Ototoxic and Neurotoxic Effects of Chemotherapy in Adults

Consequences of Modern Chemotherapy in Adults

• In the next 5 years, cancer survivors will number 19M
• 97% of those will be survivors of adult-onset cancers
• Symptoms experienced with chemotherapy include:
  • Cognitive changes
  • Mood changes
  • Fatigue
  • Peripheral Neuropathies
  • Hearing Loss
  • Tinnitus
Consequences of Modern Chemotherapy in Adults

- These numbers have led organizations like the National Comprehensive Cancer Network to develop guidelines for cancer survivorship.
- NCCN guideline is silent on any evaluation of the effects of neurotoxic CTX on the auditory system (i.e., hearing loss, tinnitus).

Relatively few studies of ototoxic drugs in adults

- Reports of hearing loss following platinum drugs range from 20-68%
- Reports of tinnitus following platinum drugs range from 19-42%
  - damaging the outer hair cells and the stria vascularis Initially, followed by the inner hair cells, and supporting cells.
  - SGC damage may be concurrent

Frisina et al., 2017; Bacon et al., 2003, Jenkins et al., 2009, Ozguroglu et al., 2006, Salvinelli et al., 2003, Skalleberg et al., 2017
Relatively few studies of ototoxic drugs in adults

- Most studies in testicular and head and neck cancers
  - Only a few small studies evaluated audiovestibular toxicities in patients with breast, gastrointestinal (GI), gynecological (GYN), or lung cancer
- Many patients receive more than one type of drug
- Few patients report even informal hearing monitoring

Reported risk factors for adult-onset cisplatin ototoxicity

- Higher cumulative dose
- Younger age at exposure
- Concomitant radiation
- Being male
- Co-administration of potential ototoxic compounds (e.g., antibiotics)
- Longer time from CTX to audiometry and older age at audiometry
- Current treatment for hypertension were associated with more severe hearing loss
- Genetic predisposition
- Pre-exposure hearing ability
- A large amount of inter-individual variability exists in the ototoxic effects of platinum

Frisina et al., 2017; Bacon et al., 2003, Jenkins et al., 2009, Ozguroglu et al., 2006, Salvinelli et al., 2003, Skalleberg et al., 2017
Taxol/ Paclitaxol / Taxane

- Commonly used with cisplatin
- Known neurotoxin
- Pre-clinical trials show cochlear, SGC and auditory nerve fiber damage in mice
  Dong et al, 2014; Atas et al, 2006
- Human study showed no significant onset of bilateral hearing changes 250 – 8000 Hz with taxane-only chemo in women
  Sarafraz and Ahmadi, 2008

Cisplatin and Taxane Compounds

- A common treatment protocol for many cancers
- Both are neurotoxic
- Recent UCSF nursing study evaluating differences in phenotypic and molecular characteristics of CTX-induced neuropathy (CIN) in 400 survivors with CIN and 200 survivors without CIN.
  - 40.6% had received only a platinum compound
  - 39.1% had received only a taxane compound
  - 20.3% had received both a platinum and a taxane compound
  - Survivors of most common cancers
Two simple questions

- Two items from the FACT/GOG-Ntx subscale evaluate hearing loss and tinnitus

(Functional Assessment of Therapy / Gynecologic Oncology Group Neurotoxicity, Huang et al., 2007)

Neuropathy and hearing loss and tinnitus

- 49% of Patients WITH Ctx-induced neuropathy reported auditory impairment

- 27.8% of Patients WITHOUT Ctx-induced neuropathy reported auditory impairment
Peripheral neuropathy

- Bilateral
- Multiple Nerves
- Polyneuropathy
- “Gloves and stockings”
- Numbness
- Tingling
- Burning
- Pain

Peripheral Neuropathy Symptoms:
1. Numbness, especially in arms and legs
2. Stabbing pain
3. Burning pain
4. Sensitivity to touch
5. Coordination difficulties
6. Muscle weakness
7. Bladder/bowel problems

$p < .001$
Peripheral neuropathy “Pain”

- Tender
- Shooting
- Sensitive
- Electrical
- Throbbing
- Cramping
- Itchy
- Unpleasant

Peripheral Neuropathy Measures
Sensation and Pain

Pain
  • Brief Pain Inventory
  • Pain Qualities Assessment Scale

Sensation
  • Light touch: Semmes Weinstein monofilaments
  • Cold sensation: Tiptherm Rod
  • Pain sensation: Neurotip
  • Vibration threshold: Vibrometer
  • Upper and lower extremities on the dominant side tested.

CIN study self-report

Auditory symptoms: 49%
Hearing loss only: 16.1%
Tinnitus only: 12.3%
HL + Tinnitus: 20.6%
Does regimen matter?

Balance, stress and QOL assessments

Balance
- Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (CIPNAT) questionnaire
- Timed get up and go test (TUG)
- Fullerton Advanced Balance (FAB) test

Symptom burden

Perceived stress
- Impact of Event Scale – Revised (IES-R)
- Perceived Stress Scale (PSS)

QOL
- Medical Outcomes Study-Short Form (SF12)
- QOL Scale-Patient Version (QOL-PV)
BALANCE

CIN+HL+TINN patients
More reported trouble with balance
Higher severity scores
Worse TUG scores
group average 13.5
greater risk of falls

STRESS
Impact of event scale - revised

How distressed are you about some event in the past?
How much stress does the event continue to cause?

I felt irritable and angry
I was jumpy and easily startled
I had trouble falling asleep
I had trouble concentrating
Reminders of it caused physical reactions
I felt watchful and on-guard

Any reminder brought back feelings about it
I had trouble staying asleep
Other things kept making me think about it.
Pictures about it popped into my mind
I found myself feeling like I was back at that time.
I had waves of strong feelings about it
I have dreams about it

I avoided letting myself get upset when I thought about it or was reminded of it
I felt as if it hadn’t happened or wasn’t real.
I stayed away from reminders of it.
I tried not to think or talk about it.
I was aware that I still had a lot of feelings about it, but I didn’t deal with them.
My feelings about it were kind of numb

Impact of Event Scale-Revised

Avoidance

Intrusion
CIN ***

Hyperarousal
CIN ***
HL **
TINN *

Below is a list of difficulties people sometimes have after stressful life events. Please read each item, and then indicate how distressing each difficulty has been for you DURING THE PAST SEVEN DAYS with respect to your cancer and its treatment:

Not at all   A little  Moderately  Quite a bit   Extremely

0    1    2    3    4

Other outcomes in survivors

Cognitive changes

Financial toxicity

Quality of Life

Anxiety and Depression

Daily function
Comparison of survivors without CIN and no auditory toxicity (n=57) to survivors with CIN and both HL and tinnitus (n=64)

CIN+HL+TINN have
- poorer functional status
- more severe comorbidity profile
- a higher level of depressive symptoms
- poorer QOL outcomes.

Differences in KPS scores, comorbidity scores, depressive symptom scores, SF-12, and MCS scores are both statistically significant AND clinically meaningful differences

Doses of CTX drugs – no differences were found between the two groups in the total doses of cisplatin, oxaliplatin, taxol, and taxotere.

Compared to the no neurotoxicity group, survivors with all three neurotoxicities (CIN+HL+tinnitus):

- were older
- less likely to be employed
- had a higher body mass index (BMI)
- had a higher number of comorbid conditions
- reported a poorer functional status
- higher levels of depressive symptoms and anxiety
- higher levels of fatigue, and sleep disturbance
- higher levels of perceived stress
- poorer QOL outcomes
- had significant decrements in light touch, cold, pain, and vibratory sensations
- significant decreases in balance and physical function

No between group differences were found in the types of CTX regimens received, the total dose of CTX administered, the length of time since the cancer diagnosis, and the number of metastatic sites.
Comparison among the three auditory groups with CIN – Survivors with HL + TINN have:
- higher levels of comorbidity
- higher levels of depressive symptoms
- poorer level of physical function
- poorer QOL scores

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CIN &amp; No Auditory Toxicity (1) (n=158)</th>
<th>CIN and Only HL (2) (n=50)</th>
<th>CIN + HL+ Tinnitus (3) (n=64)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
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<tr>
<td></td>
<td>60.5 (9.9)</td>
<td>62.7 (9.6)</td>
<td>62.4 (10.6)</td>
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<td>Karnofsky Performance Status</td>
<td>84.4 (10.7)</td>
<td>82.9 (11.9)</td>
<td>79.8 (10.0)</td>
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<td>1 &gt; 3</td>
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<td>Self-administered Comorbidity Questionnaire score</td>
<td>3.6 (2.9)</td>
<td>5.0 (4.0)</td>
<td>5.4 (3.6)</td>
<td>&lt;.001</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>1 &lt; 2 and 3</td>
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<tr>
<td>Time since cancer diagnosis (years)</td>
<td>4.2 (4.1)</td>
<td>5.6 (5.5)</td>
<td>5.6 (5.4)</td>
<td>.005</td>
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<td>Center for Epidemiological Studies-Depression scale</td>
<td>8.6 (7.3)</td>
<td>12.3 (10.2)</td>
<td>14.4 (11.6)</td>
<td>&lt;.001</td>
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<td>1 &lt; 2 and 3</td>
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<td>SF-12 Physical Component Summary score</td>
<td>44.4 (11.2)</td>
<td>41.9 (10.3)</td>
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<td>1 &lt; 3</td>
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<tr>
<td>SF-12 Mental Component Summary score</td>
<td>51.7 (8.5)</td>
<td>48.5 (9.6)</td>
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<td>Female (%)</td>
<td>90.5</td>
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<td>75.0</td>
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<td>3 &lt; 1 and 2</td>
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<td>Diagnosis (%)</td>
<td>61.4</td>
<td>50.0</td>
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<td>Breast</td>
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<td>Colon</td>
<td>2.5</td>
<td>2.0</td>
<td>1.6</td>
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<td>Lung</td>
<td>9.5</td>
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<td>Ovarian</td>
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<td>Other</td>
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<td>Chemotherapy regimen</td>
<td>18.4</td>
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<td>40.6</td>
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<td>Only platinum compound</td>
<td>53.2</td>
<td>44.0</td>
<td>39.1</td>
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<td>Only taxane compound</td>
<td>28.5</td>
<td>40.0</td>
<td>20.3</td>
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<td>platinum and taxane compound</td>
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Oncology perspective

- The PI of this initial study, shared the data on the occurrence of hearing loss and tinnitus with the six medical oncologists who were co-investigators
  - All of them were surprised at the percentage with HL and tinnitus.
  - They reported that they never assess hearing loss or tinnitus in their cancer survivors.
NEXT STEPS

- Characterization of hearing loss and tinnitus
  - Full audiometric assessment with HF, QuickSIN, OAEs, ABR
  - HHI
  - TFI
- Balance
  - MiniBEST test
- Cognitive assessment
- Blood draw
- Peripheral neuropathy testing
- Mood
- Financial toxicity

FIRSTS AND GOALS

First study to

- comprehensively evaluate HL and tinnitus in cancer survivors who received platinum and/or taxane.
- provide a characterization of tinnitus in cancer survivors who received neurotoxic CTX.
- provide a characterization of the occurrence, severity, and impact of hearing loss and tinnitus on cancer survivors.
  - Information on the causes and characteristics, as well as impact of these types of auditory toxicity will be used to plan intervention studies to improve hearing, reduce the impact of tinnitus, and assist cancer survivors to adapt to the long term effects of hearing loss and tinnitus.
FIRSTS AND GOALS

Goals:
Evaluate HL with and without tinnitus in cancer survivors experiencing other neurotoxic effects of CTX (i.e., CIN).
• Are there additive effects of the two types of neurotoxicity in cancer survivors?
Incorporate the emerging genomics of hearing loss, and genomics of CTX-induced auditory toxicity
• Blood specimens are collected and processed for future genomic analyses.
Increase oncology clinicians’ awareness of hearing loss and tinnitus in cancer survivors.

On the horizon

• Prospective study of CIN, hearing loss, tinnitus and balance.
• Monitor before during and after treatment
Have you completed chemotherapy?...

You may be eligible for a study to learn more about the signs and symptoms related to nerve damage.

What is involved?

- Completion of online questionnaires
- A one-time visit to UCSF

Participants will be paid $200 for their time

Contact us for more information

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References

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