

Potentially Effective Therapies for FOLFOX-Induced Peripheral Neuropathy

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What is the audience using for prevention of FOLFOX CIPN

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- CaMg
- Venlafaxine
- Anything else?

Topics

- **Introductory comments**
- CaMg
- Venlafaxine
- BAK
- Summary statements

FOLFOX-Induced Peripheral Neuropathy

- Major oncologic problem
- Neurosensory toxicity of oxaliplatin is dose-limiting and presents as two distinct clinical syndromes:
 - Acute symptoms
 - Cumulative peripheral neuropathy
- Common chemotherapy dose limiting toxicity
- Affects life quality

Topics

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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

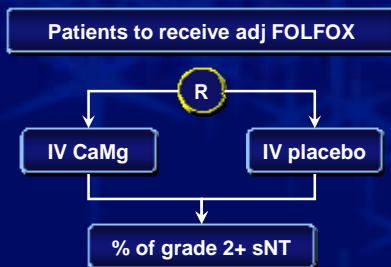
For the North Central Cancer Treatment Group

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

Background

- There were theoretical reasons to suggest that IV CaMg might decrease FOLFOX CIPN
- 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



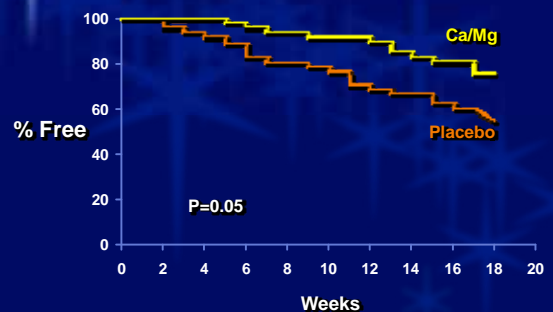
N04C7 Cancer Control Phase III Trial

- 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

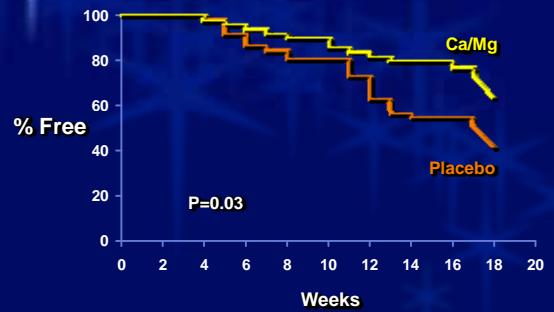
Time to Grade 2+ sNT (CTC scale)



Endpoint: Grade 2+ sNT (Oxaliplatin Scale)

Neurotoxicity grade	CaMg n=50	Placebo n=52	P
Grade 2+	28%	51%	0.018

Time to Grade 2+ sNT (Oxaliplatin scale)



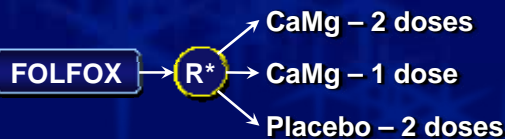
Concept Trial Story

- 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

The Use of Calcium and Magnesium for Prevention of Chemotherapy- Induced Peripheral Neuropathy

A Phase III Double-Blind Placebo-
Controlled Study N08CB



Topics

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Efficacy of venlafaxine for the prevention and relief of acute neurotoxicity of oxaliplatin: Results of EFOX, a randomized, double-blinded, placebo-controlled prospective study

J. P. Durand, G. Deplanque, J. Gorent, V. Montheil, E. Raymond, F. Scotte, E. Mitry, F. Goldwasser

J Clin Oncol 27:15s, 2009 (suppl; abstr 9533)

Background

- There are reports that venlafaxine can decrease neuropathic pain- positive Cochrane review
 - Saarto T, Wiffen PJ: Cochrane Database Syst Rev:CD005454, 2007
- Anecdotal experience and pilot reports support that venlafaxine decreases CIPN
 - Durand JP, Goldwasser F: Anticancer Drugs 13:777-80, 2002
 - Durand JP, et al: Anticancer Drugs 14:423-5, 2003
 - Ozdogan M et al: Turkish J Cancer 34:110-13, 2004
 - Durand JP et al: Anticancer Drugs 16:587-91, 2005

Methods

- Patients presenting with oxaliplatin-induced acute neurotoxicity were randomized in a double-blinded study, to receive:
 - Venlafaxine hydrochloride (50 mg 1 hour prior oxaliplatin infusion and venlafaxine extended release 37.5 mg b.i.d. from day 2 to day 11)
 - Placebo
- Neurotoxicity was evaluated using
 - A numeric rating scale of symptoms relief
 - The Neuropathic Pain Symptom Inventory

Results

Overall effect of venlafaxine on acute CIPN

% of pts	Venlafaxine (N=20/24)**	Placebo (N=22/24)**	p*
100% relief of acute neuropathy	31%	5 %	0.03
≥ 50 % relief of acute neuropathy	69 %	26 %	0.02
Incidence of reported acute neurotoxicity	37 %	77 %	0.01

*Fisher's exact test; **Evaluable/total

Results

Occurrence of chronic neuropathy

	Venlafaxine (N=20/24)	Placebo (N=22/24)	p*
Mean cumulative dose of administered oxaliplatin	1170 mg	1152 mg	-
% of pts with no neuropathy at 3 months	39 %	6 %	0.06
% of pts with grade 3 neuropathy at 3 months	0	33 %	0.03

* Fisher's exact test

Topics

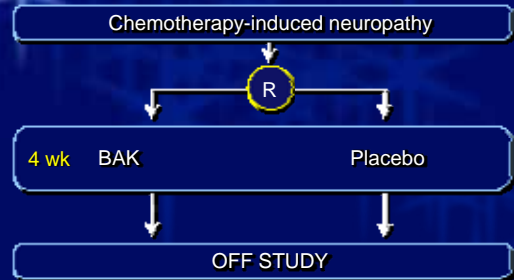
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A randomized controlled trial evaluating a topical treatment for chemotherapy-induced neuropathy: NCCTG trial N06CA

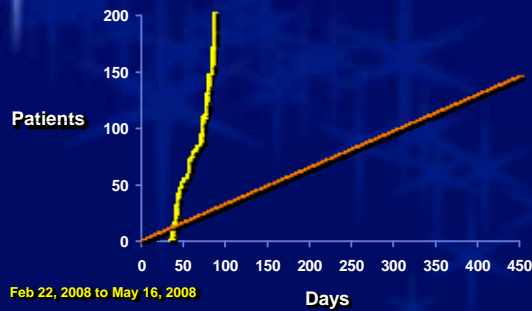
D. L. Barton, E. Wos, R. Qin, B. Mattar, N. Green, K. Lanier, J. Bearden, J. Kugler, K. Rowland, C. Loprinzi

J Clin Oncol 27:15s, 2009 (suppl; abstr 9531)

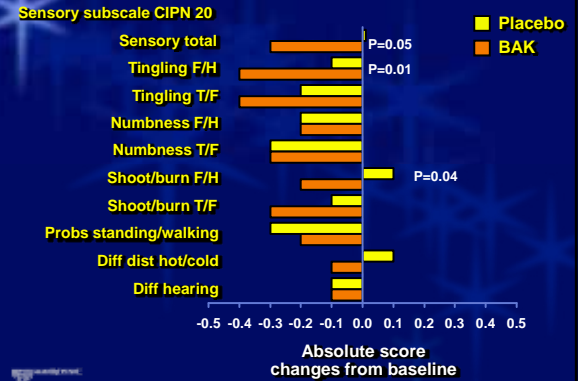
Study Schema



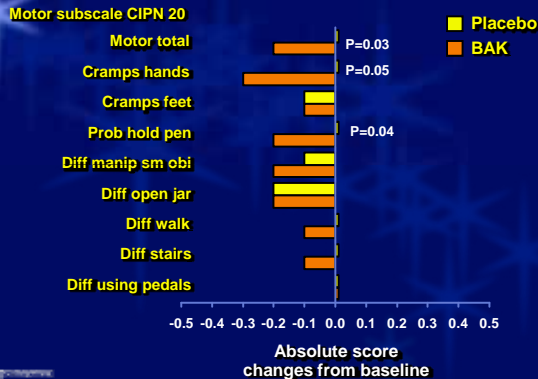
BAK Accrual



BAK EORTC CIPN-20, Sensory



BAK EORTC CIPN-20, Motor



Conclusions

- Topical BAK looks like it is worth pursuing further
- Potentially higher doses and/or different vehicle

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CP1347589-31

Summary statements

- CIPN is a major clinical problem with oxaliplatin
- There is suggestive evidence that CaMg and/or venlafaxine can prevent this problem
- There is suggestive evidence that topical BAK and/or venlafaxine can treat this problem



CP1347589-32

Thank you



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