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Prevention of Oxaliplatin-Induced Neurotoxicity With Ca²⁺/Mg²⁺ Infusions: Preliminary Results of the NEUROXA Randomized Trial in Patients With Colorectal Cancer (CRC) Receiving The FOLFOX4 Regimen

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Background: Acute or chronic oxaliplatin-induced neurotoxicity can lead to early treatment cessation and may affect patients' quality of life. We previously showed that oxalate, one of the major metabolites of oxaliplatin and a chelator of Ca²⁺ and Mg²⁺, interacts with cellular Ca²⁺ and inhibits neural voltage-gated Na⁺ channels. This prospective, double-blinded, placebo-controlled, phase III study in patients receiving FOLFOX4 (5-fluorouracil, leucovorin, oxaliplatin) for colorectal cancer (CRC) was conducted to test whether Ca²⁺/Mg²⁺ infusions reduce oxaliplatin-associated neurotoxicity. An interim analysis was performed to examine the potential effect of Ca²⁺/Mg²⁺ infusions on FOLFOX4 antitumor efficacy.

Methods: Patients with stage III and IV CRC treated with FOLFOX4 were randomized to receive either 1 g calcium gluconate and 1.5 g magnesium sulfate or placebo before and after each infusion of oxaliplatin. The primary end point was the rate of acute neuropathy.

Results: A total of 144 patients have been accrued. Preliminary results for the first 52 stage IV CRC patients are available for antitumor efficacy. As the study database is not locked yet, the blinding of the data has been maintained. Baseline characteristics are balanced in both groups of patients. Responses were confirmed and also independently

reviewed. No differences in terms of overall survival, progression-free survival, and response rates were observed between the two groups. The median follow-up is currently 15.4 months, and follow-up on the remaining study patients is ongoing.

	Arm A (n=26)	Arm B (n=26)	<i>P</i> value*
Age in years, mean ± SD	66±10	64±8	
No. of metastatic sites: 1	16	13	
> 1	10	13	
Median overall survival (mo)	25.1±4	25.5±4.1	.45 ⁽¹⁾
Progression-free survival (mo)	12±0.6	12±0.5	.79 ⁽¹⁾
Response rate at 3 months (%)			
Complete response	3.8	1.5	.45 ⁽²⁾
Partial response	46.2	51.5	
Stable disease	34.6	29.2	
Progressive disease	14.5	18.3	

*Tests: Statistics for Equality of Survival Distributions for BRAS⁽¹⁾ and X²⁽²⁾

Conclusions: Preliminary results of this study suggest that Ca²⁺/Mg²⁺ infusions do not have any adverse effect on oxaliplatin efficacy.