# A correlative blood assay to monitor patients at risk for chemotherapy-induced peripheral neuropathy

Angeleah Dadivas, OMS-II, Kinjal Parikh, MD, John Kennedy, BS, Amy Brady, OMS-I, Margaretha Wallon, PhD
Lankenau Institute for Medical Research, Wynnewood, Pennsylvania

## Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a disabling side effect of platinum-based chemotherapies like cis-, oxali- and carboplatin. These therapies cause bursts of reactive oxygen species (ROS), which can trigger structural changes in peripheral nerves including neuronopathy, axonopathy and/or myelinopathy. There is no effective CIPN prevention strategy and medications to alleviate neuropathy often lack efficacy and/or have unacceptable side-effects.

## Background

The “stocking and glove” distribution of neuropathy is primarily due to the vulnerability of long nerves in the peripheral nervous system. A meta-analysis of 31 CIPN studies involving 4,179 patients indicated CIPN in 48% of patients. Within the first month of completing chemotherapy, the prevalence of CIPN was 68.1%; after 6 months of completing chemotherapy, the prevalence of CIPN decreased to 30.0%.[1] A separate study indicated colon cancer patients who received oxaliplatin-based adjuvant chemotherapy had numbness or tingling of hands and feet up to 6 years from starting treatment.[2] Due to the high frequency of neuropathy, there is a need for a test that can help clinicians better guide therapy and prevent this detrimental outcome.[3]

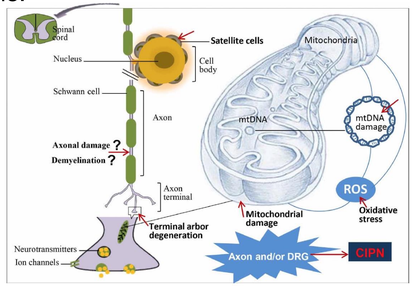



Image from Han and Smith. “Pathobiology of cancer chemotherapy-induced peripheral neuropathy.” *Frontier’s in Pharmacology.* Dec 2013. Volume 4. Article 156.

## Objective

Glutathione, an antioxidant, plays an important role in red-ox homeostasis and the recycling of glutathione can be determined by the ChemoTox assay.[4] The aim of this study was to determine if ChemoTox can provide clinicians with a blood assay to quantitate platinum-induced neuropathy.

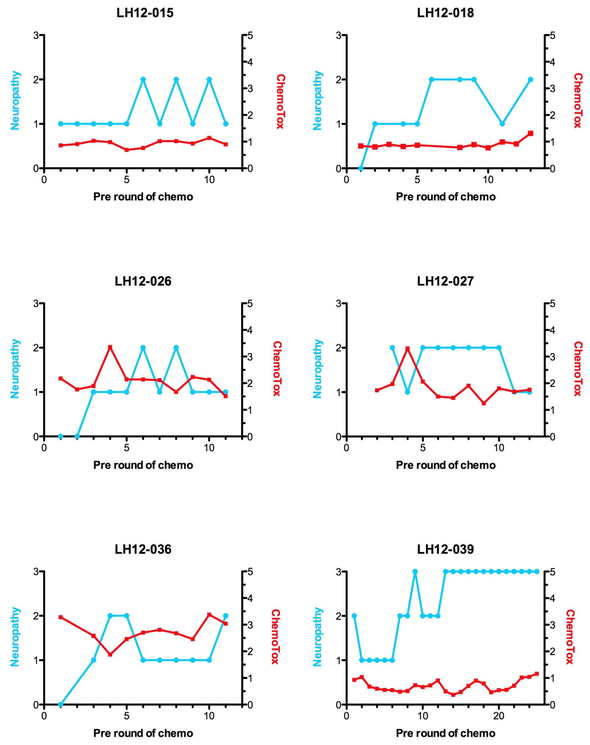
## Materials & Methods

The cohort of cancer patients are from the Lankenau Medical Center outside of Philadelphia, PA. The hospital sees ~1,100 cancer patients per year. Colorectal patients constitute 14.7% while 10.4% are lung cancer patients. Of the patients enrolled in this study, 84.4% are Caucasian, 14.0% are African-American and 1.6% are Asian.

Blood drawn from consented and chemotherapy naïve patients (N= 59) were tested for glutathione recycling capacity and normalized to total red cell numbers. Patients reported neuropathy using the Rotterdam Symptom Check List. Patient’s glutathione recycling capacities were correlated to self-reported neuropathy.

| Characteristics | Patients (%) | | Number of patients |
|---|---|---|---|
| Number of patients | | | 59 |
| Age (M ±SD) | | 63.4 ± 12.8 | |
| Median age (range) | | 64 (24 – 91) | |
| Female | 47.5 | | 28 |
| **Primary Tumor** | | | |
| Colorectal | 55.9 | | 33 |
| Lung | 44.0 | | 26 |
| **Chemotherapy treatments** | | | |
| No. of chemotherapy agents used per patient (M ±SD) | | 2.7 ± 0.70 | 59 |
| Patients receiving ≥3 chemotherapy agents | 52.7 | | 35 |
| Oxaliplatin | 52.5 | | 31 |
| Carboplatin | 38.9 | | 23 |
| Cisplatin | 8.47 | | 5 |

## Results




**42 of 59** patients stated they experienced neuropathy during chemotherapy. **21 high risk patients** were identified as those who reported experiencing neuropathy as a “2”, or “quite a bit” on the Rotterdam Checklist. 19 of the 21 patients experienced increasing neuropathy within their first 5 treatments. Select correlates above are patient-reported neuropathy (0-3) in **blue**, and ChemoTox quantities (ng / ml plasma and $10^6$ RBC) in **red**.

## Discussion

- 72.2% reported neuropathy during chemotherapy and 35.6% were recognized as high risk patients for progressive CIPN. These outcomes, despite the small cohort size, are representative of larger studies.
- **Patients LH12-015, LH12-018 and LH12-039** display trends that initially show decreased glutathione recycling capacities and remain low over time. This correlation detects a patient population that can be addressed earlier as to the direction of treatment.
- **Patients LH12-026, LH12-027 and LH12-036** illustrate a patient population that initially display adequate glutathione recycling capacity. However, the inability to maintain turnover during extended treatment cycles identifies the inverse correlation as a trend of concern.
- Low glutathione recycling also has a corollary to an increased risk for chemotherapy induced nausea and vomiting (CINV). Among the patients shown in results, 5/6 patients reported some level of nausea, and 4/6 reported moderate to severe delayed nausea.[4]

## Future Directions

- Taxane therapies, another culprit for causing CIPN via ROS, is a target population for future studies of ChemoTox efficacy.
- Platinum therapy as a treatment for breast cancer should be explored to see if systemic ROS provides a similar pattern to that of patients with lung and colon cancer.

## References

(1) Trivedi MD, Meghna S., et al. “Management of Chemotherapy-Induced Peripheral Neuropathy.” *The American Journal of Hematology/Oncology*, vol. 11, no. 1, Jan. 2015, pp. 4–10., www.gotoper.com/publications/ajho/2015/2015jan/management-of-chemotherapy-induced-peripheral-neuropathy.
(2) Kidwell KM, Yothers G, Ganz PA, et al. Long-term neurotoxicity effects of oxaliplatin added to fluorouracil and leucovorin as adjuvant therapy for colon cancer: results from National Surgical Adjuvant Breast and Bowel Project trials C-07 and LTS-01. Cancer. 2012;118(22):5614-5622.
(3) Seretny, Marta, et al. “Incidence, Prevalence, and Predictors of Chemotherapy-Induced Peripheral Neuropathy: A Systematic Review and Meta- Analysis.” *Pain*, vol. 155, no. 12, 2014, pp. 2461–2470., doi:10.1016/j.pain.2014.09.020.
(4) Kutner, Thomas, et al. “Preliminary Evaluation of a Predictive Blood Assay to Identify Patients at High Risk of Chemotherapy-Induced Nausea.” *Supportive Care in Cancer*, vol. 25, no. 2, 2016, pp. 581–587., doi:10.1007/s00520-016-3442-5.