Identification of Lipidomics Predictors of Sensory Paclitaxel-induced Peripheral Neuropathy

Ciao-Sin Chen,[1] Alla Karnovsky,[2] N Lynn Henry,[3] Kathleen A Stringer,[1,4] Daniel L Hertz [1,3]

[1] Department of Clinical Pharmacy, University of Michigan College of Pharmacy, Ann Arbor, Michigan, USA.
[2] Department of Computational Medicine and Bioinformatics, University of Michigan Medical School, Ann Arbor, Michigan, USA.
[3] Rogel Cancer Center, University of Michigan Health, Ann Arbor, Michigan, USA.
[4] NMR Metabolomics Laboratory, University of Michigan College of Pharmacy, Ann Arbor, Michigan, USA.

Background

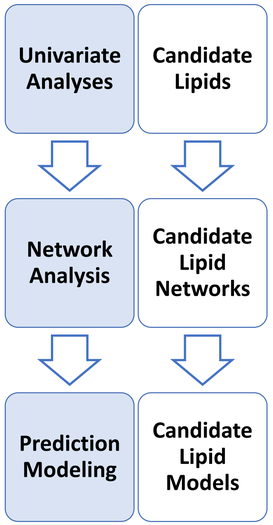
- Chemotherapy-induced peripheral neuropathy (CIPN) is a common and dose-limiting side effect of paclitaxel in patients with breast cancer.[1,2]
- Prior studies suggest some lipid levels can indicate CIPN severity,[3-5] including paclitaxel-induced PN.[3]

Objective

- Discover pre-treatment lipids that are associated with higher severity of paclitaxel-induced PN.

Methods

- **Patient cohort:** NCT02338115 is an observational study of adult female patients with early-stage breast cancer scheduled to receive paclitaxel 80 mg/m^2 1-hour infusion weekly for 12 doses.[6]
- **Patient selection:** Patients did not have pre-existing severe peripheral neuropathy and received at least 25% of the scheduled treatment (3 doses).
- **Sensory CIPN measurement:** CIPN8 sensory subscale of the CIPN20 patient-reported outcome questionnaire weekly before infusions.[7]
- **Lipidomics measurement:** 36 patients had end-of-first-infusion plasma samples available as pseudo baseline. 854 lipids measured by untargeted shotgun lipidomics via LC-MS/MS. Identified by LipidBlast. Quantified by Multiquant. Imputed using K-nearest neighbors. Normalized using internal standards and then $\log_2$ transformed.[8]
- **Statistical analyses:**



Linear regression with false discovery rates (FDR) <10% to correct for multiple comparisons

Max CIPN8 ~ lipid ± baseline CIPN8

Debiased sparse partial correlation (DSPC)[9]

Group least absolute shrinkage and selection operator (LASSO) with 5-fold repeated cross validation to reduce overfitting[10]

Results

Table 1. Clinical Data of Analyzed Patients (n=36)

Demographics	N (%) or Mean [range]
Age (years)	53 [28, 71]
Race – Caucasian	33 (92%)
Body mass index (kg/m^2)	27 [19, 41]
Number of doses received	11 [6, 12]
Treatment disruption due to CIPN	10 (29%)
Diabetes or Hb_{A1C} ≥6.5% (n=24)	10 (29%)
Use of alcohol	20 (56%)

Table 2. 29 Lipids Associated with Higher and Lower CIPN Severity

Sphingolipids	Phospholipids					Glycerolipids
Cer 36:0;O2	LPC 19:0	PC 36:4	LPE 17:0	PE 38:2	PI 34:2	DG 34:2
Cer 36:1;O2	LPC 20:0	PC 37:2	LPE 22:6	PE O-34:2		DG 36:2
Cer 40:1;O2	LPC 22:5	PC O-34:3		PE O-34:3		TG 52:2
SM 43:1;O2		PC O-36:2		PE O-35:3		
SM 42:6;O2		PC O-37:5		PE O-36:3		
SM 44:3;O2				PE O-38:4		
				PE O-40:6		
				PE O-40:7		
				PE O-42:7		

Figure 1. 9 Candidate Lipid Networks (FDR<25%)

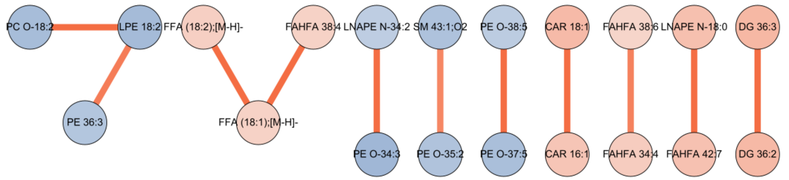
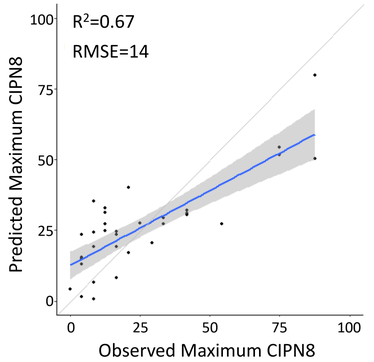


Figure 2. A predictive model composed of networks of phosphatidylethanolamines (PE) and long-chain ceramides (Cer) demonstrated good prediction performance. (R^2, coefficient of determination; RMSE, root mean square error)



Conclusion

- Our findings suggest that pretreatment levels of sphingolipids, phospholipids, and glycerolipids may predict the severity of paclitaxel-induced PN and identify patients at higher risk of severe CIPN.

Future Work

- Discover and validate lipid signatures of CIPN risk in larger patient cohorts, such as SWOG 1714.
- Investigate whether personalizing treatment based on CIPN risk, as predicted by lipid signatures, can reduce CIPN and improve treatment outcomes in patients with breast cancer.
- Examine the mechanistic pathways between these lipids and CIPN occurrence or severity.

References

1. Seretny, M., et al. "Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis." Pain (2014) 155(12): 2461-2470.
2. Speck, R. M., et al. "Impact of chemotherapy-induced peripheral neuropathy on treatment delivery in nonmetastatic breast cancer." J Oncol Pract (2013) 9(5): e234-240.
3. Kramer, R., et al. "Neurotoxic 1-deoxysphingolipids and paclitaxel-induced peripheral neuropathy." Faseb j (2015) 29(11): 4461-4472.
4. Maekawa, K., et al. "Serum lipidomics for exploring biomarkers of bortezomib therapy in patients with multiple myeloma." Cancer Sci (2019) 110(10): 3267-3274.
5. Verma, P., et al. "A Metabolomics Approach for Early Prediction of Vincristine-Induced Peripheral Neuropathy." Sci Rep (2020) 10(1): 9659.
6. Hertz, D. L., et al. "Paclitaxel Plasma Concentration after the First Infusion Predicts Treatment-Limiting Peripheral Neuropathy." Clin Cancer Res (2018) 24(15): 3602-3610.
7. Lavoie Smith, E. M., et al. "Assessing patient-reported peripheral neuropathy: the reliability and validity of the European Organization for Research and Treatment of Cancer QLQ-CIPN20 Questionnaire." Qual Life Res (2013) 22(10): 2787-2799.
8. Afshinnia, F., et al. "Lipidomics and Biomarker Discovery in Kidney Disease." Semin Nephrol (2018) 38(2): 127-141.
9. Basu, S., et al. "Sparse network modeling and metscape-based visualization methods for the analysis of large-scale metabolomics data." Bioinformatics (2017) 33(10): 1545-1553.
10. Iyer, G. R., et al. "Application of Differential Network Enrichment Analysis for Deciphering Metabolic Alterations." Metabolites (2020) 10(12).

This study was funded by grants from the National Center for Advancing Translational Sciences (KL2TR000434 and 2UL1TR000433, DLH) and University of Michigan Michigan Institute for Clinical and Health Research (UL1TR002240, DLH). Contact Information: CSCChen@umich.edu