabilize nerve membranes and prevent the accumulation of oxaliplatin in DRG
- In a retrospective, non-randomized study, intravenous administration of calcium and magnesium salts (CaMg) was associated with reduced oxaliplatin-induced PSN **(Gamelin: Clin Cancer Res, 2004)**

N04C7 Cancer Control Phase III Trial – Study Design



N04C7 Cancer Control Phase III Trial

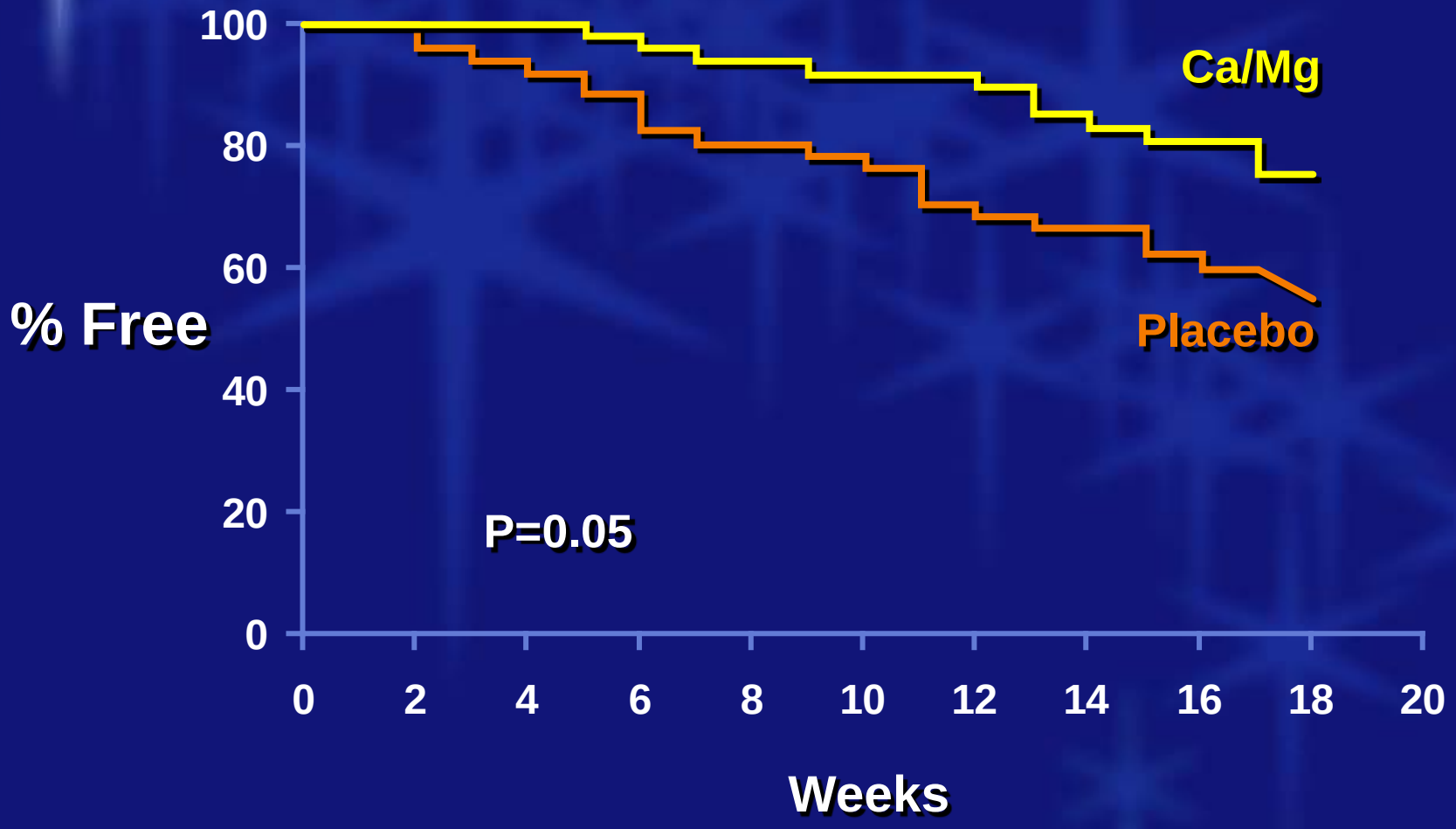
– Study Stopped Early

– 102 pts/300 planned

Primary Endpoint Grade 2+ sNT (CTCAE Scale)

Neurotoxicity grade	CaMg n=50	Placebo n=52	P
Grade 2+	22%	41%	0.038

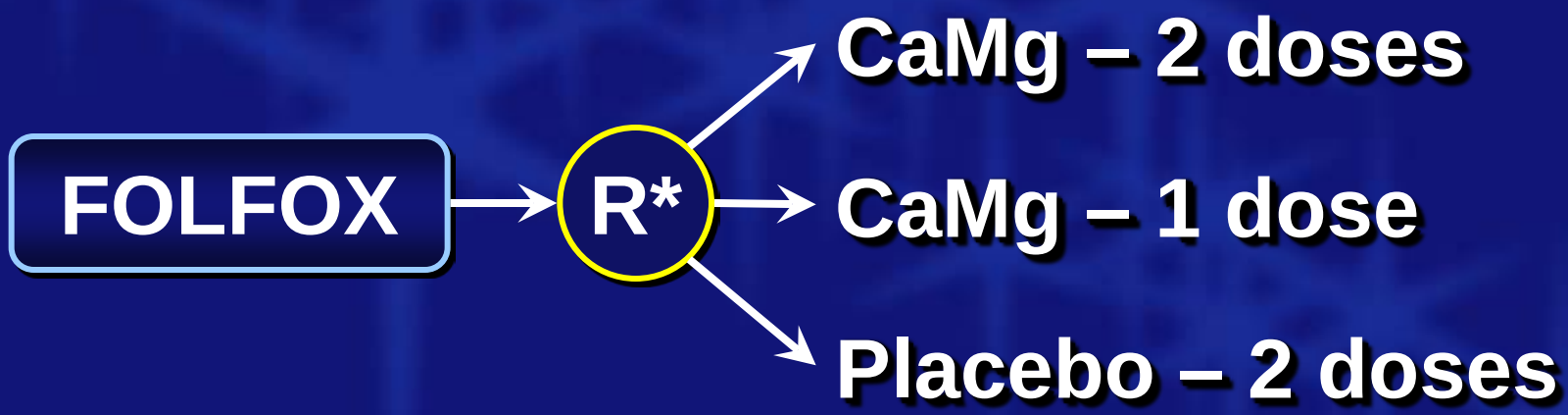
Time to Grade 2+ sNT (CTC scale)



Concept Trial Story

- Stop and go oxaliplatin question
- CaMg vs not question
- Slower accrual than desired
- Stop CaMg vs placebo part….all to get CaMg
- Data management committee….

Hochster HS, Grothey A, Childs BH. Use of calcium and magnesium salts to reduce oxaliplatin-related neurotoxicity. Journal of Clinical Oncology 2007;25(25):4028-4029


FOLFOX
R*
CaMg – 2 doses
CaMg – 1 dose
Placebo – 2 doses

Other Promising Appearing Agents

- Glutathione
- Alpha lipoic acid/ thiotic acid
- Acetyl-L-carnitine
- Duloxetine/Cymbalta
- Baclofen/amitriptyline/ketamine

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Summary statements

- CIPN is a major clinical problem
- Chemotherapy can cause structural nerve damage
- There is sufficient rationale for conducting high quality clinical trials

Summary statements

- Efforts are needed to
  - better understand genetic variations that will predict for CIPN
  - better define CIPN targets and mechanism based therapies to prevent and/or treat CIPN

- There is a need for more animal model experiments to help direct clinical trial options

Summary statements

- I, even as a conservative investigator, firmly believe that positive clinical trials, with clinically significant results, will be forthcoming within the next few years
- More mechanism based research will improve efforts to define effective therapies

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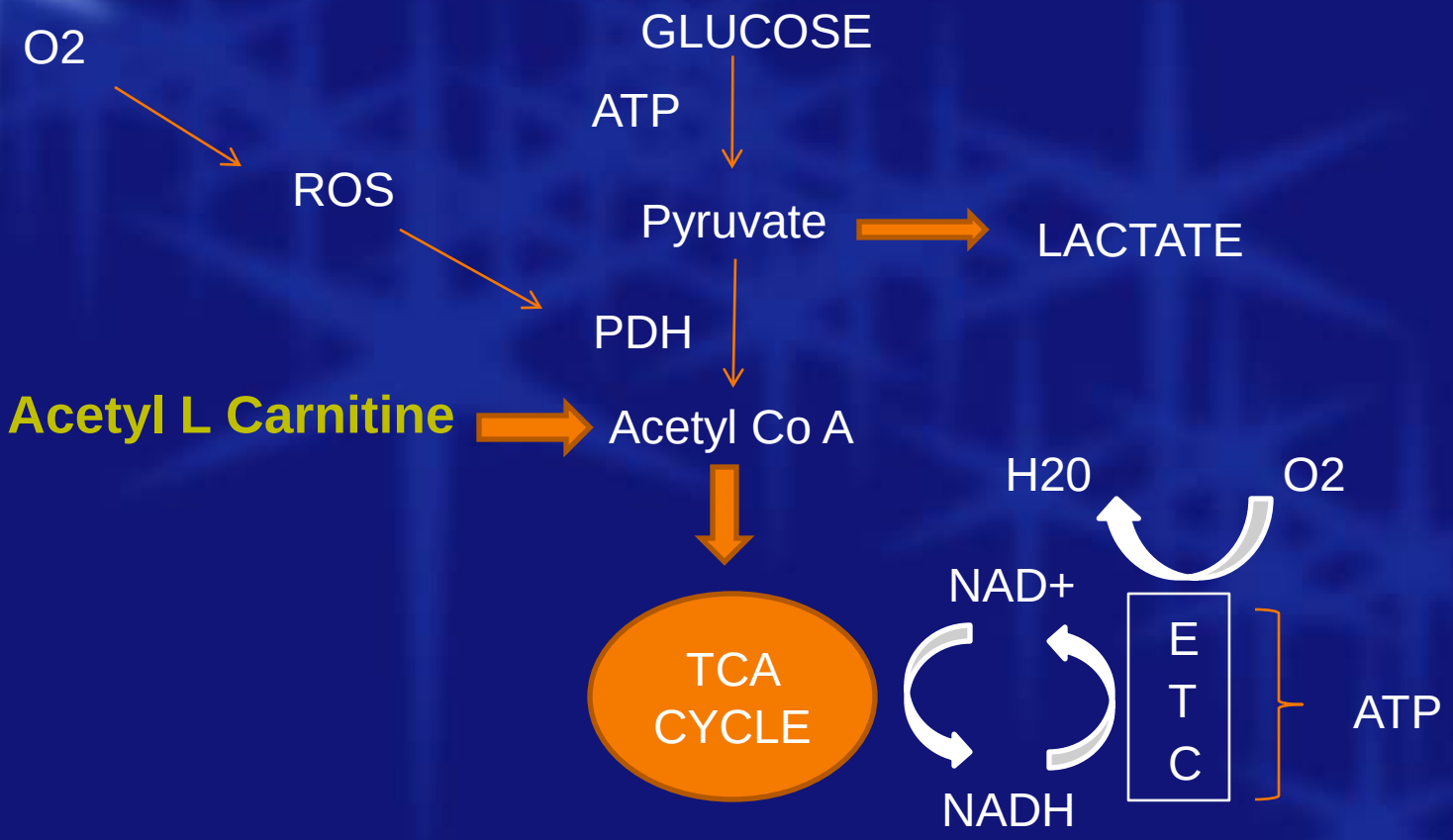
Thank you

Prevention of CIPN

- Acetyl L-Carnitine (ALC)

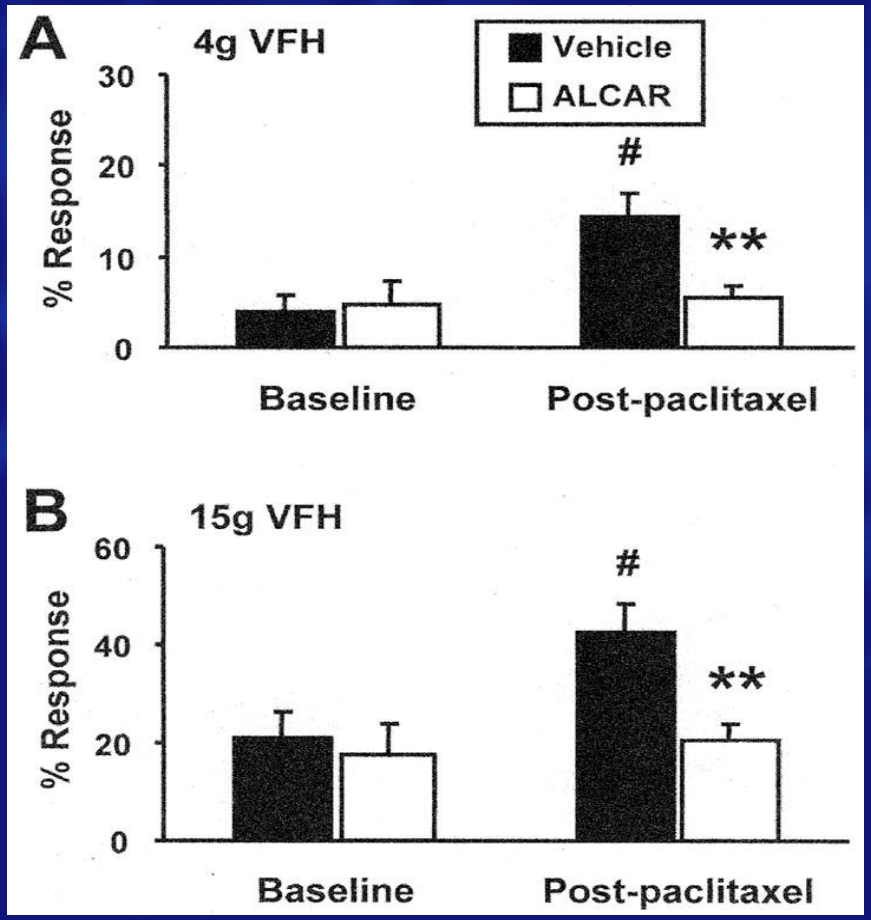
Acetyl L-Carnitine (ALC)



Neuropathy results from disruption of mitochondrial DNA synthesis in nerve cells.

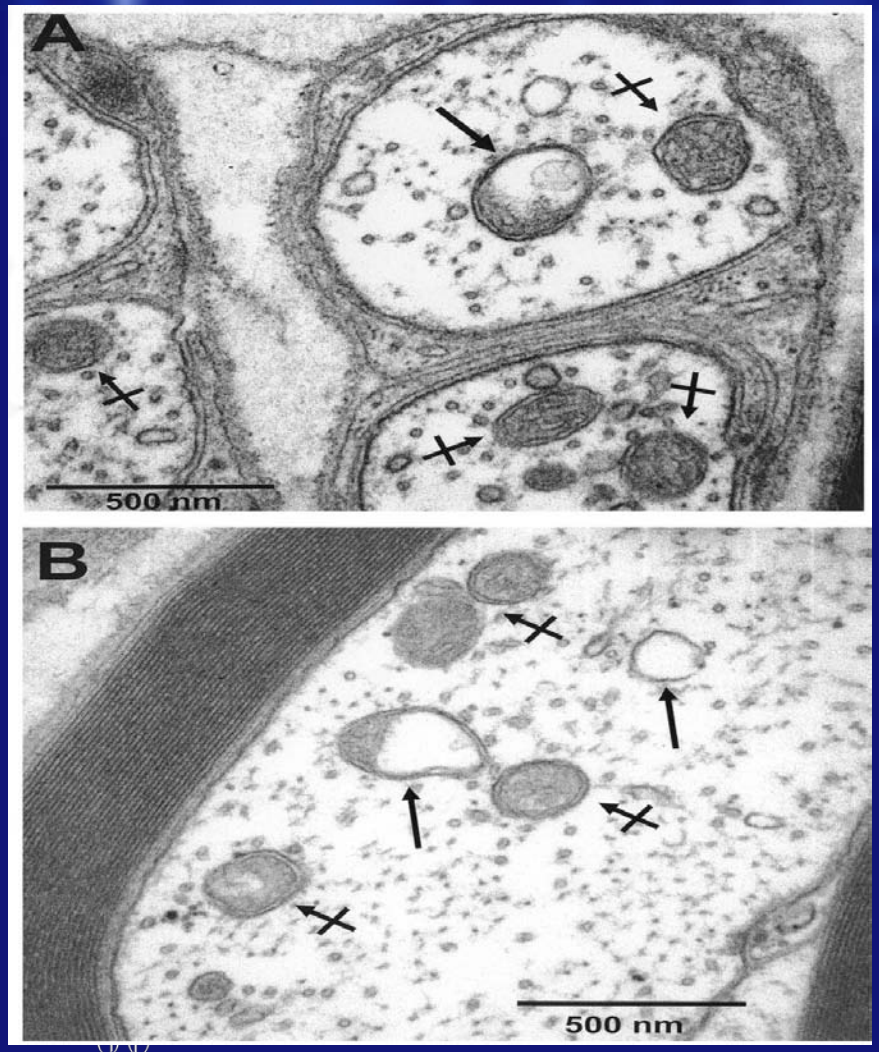
Mitochondrial metabolism in the neurons is decreased and the cells' long peripheral axons die back, causing pain, tingling, and numbness

Prevention of paclitaxel-evoked painful peripheral neuropathy by acetyl-L-carnitine



Withdrawal responses from hind paws Normal rats rarely withdraw from the 4 g stimulus; increased responding after paclitaxel treatment is indicative of mechano-allodynia.

Axonal Mitochondria



- Atypical and normal mitochondria in C-fibers (A) and A-fibers (B).
- Swollen and vacuolated mitochondria shown at arrows; barred arrows point to normal mitochondria.
- A mixture of normal and swollen and vacuolated mitochondria were often found within the same axon.
- These examples are from a paclitaxel-treated rat that received ALCAR injections.

S0715: Randomized Placebo-Controlled Trial Of Acetyl L-Carnitine For The Prevention Of Taxane Induced Neuropathy

History of stage I, II, or IIIA, About to initiate taxane-based chemotherapy

- **Paclitaxel at 175 mg/m2 QOWx 4**
- **Paclitaxel at 80 mg/m2 x 12 w**
- **TAC (docetaxel 75 mg/m2) q3weeks x 6**
- **TC**

(N = 190/arm)

RANDOMIZE

→ **ALC**
1 gm TID x 24 weeks

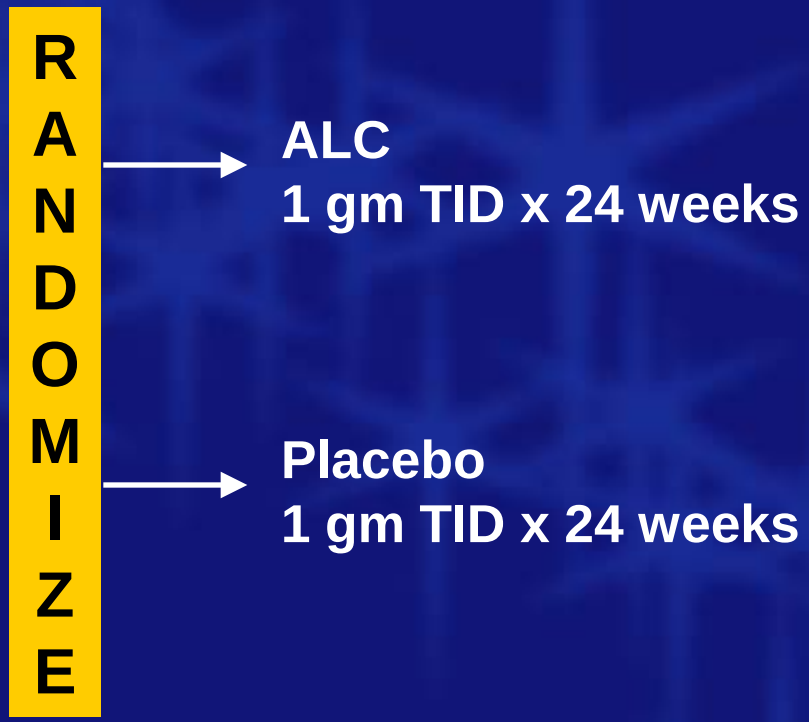
→ **Placebo**
1 gm TID x 24 weeks

Follow-up: 12 weeks, 24 weeks, 36 weeks, 1 year
Main Outcome: Change in Neurotaxane subscale of the FACT-TAX
Secondary: CTC; Fatigue; NGF; Dose/Compliance

Bayer: Phase II Randomized Placebo-Controlled Trial Of Acetyl L-Carnitine For The Prevention Of Sagopilone Induced Neuropathy

Prostate or Ovarian Cancer
Grade 0 CTC PN
About to initiate Sagopilone on efficacy trial

(140)



Follow-up: 6 cycles
Main Outcome: CTCAE PN Grade
Secondary Outcomes- treatment discontinuation; incidence of grade 3/4

Prevention of CIPN

- Alpha-Lipoic Acid / Thiotic Acid

Alpha-Lipoic Acid / Thiotic Acid

- A potent lipophilic antioxidant
- Oxidative stress implicated in pathogenesis of diabetic PN
- 7 RCTs trials of thioctic acid in diabetic PN completed
- Meta-analysis conclusions
  - Short-term treatment using IV thioctic acid 600 mg/day reduces symptoms of diabetic PN
  - Improvement of neuropathic deficits
  - Oral treatment for 4-7 m. reduces neuropathic deficits
  - Improve cardiac autonomic neuropathy
  - Studies revealed a favorable safety profile

MDACC: Prevention of Cisplatin or Oxaliplatin-induced PN with Alpha Lipoic Acid: A Placebo-Controlled Phase III Trial

Scheduled to receive platinum
No clinical neuropathy
No neurotoxic chemo for
6 mos prior
Stratified
prior platinum therapy

(N = 244 pts)

RANDOMIZE

→ Alpha Lipoic Acid
TID x 24 weeks

→ Placebo
TID x 24 weeks

Follow-up: 6-8; 12; 24; 36; 48
Main Outcome: Severity and frequency of PN; FACT-GOG-NTX
Secondary: functional tests, chemotherapy courses/doses,

Prevention of CIPN-Glutathione

Glutathione

- Tripeptide consisting of 3 amino acids: glutamyl-cysteinyl-glycine
- Naturally occurring compound
- Felt to be nontoxic
- High affinity for heavy metals

Glutathione


Glutathione
Glutathione S
transferase
Sulfur
substituted
glutathione

Glutathione

- There are no known human drug interactions of concern
- Administered IV, IM, or by inhalation

Glutathione

- Initially thought to be able to prevent cisplatin-induced nephrotoxicity
- In animal studies utilizing cisplatin, GSH did decrease nephrotoxicity and neurotoxicity

Glutathione

- Some evidence that GSH decreases cisplatin-induced nephrotoxicity in humans
- Some preliminary clinical trials, designed to look at nephrotoxicity, revealed a lower than expected incidence of neurotoxicity

Platinum neurotoxicity

From accumulation of platinum in dorsal room ganglia

Glutathione

- Decreases the accumulation of platinum in dorsal root ganglia
- Regulates calcium channel kinetics
- This might be responsible for how it helps to prevent neurotoxicity
- It may also affect other ion channel pathways

Randomized Glutathione Trials

Glutathione for Advanced Gastric Cancer/CDDP

	GSH n=25	Placebo n=25
Response rates		
Complete response	20%	12%
Partial response	56%	40%
Overall response	76%	52%
Median overall survival	14 mo	10 mo
Neuropathy		
Week 9	0%	66%
Week 15	17%	88%

Cascinu et al: J Clin Onc 13(1):26, 1995

Glutathione for Oxaliplatin/Advanced Colorectal Cancer (1)

	Glutathione n=26	Placebo n=26
Therapy administered		
Total cycles	175 (median – 8)	172
Dose intensity	39.2 mg/m^2/wk	38.8 mg/m^2/wk
Median total dose	782 mg	783 mg

Cascinu et al: J Clin Onc 20(16):3478, 2002

Glutathione for Oxaliplatin/Advanced Colorectal Cancer (2)

	Glutathione n=26	Placebo n=26
Antitumor activity		
Partial response	27%	23%
Median progression-free survival	7 mo	7 mo
Median overall survival	16 mo	17 mo

Cascinu et al

Glutathione for Oxaliplatin/Advanced Colorectal Cancer (3)

	Glutathione n=26	Placebo n=26	P
Neuropathy			
After 4 cycles			
Grade I-II	27%	42%	
After 8 cycles			
Any	43%	79%	0.04
Grade II-IV	10%	58%	0.003
Grade III-IV	0%	26%	0.01
12 cycles			
Grade II-IV	30%	100%	0.004

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Cascinu et al

Glutathione for Advanced Ovarian Cancer/CDDP (1)

	Glutathione n=74	Placebo n=77	P
Treatment received			
Received 6 cycles	58%	39%	0.04
Received 6 cycles at 100 mg/m^2	23%	15%	
Mean no. of full dose courses	3.61	3.14	0.14
Mean total no. of course received	4.80	4.38	0.19
Mean total dose	440 mg/m^2	441 mg/m^2	0.13

Smyth et al: Ann Onc 8(9):569, 1997

Glutathione for Advanced Ovarian Cancer/CDDP (2)

	Glutathione n=74	Placebo n=77	P
Response rates			
Overall response rate	73%	62%	0.25
Complete response via second look laparotomy	6/13 pt	1/11 pt	0.014
Survival			0.99
Toxicity			
Mean weight gain	2 kg	0	0.01
Increased creatinine	39%	49%	
Neurosensory toxicity	39%	49%	0.22

Smyth et al: Ann Onc 8(9):569, 1997

Glutathione for Relapsed Ovarian Cancer/CDDP (n=33)

	Glutathione n=33/2	Placebo n=33/2
Therapy delivered		
Greater than 85% dose intensity	94%	60%
Antitumor activity		
Overall response rate	75%	60%
Complete response	44%	27%
Median survival	21 mo	15.9 mo
Mean sural nerve sensory amplitude potential after 9 wk, compared to baseline values	-26%	-43%

Colombo et al: Int J Gynecol Cancer 5(2):81, 1995

Glutathione for Ovarian Cancer/CDDP

	Glutathione n=16	No treatment n=17
Overall response rate	75%	60%

Bogliun et al: Ital J Neurol Sci 13(8):643, 1992

Glutathione Neuropathy Prevention, N08CA