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UNIVERSITY OF NORTHERN COLORADO

Greeley, Colorado

The Graduate School

OTOTOXICITY MONITORING PROTOCOLS FOR COMMON CHEMOTHERAPEUTICS

A Scholarly Project Submitted in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Audiology

Megan Pamela Kennedy

College of Natural and Health Sciences
Communication Sciences and Disorders
Audiology

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This Doctoral Scholarly Project by: Megan Pamela Kennedy

Entitled: *Ototoxicity Monitoring Protocols for Common Chemotherapeutics*

has been approved as meeting the requirement for Degree of Doctor of Audiology in the College of Natural and Health Sciences in the Department of Communication Sciences and Disorders, Program of Audiology.

Accepted by the Doctoral Scholarly Project Research Committee

_____

Deanna K. Meinke, Ph.D., CCC-A, Research Advisor

_____

Diane L. Erdbruegger, Au.D., CCC-A, Committee Member

_____

Jennifer E. Weber, Au.D., CCC-A, Committee Member

ABSTRACT

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Cancer is a major public health concern and is increasingly prevalent worldwide. Sung et al. (2021) states that there were 19.3 million new cases of cancer across the globe, and almost 10 million deaths related to cancer in 2021. Sung et al. (2021) also notes that the United States accounts for 8% of all global cases, with an average of 1.7 million new cases annually. The top five most common adult cancers in the United States include: (1) breast, (2) prostate, (3) lung and bronchus, (4) colorectal, and (5) invasive melanoma of the skin. These cancers can be treated with techniques such as surgery, radiation, biologic/immunotherapy, and chemotherapy. Some chemotherapeutics used in treatment regimens are toxic to the auditory system and cause unwanted hearing loss or other unwanted side effects, such as tinnitus or dizziness. This occurrence is known as ototoxicity. Known ototoxic chemotherapeutic agents affect the auditory system in different ways due to the way they interfere with cancer cells and non-cancerous cells within the body. This requires the need to monitor for ototoxicity during cancer treatment.

The responsibility for monitoring for potential ototoxicity of chemotherapeutics falls upon audiologists. The American Academy of Audiology (Durrant et al., 2009) and the American Speech-Language-Hearing Association (Fausti et al., 1993) have published guidelines for ototoxicity monitoring which are designed for only one chemotherapeutic, cisplatin. Other agents, such as carboplatin, oxaliplatin, nedaplatin, vincristine, vinblastine, and

difluoromethylornithine (DFMO), have adverse effects on the auditory system in areas differing from cisplatin. Carboplatin causes damage to the spiral ganglion neurons and inner hair cell function before outer hair cells are affected (Dalian et al., 2012). Nedaplatin and oxaliplatin affect the auditory nerve fibers and both inner hair cell and outer hair cell stereocilia (Ding et al., 2012). Vincristine and vinblastine generally cause a hearing loss that is reversible once treatment is finished (Tazi et al., 2014) but also have neurotoxic affects to the auditory nerve fibers (Magge & DeAngelis, 2015). DFMO has been shown to decrease the number of polyamines in the inner ear (Nie et al., 2005) and affects the function of IHCs and OHCs (Salzer et al., 1990). Consequently, ototoxicity monitoring programs differ depending on the chemotherapy regime.

It is important for audiologists to understand the pathophysiology of the auditory damage that may occur for each chemotherapeutic to implement proper and effective ototoxic monitoring programs. In this document, audiologists are provided with examples of ototoxicity monitoring protocols for both responsive and non-responsive patients receiving carboplatin, oxaliplatin, nedaplatin, Difluoromethylornithine (DFMO), vincristine, and vinblastine. Gaps and limitations in the literature are identified and directions for further research are discussed, including the use of otoprotectants to prevent or decrease the ototoxic effects.

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TABLE OF CONTENTS

APPENDICES continued

LIST OF TABLES

TABLE

LIST OF FIGURES

FIGURE

LIST OF ABBREVIATIONS

AAA	American Academy of Audiology
ABR	Auditory Brainstem Response(s)
ASHA	American Speech-Language-Hearing Association
CAA	Council on Academic Accreditation
CHOP	Cyclophosphamide, Doxorubicin (Adriamycin), Vincristine (Oncovin), Prednisolone
CI	Cochlear Implant
dB	Decibel
DFMO	Difluoromethylornithine
DNA	Deoxyribonucleic Acid
DP	Distortion Product
DPOAE	Distortion Product Otoacoustic Emission(s)
ECochG	Electrocochleography
EHF	Extended High Frequency
EHFA	Extended High Frequency Audiometry
EP	Endocochlear Potential
HL	Hearing Level
Hz	Hertz
IHC	Inner Hair Cell(s)
k	Thousand

MA	Medical Assistant
MET	Mechanoelectrical Transduction
MRI	Magnetic Resonance Imaging
NP	Nurse Practitioner
OAE	Otoacoustic Emission(s)
ODC	Ornithine Decarboxylase
OHC	Outer Hair Cell(s)
PA	Physician's Assistant
RNA	Ribonucleic Acid
ROS	Reactive Oxygen Species
SGN	Spiral Ganglion Neuron
SIN	Speech in Noise
SNR	Signal-to-Noise Ratio
SRO	Sensitive Range for Ototoxicity
TEOAE	Transient Evoked Otoacoustic Emission(s)
U.S.	United States

CHAPTER I

INTRODUCTION AND REVIEW OF THE LITERATURE

In today's world, it is difficult to have never met someone affected by cancer in one way or another. Cancer is a common disease that can be treated in a variety of ways. Chemotherapeutic agents are one common way to treat cancer, but these can have some undesirable side-effects, such as damage to the auditory system. Audiologists monitor for auditory and vestibular toxicity in clinics across the United States (U.S.), but many are not aware of the differences in damage these chemotherapeutic agents cause. The purpose of this manuscript is to review common types of adult cancer, relevant chemotherapeutic agents and their effects on the auditory system, and how best to monitor toxicity in cancer patients based on each chemotherapeutic agent.

Epidemiology of Cancer

Cancer is a major public health concern and is increasingly prevalent worldwide. Sung et al. (2021) states that there were 19.3 million new cases of cancer globally, with almost 10 million deaths. Sung et al. (2021) also notes that the U.S. accounts for 8% of all global cancer cases, with a reported average of 1.7 million new cases in the U.S. annually. Cancer is the second-leading cause of death in the U.S. and an estimated 600,000 people die from it every year (Sung et al., 2021), and only about 1,000 deaths attribute to people fifteen years of age and younger (American Cancer Society, *Key statistics for childhood cancers*, 2020). Many people survive cancer, and the death rate is decreasing with time, possibly due to new treatment options and better screening methods (State Cancer Profiles, 2021). The American Cancer Society

estimates that 16.9 million Americans have had cancer at some point in their lives and have survived it (Siegel et al., 2020). In the U.S., the incidence rate for late-stage cancer is 448.7 per 100,000 people when referencing a 95% confidence level, or 1,673,000 people annually, averaged over 5 years (2015-2020). Siegel et al. (2021) also states that although cancer is a leading cause of death in the United States, there were 2.9 million fewer cancer deaths from the years 1991 to 2017, which is a 29% decrease in cancer rates over the 26-year span. This decline in new cases can be attributed to overall lifestyle changes from the 20th century into the 21st century, in addition to the increased availability of improved cancer screenings and treatment options available to patients in the U.S. Better treatment options often means that more people are living with chronic cancers (Boele et al., 2019).

According to the Siegel et al. (2021) and the American Cancer Society, the five most common adult cancer types in the United States for the year 2020, based upon the highest number of newly presenting cases, include: female breast (276,480 new cases in the U.S., 4,530 in Colorado), lung & bronchus (228,820 new cases in the U.S., 2,550 in Colorado), prostate (191,930 new cases in the U.S., 3,140 in Colorado), colon & rectal (147,950 new cases in the U.S., 2,040 in Colorado), and melanoma of the skin (100,350 new cases in the U.S., 1,920 in Colorado) (Siegel et al., 2020). In the state of Colorado, the incidence rate for late-stage cancer is 399.1 per 100,000 people at 95% confidence level, or 23,233 people annually. Table 1 provides summary information regarding incidence and mortality rates of adult cancer in the United States, by sex in 2021.

Table 1

New Cancer Cases by Sex, United States, 2021

Cancer Type	Female	Male	Both Sexes
Total	927,910	970,250	1,898,160
Digestive System	**147,000**	**191,090**	**338,090**
Oral Cavity & Pharynx	15,210	38,800	54,010
Esophagus	3,950	15,310	19,260
Stomach	10,400	16,160	26,560
Small intestine	5,260	6,130	11,390
Colo-Rectal	*69,980*	*79,520*	*149,500*
Pancreas	28,480	31,950	60,430
Liver	12,340	29,890	42,230
Respiratory System	**121,260**	**132,910**	**254,170**
Larynx	2,680	9,940	12,620
Lung & Bronchus	*116,660*	*119,100*	*235,760*
Bones & Joints	**1,510**	**2,100**	**3,610**
Soft Tissue (including heart)	**5,740**	**7,720**	**13,460**
Skin (excluding basal & squamous)	**47,200**	**68,120**	**115,320**
Melanoma	*43,850*	*62,260*	*106,110*
Other	3,350	5,860	9,210
Breast	***281,550***	***2,650***	***284,200***
Uterine Cervix	14,480	----------	----------
Uterine Corpus	66,570	----------	----------
Ovary	21,410	----------	----------
Vulva	6,120	----------	----------
Vagina & other	8,180	----------	----------
Prostate	----------	*248,530*	----------
Testis	----------	9,470	----------
Penis & other	----------	2,210	----------
Urinary System	**48,250**	**115,750**	**164,000**
Urinary bladder	19,450	64,280	83,730
Kidney & renal pelvis	27,300	48,780	76,080
Eye & orbit	**1,570**	**1,750**	**3,320**
Brain & other Nervous System	**10,690**	**13,840**	**24,530**
Endocrine System	**33,470**	**13,730**	**47,200**
Thyroid	32,130	12,150	44,280
Other	1,340	1,580	2,920
Lymphoma	39,930	50,460	90,390
Hodgkin lymphoma	4,000	4,830	8,830

Table 1 (continued)

Cancer Type	Female	Male	Both Sexes
Blood	**41,160**	**54,850**	**96,010**
Myeloma	15,600	19,320	34,920
Leukemia	***25,560***	***35,530***	***61,090***
Acute lymphocytic leukemia	2,690	3,000	5,690
Chronic lymphocytic leukemia	8,210	13,040	21,250
Acute myeloid leukemia	9,010	11,230	20,240
Chronic myeloid leukemia	3,960	5,150	9,110
Other leukemia	1,690	3,110	4,800
Other & unspecified primary sites	16,610	16,270	32,880

Note. Adapted from "Cancer Statistics, 2021" in *CA: A Cancer Journal for Clinicians*, by R. L. Siegel., K. D. Miller., H. E. Fuchs., & A. Jemal, 2021, American Cancer Society. Copyright 2021 by R. L. Siegel, et al.

Note. Red italicized text indicates the top five most common cancer types in the U.S.

Note. Bolded text indicates categories of cancer. Bolded italicized text indicates sub-categories of cancer.

Breast

According to Siegel et al. (2020), breast cancer is the most common type of cancer in the United States and affected 276,480 women and 2,620 men in 2020. It is estimated that 42,690 people died from breast cancer in 2020. This cancer is most common in women aged 20 to 49 years of age and of non-Hispanic white heritage (Siegel et al., 2020). DeSantis et al. (2019) estimates that women living in the U.S. have a 1 in 8 chance of developing breast cancer in their lifetime, and a 1 in 39 chance in dying from breast cancer. Siegel et al. (2020) also states that breast cancer alone accounts for 30% of all cancers in women. A slight increase in breast cancer rates in women over the past few decades has been attributed to an increase in prevalence of

obesity and decline in fertility rate, both of which are recognized risk factors. Breast cancer also has one of the highest survival rates (90%), potentially due to the high screening rates that can detect the cancer in early stages. Death rates due to breast cancer have also gone down by 40% since 1989 (Siegel et al., 2020).

Lung and Bronchus

Siegel et al. (2020) estimates that 236,740 new cases of lung cancer will be found in 2022, and that 130,180 people will die from lung cancer in 2022 in the U.S. About a quarter of all cancer deaths in the U.S. can be attributed to lung and bronchus cancers and the death rates are high compared to some other cancers. Despite this fact, the incidence of cancer rates of the lung and bronchus has decreased twice as fast for men as women in recent decades. This incidence rate reflects the historical patterns of smoking in males, in which the number of male smokers has been higher than female smokers. Lung cancer incidence rates among males decreased from 2007 to 2016 by 2.6% each year and in females from 2006 to 2016 by 1.1% each year (Siegel et al., 2020). According to Henley et al. (2020), the survival rate for lung cancer in the U.S. is 19% and is among the lowest survival rates for cancer based on type, with only pancreatic cancer exhibiting a lower survival rate (9%).

Prostate

In the U.S. prostate cancer is the third most common type of cancer. Schatten (2018), states that lung and prostate cancer are the two most common types in men, and that in 2014, there were 233,000 new cases that caused 29,480 deaths from prostate cancer in the United States. In the 1980s and 1990s, there was an increase in rates for this cancer due to the development of the prostate-specific antigen in the mid-1980s. More recently, the incidence rate has decreased since the 2000s, possibly due to changes in screening guidelines. Death rates have

dropped by 52% since 1993 and have stabilized in recent years. The probability that a man will get prostate cancer increases with his age, with the highest probability being when he reaches 70 years of age or older. The possibility of being diagnosed with prostate cancer over the course of a man's lifetime is one in eight, and one in every thirty-nine men diagnosed with prostate cancer will die of it even when considering advances in life expectancy in the past few years (Schatten, 2018).

Colorectal

There were 104,610 cases of colon cancer and 43,340 cases of rectal cancer in the year 2020 in the U.S. (Siegel et al., 2020) The total number of deaths from these two cancers adds up to 53,200 people in 2020. These numbers represent an overall decline in incidence since the 1980s due to increased screening measures and greater widespread knowledge of risk factors. Risk factors include smoking, consumption of red meat, and use of aspirin. Incidence and mortality rates for colorectal cancer are higher in men than in women over 55 years of age but are not significantly different between the sexes for those under 40 years of age. Incidence and mortality rates also show a racial and ethnic disparity, with mortality rates being 40% higher for non-Hispanic blacks than for non-Hispanic whites (Siegel et al., 2017)**.**

Invasive Melanoma of the Skin

Siegel et al. (2021) states that cases of invasive melanoma of the skin only account for 1% of all skin cancer types; however, an estimated 7,650 deaths a year in the United States are attributed to invasive melanoma. These statistics rank it as the fifth most common cancer type in the U.S. Invasive melanoma of the skin is estimated to have 99,780 new cases in 2022 and incidence is most common in non-Hispanic whites and women (before age 50) and men (after age 65). Males have a 1 in 27 chance and women have a 1 in 40 chance of developing invasive

melanoma of the skin throughout life (Siegel et al., 2021). Mortality trends vary by age and gender, but in those younger than 50 years of age, mortality rates have been dropping by 7.0% each year since 2013. In those older than 50 years of age, mortality rates have been dropping by an average of 5.7% per year since 2013. Risk factors include personal or familial history of melanoma and the presence of more than 50 moles, atypical moles, or large moles, excess sun exposure or indoor tanning, and those who sunburn easily (Siegel et al., 2020).

There are a broad range of continuously researched and improved medical treatment options to decrease mortality rates while increasing quality of life as the patients go through cancer treatments (Siegel et al., 2021).

Overview of Cancer Treatments

There are many kinds of medical treatments for cancer, which can vary in effectiveness based on the type and location of the cancer within the body, as well as stage of progression and other patient factors. Four common types of cancer treatments include: surgical (Kuerer et al., 2004) (Tohme et al., 2017), radiological (Koch et al., 2010), biological (Schirrmacher, 2019), and pharmacological (Sugerman, 2013); and many practitioners utilize a combination of treatments to remove or prevent growth of existing abnormalities and, in turn, decrease the chances of remission. Each of these types of cancer treatment is accompanied by its own set of risks and side-effects that can be partially or fully ameliorated throughout treatment. These treatment risks are typically outweighed by the potential for eradication of cancer within the patient's body, which may often be life-threatening (Cancer.net Editorial Board, 2021). The ultimate goal of cancer treatment is to cure the cancer and prolong the patient's life (Xue et al., 2021).

Surgical

Surgical treatment of cancer is typically an invasive procedure and is commonly used to remove tumors and nearby healthy tissues to manage possible recurrence of cancerous cells (Tohme et al., 2017). Surgical methods are routinely used to treat the top five most common cancers: breast (Fish et al., 2020) lung and bronchus, colorectal (Ricciardi et al., 2022), malignant melanoma (McKay et al., 2022), and prostate cancers (Elsherif et al., 2019). The goal of surgical treatment is to save the life or extend the life expectancy of a patient with cancer but typically is used in conjunction with other therapies to gain complete removal of a tumor to achieve this goal (Tohme et al., 2017). A non-exhaustive list of surgical methods include: partial- or full-mastectomy of the breast (Kuerer et al., 2004); or partial resection of the breast, such as wedge restriction, which preserves the lymph nodes but still removes the tumor (Tandberg et al., 2018); curative surgery in the form of a full lobectomy for lung/bronchus cancer (Sugarbaker & Strauss, 2000); and a minimally-invasive complete removal of the prostate gland via prostatectomy or open removal of the prostate gland, tumor, and surrounding tissues (Hu et al., 2009). The decision for which surgery type is used is based on the type and location of the tumor, and whether the patient can physically endure the specific surgical procedure that is preferred (Tandberg et al., 2018). Surgical treatment is often used in conjunction with radiology, biological therapy, and chemotherapy to excise tumors and reduce the amount of tissue that other therapies may need to target. Surgical treatment is also used as salvage therapy after other therapy sessions are completed to remove residual tumors or fragments that were not eradicated during the initial therapy session (Pontes et al., 1993).

Recurrence of tumors is possible with most surgical procedures that involve removing the tumor and surrounding tissues, as it is possible for surgeons to overlook some cancerous tissues

and not realize it, so treatment with other therapies is usually necessary to assure complete eradication of the tumor(s) (Tandberg et al., 2018). Areas of surgical complication and associated risks include: cardiac, respiratory, and vascular issues, among other less common risks (Hu et al., 2009). Associated surgical risks can be influenced by the type, stage, and location of the cancerous mass, as well as an individual's ability to tolerate surgical procedures near the mass (Januszek et al., 2021; Tokunaga et al., 2020).

Radiation

Radiation treatment is commonly used to treat cancerous tumors that are small-cell (and cannot be surgically removed), cases when other surgical or pharmaceutical treatments are not fully effective (Koch et al., 2010) and require adjuvant treatment (Schirrmacher, 2019), or before beginning other types of cancer treatments. Radiation therapy works by damaging the DNA (deoxyribonucleic acid) in cancer cells beyond repair, so the cancerous cells stop dividing or die. Radiation treatments can take multiple days or weeks to eradicate or lessen the severity of cancerous tumors and are commonly used in treatment regimens with co-occurring and/or adjuvant chemotherapy and/or surgery (Xu et al., 2021). Research shows that cancer stem cells may even become resistant to radiation treatment and other treatment types may need to be done to completely remove the cancer threat (Koch et al., 2010).

There are two types of radiation treatment: external beam and internal radiation therapies. External beam radiation is a local treatment that only affects the tumor(s) and area(s) surrounding the tumor(s) (Brown et al., 2015), and is commonly used for prostate (Hu et al., 2009) and breast cancers (Brown et al., 2015). Internal beam radiation can be localized to one area, affecting only the tumor and surrounding tissues, or it can be systemic, meaning throughout the whole body (J. B. Yu et al., 2015). Internal radiation is commonly used for treating tumors in

the lungs, and one example of this is stereostatic body radiotherapy, which is a noninvasive treatment that targets radiation at tumors and surrounding tissues (J. B. Yu et al., 2015). Both types of radiation treatment can also be used to break tumors into smaller pieces, making it more feasible to remove the tumor with surgery post-radiation treatment (Ashayeri et al., 1988).

Like any other kind of cancer treatment, radiation treatment can carry risks. Treatment choice is often driven by provider preferences and experiences, as well as treatment timelines, costs, and toxicity potential (Alyamani et al., 2021). One risk of radiation treatment is that it has a chance of causing radiation-induced secondary malignancies (Nugent et al., 2022), especially when used in combination with chemotherapy (Morton et al., 2014). Some sites for radiation-induced secondary malignancies include breast, prostate, Hodgkin's lymphomas, and cervical cancers (Dracham et al., 2018). Other risks of radiation treatment include high-dose radiation-induced ischemic heart disease (Lorenzen et al., 2020) or generalized cardiotoxicity (Leonard & Wazer, 2019), lymphedema (Daniell et al., 2019), tissue fibrosis (Plichta et al., 2019), and pulmonary toxicities (Parekh, 2019). The potential risk of radiation treatment to the patient varies based on the patient's age, gender, type of cancer, location of cancer, type of radiation treatment, length of radiation treatment, and amount of radiation treatment needed (Koch et al., 2010), and risk of secondary malignancies increases with younger age at time of radiation, increased dose, larger radiation field, and concurrent use of adjuvant chemotherapeutics (Dracham et al., 2018).

Biologic/Immunotherapy

Biologic treatment of cancer uses the body's natural mechanisms to help fight off cancer. Schirrmacher (2019) states that biologic therapy is novel to cancer treatment and is being researched as an alternative to chemotherapeutic drugs that are cytostatic in nature and tend to

have low tumor specificity and high toxicity. Immunotherapy is a type of biologic treatment that utilizes your immune system to help combat cancer cells.

The immune system's mechanisms for the destruction and removal of foreign cells, as well as the immune response memory system, are key to understanding how immunotherapy is used as a cancer treatment (Schirrmacher, 2019). Yang (2015) states that the body's immune system is important for recognizing and eliminating malignant cancer cells that transform and mutate, but it also helps in promoting the progression of tumors via cancer cells' use of myeloid-derived suppressor cells to metastasize and spread the cancer, as well as make them more immune to treatment (Yang et al., 2020). The immune system has a dual role in supporting cancer cells, but also suppressing them in three phases: elimination, equilibrium, and escape (Yang, 2015). This three-phase suppression is helpful in creating immunoediting techniques. Elimination occurs when the body's natural immunity recognizes and destroys cancer cells before they are clinically recognized. The equilibrium phase occurs when certain tumor cells are not fully eliminated, and adaptive natural immunity edits the tumor cell's own immunity. Escape occurs last and happens when the tumor cells progress in growth with no restraint, and eventually cause clinical signs to occur (Mittal et al., 2014). Tumor cells escaping from control of the immune system and making it past phase three is a hallmark of cancer (Vesely & Schreiber, 2013). Using immunotherapy, the body is tricked into making more immune cells that recognize, target, and eliminate cancer cells during these phases without harming good cells or causing any kind of toxicity to the body.

The following three types of treatments are part of a non-exhaustive list of possible biologic and immunotherapy treatments available. Monoclonal antibodies target the cancer cells with tumor-specific surface antigens that inhibit DNA replication and prevent protein and RNA

(ribonucleic acid) synthesis, keeping the cancer cell from further replicating (Fathian-Kolahkaj et al., 2019). Gene therapy is the process by which cells deposit healthy gene copies to cancer cells with mutated genes to treat the mutation. This type of therapy has recently been approved for treatment of prostate cancer (Xue et al., 2021). Bio-chemotherapy is the use of a combination of a monoclonal antibody and a chemotherapy agent and is currently being studied for use in treating malignant melanoma (Sood et al., 2021). Biologic treatment and immunotherapy are commonly used to treat advanced melanoma of the skin, renal cell carcinoma, non-small-cell-lung cancer, Hodgkin's lymphoma (Sharma et al., 2017), and other hematologic malignancies (cancers of the blood).

There appear to be a variety of different risks associated with these kinds of therapy, many of which are not confirmed, as this type of treatment is still in the research and developmental stages. There also appears to be instances of patients who respond well to immunotherapy but eventually relapse, indicating a level of resistance to the immunotherapy (Sharma et al., 2017). Some potential risks include dose-dependent side-effects that are similar to chemotherapeutic side-effects, such as cardio toxicity and low blood-cell counts, hair loss, nausea and vomiting, bone suppression (Fathian-Kolahkaj et al., 2019), diarrhea, colitis, and impaired function of the liver (Sood et al., 2021).

Pharmacologic

The purpose of chemotherapeutics in the role of combating cancer is to attack cancer cells before they can metastasize and duplicate, affecting more areas within the body (Rybak et al., 2007). Pharmacologic treatment of cancer utilizes antineoplastic agents, or chemotherapeutics, to inhibit the growth of cancer cells, either directly or indirectly. Pharmacologic treatment of cancer can come in many forms and each attacks the cancer

differently. Some pharmacologic treatments involve the immune system, some are targeted therapy, some focus on changing hormones, and others focus on blocking or slowing the growth of cancer cells by killing them or stopping division from occurring with the use of clinical drugs (Sugerman, 2013), (Rybak et al., 2007). Sugerman (2013) states that chemotherapeutics can be administered orally, via injection, dermally, or through blood infusion into a vein or artery.

Some common types of chemotherapeutics include platinum-based agents, such as carboplatin, cisplatin, and oxaliplatin (Galluzzi et al., 2012), or other types, such as recombinant human endostatin, pirarubicin, adriamycin, cyclophosphamide (Wang et al., 2017); plant-derived drugs, otherwise known as vinca alkaloids like docetaxel; or other drugs such as difluoromethylornithine (DFMO). Each of these has a different effect on the cell cycle, and how and where in the cell life cycle the death of the cell occurs (Sugerman, 2013).

Chemotherapeutics tend to be grouped together by how they work in the body, what their chemical structure is, and how they relate to other drugs. Because of their extreme toxicity to the body and many unpleasant side effects, chemotherapeutics are used with caution. Chemotherapy is more commonly used when other treatment methods are not working properly, or when other treatment methods are not indicated for the type of cancer being treated. Chemotherapeutics are also commonly used in a cancer treatment regime in combination with other treatment types such as surgery or radiation (Sugerman, 2013).

Due to the systemic properties of chemotherapeutics, the agents are toxic to both cancer cells and healthy cells and can cause damage to various other tissues and bodily processes. Some side effects of chemotherapeutics and their toxicity include nausea and vomiting, hair loss, fatigue, mouth and skin changes, and hematological changes (Sugerman, 2013), such as the risk of a venous thromboembolism. Chemotherapeutics can cause toxicity to the functioning of an

organ, such as the kidney (nephrotoxicity) or liver (hepatotoxicity). Some are also toxic to the inner ear sensory cells and other inner ear structures, which is known as ototoxicity (Bielefeld et al., 2021).

Ototoxicity of Chemotherapeutics

Overview of the Anatomy and Physiology of the Auditory System

To properly understand the ototoxicity of chemotherapeutics, one must first understand the general anatomy and physiology of the auditory system. The auditory system can be broken down into the following sections: the outer ear, middle ear, inner ear, auditory nerve, brainstem, and auditory cortex. Pensak and Choo (2015) state that hearing begins when acoustical waveforms are collected by the pinna, the portion of the outer ear we can easily see with our eyes. The pinna funnels the sound waves down the external auditory meatus to the tympanic membrane, which is more commonly known as the eardrum. Acoustical energy is transformed into mechanical energy at the tympanic membrane, the boundary of the middle portion of the ear. This now mechanical signal is sent through the vibrations of the tympanic membrane that moves the ossicular chain, tiny bones otherwise known as the malleus, incus, and stapes. The pressure and movement of the ossicular chain cause the stapes to press into the round window of the cochlea, a tiny snail-shaped structure embedded deep in the skull. This is the boundary to the inner ear.

Within the cochlea, the pressure of the stapes into the round window causes fluid within the cochlea to move, known as endolymph. There are three sections of the cochlea: the scala vestibuli, scala media, and scala tympani. Reissner’s membrane separates the scala vestibuli from the scala media, and the Basilar membrane separates the scala media from the scala tympani. Each section contains a specifically ionically charged fluid. The scala vestibuli and

scala tympani contain perilymph, and the scala media contains endolymph, which is important for the transduction of sound. Within the scala media lies the Organ of Corti, which is the sensory organ of hearing. The Organ of Corti's sensory component is comprised of outer hair cells (OHCs) and inner hair cells (IHCs) and are supported by support cells and Dieters cells. The endolymph in the Scala Media is produced by a structure known as the stria vascularis. The precise movement of endolymph and perilymph throughout the cochlea causes the upward and downward movement of the basilar membrane, on which the OHCs and IHCs sit (Lanvers-Kaminsky et al., 2017). There are three to five rows of OHCs within the cochlea (approximately 12,000 to 15,000 in humans) that provide amplification of hydromechanical sound waves (Pensak & Choo, 2015). OHCs change their shape in response to stimulation, and this is known as electromotility. OHCs also produce and emit their own distortion products (reverse sound waves), which can be measured using special otoacoustic emission equipment (Brownell, 1990). There is one row of IHCs (approximately 3,000-3,500 in humans) that electromechanically transduce sound to the cochlear nerve fibers in the spiral ganglion so the central auditory brain structures can begin to process auditory information up to the auditory cortex for comprehension and understanding (Brugge, 2013).

Ototoxic Effects of Chemotherapeutics on the Auditory System

Ototoxicity is induced by therapeutic chemical compounds and is manifested in two forms in the auditory system: cochleotoxicity, defined as a drug-induced transient or permanent disorder of the cochlea and/or connecting nerves, and vestibulotoxicity, defined as a drug-induced disruption to the balance system (Patatt et al., 2021). Current research shows that certain chemotherapeutics affect the hair cells within the cochlea, the stria vascularis, and/or the spiral ganglion of the auditory nerve (Dalian et al., 2012; Devarajan et al., 2002; Zhang et al., 2020).

Common symptomatic indications of ototoxicity are tinnitus (ringing of the ears), disequilibrium, or decreased hearing sensitivity (Bisht & Bist, 2011).

Types of Chemotherapeutics and Their Effects on the Auditory System

The process of creating chemotherapeutics involves the use of many chemical agents with the purpose of attacking cancer cells and causing apoptosis. As previously discussed, chemotherapeutics not only attack cancer cells, but also result in collateral damage to healthy cells throughout the body. Each type of chemotherapeutic utilizes a different chemical agent and has different effects on the body and the auditory system (Sugerman, 2013). Below is a review of common types of chemotherapeutics used to treat the most common cancers described previously, as well as a review of associated effects on the auditory and/or vestibular systems.

Platinum-Based Chemotherapeutics. Platinum-based chemotherapy is effective in treating cancers that are in the neck and head, lung, testicle, and ovary in adults. Patatt et al. (2021) found that after the use of platinum-based antineoplastic drugs, such as carboplatin and cisplatin, a hearing change occurs, which is often irreversible, even after conclusion of drug treatments. Patatt et al. (2021) also found that cisplatin has a higher potential to be irreversible, due to the high possibility of ototoxicity, and that irreversible hearing loss occurred in 45% to 83.3% of the study's subjects, with higher doses of cisplatin being associated with more potential for ototoxicity. The authors state that "auditory changes after the use of platinum-based antineoplastic drugs were found, however, there was an important heterogeneity regarding the frequency of ototoxicity and the cumulative dose of the drugs used" (Patatt et al., 2021).

The amount of ototoxicity in each patient treated with platinum-based chemotherapeutics fluctuates and can be affected by individual tissue susceptibility to the drug, what kind of platinum-based drug is utilized, or concurrent use of other ototoxic drugs or other treatment

types, such as radiation. Typically, the difference between the platinum-based antineoplastic drugs is based in the chemical composition of each, the difference in metal transporters that help to regulate how much of the drug is utilized by the body, and the effectiveness in treating different types of cancer (Ding et al., 2012). Cisplatin is generally the most ototoxic of all platinum-based compounds, followed by carboplatin and oxaliplatin (Landier, 2016).

Cisplatin. Cisplatin is a platinum-based compound that is most commonly used to treat lung, breast, ovarian, and testicular cancers (Bielefeld et al., 2021). This agent works by attaching itself to sections of DNA in each cancer cell and generating lesions in the DNA strand, otherwise known as cisplatin-induced adducts (Rocha et al., 2018). This causes apoptosis, where the mitochondria attack and the cell dies. While this type of chemotherapeutic is highly effective at targeting cancer cells, cisplatin is also toxic to many normal processes and healthy cells within the body, including the kidneys, peripheral nerves, and the function of the inner ear (Devarajan et al., 2002). The use of cisplatin can result in damage to the auditory system in multiple areas. OHC damage from cisplatin occurs due to cellular stressors such as ischemia, or an inadequate blood supply to the OHCs and stria vascularis, causing an inability to properly produce endolymph (Steyger, 2021). Damage can also occur from ototoxins being delivered directly to the OHCs (Devarajan et al., 2002).

Generally, the ototoxic effects of cisplatin can be seen in the stria vascularis of the cochlea before any damage occurs to the OHCs or other structures in the Organ of Corti. This initial damage to the stria vascularis may be due to ischemia, or an inadequate blood supply (Steyger, 2021). When the stria vascularis cannot function properly, it will produce an improper amount of endolymph, a fluid found in the scala media of the cochlea. Endolymph maintains the proper endocochlear potential (EP) needed for mechanoelectrical transduction (MET) of

mechanical sound signals to electrical sound signals for the nerve fibers in the brain (Gagov et al., 2018). The EP allows for electrical manipulation and processing of the sound signal's pitch specificity through the MET (Zhang et al., 2020), (Devarajan et al., 2002).

Ischemia to the stria vascularis causes an increased metabolic stress within the cochlea, which leaves the cochlea more susceptible to damage due to noise or toxins, such as those found in cisplatin. This increased metabolic stress and susceptibility to damage is thought to increase oxidative stress within the cochlea. Cisplatin increases the generation of reactive oxygen species (ROS) in the body and can cause damage to healthy cells, including those within the cochlea such as the stria vascularis, IHCs and OHCs, and supporting cells (Sheth et al., 2017).

The electromotility or change in shape of OHC cells due to differing voltages between OHCs and endolymph, of OHCs is fueled by current that is generated by the stria vascularis and spiral ligament of the cochlea. With a damaged stria vascularis, OHC electromotility is affected (Brownell, 2017) due to a decreased amount of current flowing through the endolymph, potentially causing a change in active potassium channels in the hair cells (Lu et al., 2020). Decreased electromotility of the OHCs has been shown in cisplatin-treated guinea pigs (Rybak et al., 2007; van Ruijven et al., 2005). Another physiological change that occurs in the auditory system following cisplatin treatment that leads to further hearing impairment is detachment of the myelin sheath on the spiral ganglion cells of the auditory nerve (Chirtes & Albu, 2014).

Cisplatin's direct effect on important structures of the auditory system typically causes a bilateral symmetrical sloping high-frequency sensory hearing loss (Bokemeyer et al., 1998). The prevalence of ototoxicity from cisplatin across the U.S. population ranges from 42% to 55% after treatment cessation (Dillard et al., 2022). Minasian et al. (2018) states that tympanometry outcomes will typically report middle-ear compliance and ear canal volume within normal limits

unless there is a conductive component due the presence of otitis media or other conductive cause. Tympanometry is important for correctly interpreting the DPOAE and pure-tone audiometry results (Minasian et al., 2018). The cisplatin-induced ischemia and ROS affect hair cells at the basal-end of the cochlea, which code for higher pitches/frequencies (Patatt et al., 2021). Therefore, when pure-tone audiometry is conducted, the higher frequency thresholds will typically show more hearing loss than low or mid-frequency thresholds. This loss can extend into the mid-frequencies if greater damage to the auditory system occurs (Bokemeyer et al., 1998). Extended-high frequencies (EHF) (9-10 kHz) will show a poorer change in threshold before frequencies tested in routine pure-tone audiometry (0.25 to 8 kHz). OAE responses will be absent at any frequency where behavioral thresholds are equal to or worse than 25 dB HL due to cisplatin's effect on the OHCs and their electromotility. Speech audiometry, either in quiet or in noise, will generally be within normal limits unless pure-tone thresholds in the 0.25-8 kHz range are elevated. Auditory Brainstem Response (ABR), if tested on those with limited or no behavioral responsiveness, will show an increased latency of Wave I and subsequent waves, due to damage to the outer hair cells at the cochlear level. The degree of auditory damage is dose-dependent, and the longer that cisplatin remains in the body, the greater the detrimental effect on hearing thresholds due to the increase in generation of ROS (Patatt et al., 2021).

A common otologic side effect of cisplatin treatment is tinnitus, which is a ringing/buzzing noise in the ears only heard by the listener. Tinnitus can be attributed to the loss of the OHC's electromotility, as well as other disruptions along the auditory pathway (Patatt et al., 2021). Older age at diagnosis and higher cumulative cisplatin dose is associated with higher incidents of cisplatin-induced tinnitus (Frisina et al., 2016). Historical incidence rates of tinnitus in those treated with chemotherapeutic agents vary study to study, ranging from 10.7% reported

by Arora et al., (2009) to 15-38% reported by Rybak (2005) and 12% by Dille et al., (2010). In a study by El Charif et al., (2019) poorer health ($P < 0.0001$) and higher psychotropic medication use ($P = 0.003$) were reported when compared to control groups without cisplatin-induced tinnitus, as well as worse hearing at each frequency (0,25-12k Hz, $P < 0.0001$) and more vertigo ($P < 0.0001$) than control groups. A study by Frisina et al. in 2016 confirmed that tinnitus was correlated with reduced hearing at each test frequency.

There are other factors that affect the severity of ototoxicity of cisplatin, including the mode of drug administration, the tumor site, patient age, prior or simultaneous administration of other chemotherapeutic agents, concomitant noise exposure, simultaneous cranial-radiotherapy, and preexisting hearing loss (Rybak et al., 2009). Simultaneous cranial-radiotherapy has been shown to cause a significantly higher incidence of ototoxicity than other chemotherapeutic agents (Tang et al., 2021) or cisplatin without cranial-radiotherapy. Cisplatin is used routinely for cancer treatment but has limitations when it comes to cell resistance over time and the inclusion of serious side effects (Patatt et al., 2021).

Carboplatin. Carboplatin is known as a second-level platinum-based agent that works in a similar way to cisplatin but is shown to be less ototoxic in nature. According to Dalian et al. (2012), carboplatin forms inter-DNA cross-links and works to cause cell apoptosis via the mitochondria of the cancer cells in a similar way to cisplatin. Due to its efficiency in attacking cancer cells and the fact that it causes less unwanted side-effects than cisplatin, carboplatin is routinely used to treat a wide variety of tumor types in many different areas of the body. However, caution is still used as nephrotoxicity (damage to the kidneys) and ototoxicity are still common side-effects (Dalian et al., 2012).

According to Dreisbach et al. (2017), hearing loss can occur in up to 60% of patients who receive carboplatin as a cancer treatment. A meta-analysis by Dillard et al. (2022) looked at 5077 individuals from 87 sets of records, which revealed the prevalence of hearing loss in those treated with carboplatin ranged from 8% to 20%. Moderate doses of carboplatin can affect the spiral ganglion neurons (SGNs) in the auditory nerve, as well as the functionality of IHCs before damaging OHC function. For IHCs, the lesion tends to be uniform along the basilar membrane of the cochlea; while damage to the OHCs tends to be greatest in the basal end and to a lesser degree in the apical end. Once the carboplatin dose reaches a higher concentration within the body (>100µM), the OHCs will become affected more than the IHCs, but at 500µM both types of hair cells are affected equally (Dalian et al., 2012). In a study conducted on rats' and chinchillas' explanted cochleae, the researchers dramatically increased the dose of carboplatin to 1000µM and observed a decrease in damage to the hair cells with an increase in damage to the SGNs (Dalian et al., 2012).

When monitoring the hearing sensitivity of patients treated with carboplatin, a higher dose (>100 µM per treatment) will be more likely to show changes in auditory function. Tympanometry and otoscopy will show results within normal limits unless the patient has otitis media. For conventional audiometry (pure-tone testing from .25 to 8 kHz), carboplatin is shown to have less effects on hearing sensitivity at those frequencies than cisplatin, possibly due to the higher dose needed to induce auditory damage at those frequencies. This makes carboplatin a more desirable choice for treatment than other chemotherapeutics; however, the ototoxic effects are not explicitly compared in any literature for cisplatin and carboplatin at the extended high frequencies of 10 to 20 kHz. DPOAEs in patients on a carboplatin regimen may show normal distortion product responses if the OHCs have not yet been affected. For ABR testing, if auditory

damage is present at the level of the hair cells in patients treated with carboplatin, the latency of waves I-V will be delayed. However, if damage is only present at the level of the SGNs, the ABR may show normal Wave I latencies with later Wave III and Wave V latencies and longer interpeak latencies, indicating a more retrocochlear site of damage. The ototoxicity to the inner ear and its structures is also dose-dependent, like cisplatin (Dreisbach et al., 2017). Patients receiving higher doses of carboplatin have a higher chance of ototoxicity than those administered a lower dose.

Nedaplatin & Oxaliplatin. Nedaplatin and oxaliplatin are platinum-based agents that are second- and third-generational forms of cisplatin, respectively. According to Ding et al. (2012), they are commonly used to treat ovarian cancers, and other cancers that are generally resistant to cisplatin treatments. Oxaliplatin is also commonly used to treat colorectal tumors (Hellberg et al., 2009) and nedaplatin is used to treat small and non-small cell lung cancer (Liu et al., 2015). Nedaplatin and Oxaliplatin differ from cisplatin and carboplatin in that they are generally less toxic in general but have similar action mechanisms when targeting cancer cells. One side-effect of nedaplatin treatment that is uncommonly seen with other platinum-based agents is thrombocytopenia, but treatment with nedaplatin has been shown to cause less nausea, vomiting, and renal toxicity than cisplatin-based treatment regimens (Liu et al., 2015).

In comparison, these alternative platinum-based agents are less ototoxic to the structures of the inner ear than cisplatin or carboplatin, but they are still ototoxic. Nedaplatin and oxaliplatin treatment is consistent with ototoxicity due to extensive damage to the auditory nerve fibers and stereocilia on the hair cells in rat cochleae, which audiologists and doctors can assume is the same in human cochleae (Ding et al., 2012). The uptake of these agents into the cochlear structures varies greatly but is considerably less than that of cochlear uptake of cisplatin or

carboplatin, potentially contributing to the less ototoxic effects of the agents (Geoerger et al., 2008), (Hellberg et al., 2009).

A population cohort study completed in 2021 by Tang et al. on 398 patients receiving concurrent chemoradiotherapy with either nedaplatin or cisplatin to treat nasopharyngeal carcinoma revealed that when nedaplatin treatment is combined with cranial-radiotherapy, it has been shown to cause an increase in the cumulative potential for ototoxicity. However, nedaplatin's potential for ototoxicity does not carry the same level of risk as treating cancer with cisplatin and concurrent radiotherapy.

When given at higher doses, oxaliplatin and nedaplatin still cause sensory neuropathies such as auditory neuropathy, a disorder of the inner ear caused by altered IHC ribbon synapses, impaired spike generation, or altered synaptic transmission from the SGNs to neurons in the cochlear nucleus. This damage causes poor temporal processing wherein patients can detect but cannot discriminate speech well (Shearer & Hansen, 2019). The best way to detect damage that causes neuropathies is to use speech-in-noise tests for detecting large signal-to-noise ratio (SNR) losses, and to compare two ABR waveforms at a high-intensity click: rarefaction-elicited and condensation-elicited waveforms, to see if the waveforms mirror each other. Patients with auditory neuropathies due to damage from chemotherapeutics will show normal pure-tone thresholds in both conventional audiometry and extended high-frequency audiometry if the cochlea is not affected, but will have abnormal ABR results with a mirrored cochlear microphonic at the beginning of the waveforms when utilizing rarefaction- and condensation-elicited waveforms, and an abnormal Summating Potential /Action Potential ratio with an increased Action Potential amplitude in Electrocochleography testing.

Vinka Alkaloids. The use of vinka alkaloids is most common in treating pediatric

leukemia, but has also been found effective to treat small-cell lung cancer and malignant melanoma in adults. Vinka alkaloids are the second-most-used class of chemotherapeutics (Moudi et al., 2013). These chemotherapeutic agents cause cell apoptosis during the mitosis part of the cell cycle, or when the cells divide to form more cells (Tazi et al., 2014) and are commonly used in conjunction with the platinum-based agents to obtain a greater chemotherapeutic effect (Hansson, 1997).

Vinka alkaloids are rarely ototoxic when used independently and not in combination with known ototoxic chemotherapeutic agents (Yousif et al., 1990). Historical evidence suggests that vinka alkaloids can cause peripheral nerve damage affecting hearing sensitivity, and that the damage is dose dependent (Postma et al., 1993). More recently, it has been shown that when vinka alkaloids cause a hearing loss and are not being used with other known ototoxic agents, the hearing loss is generally reversible once treatment is ceased (Tazi et al., 2014). Two examples of more commonly used vinka alkaloids are Vinblastine and Vincristine.

Vinblastine. Vinblastine is commonly used to treat malignant melanoma in combination with cisplatin (Hansson, 1997), and is used as palliative treatment for renal cell carcinoma, lung (Dhyani et al., 2022), breast, and testicular germ cell cancers (National Institutes of Health, 2021). The agent binds to tubulin within the cell and causes depolymerization of the microtubules, inducing an arrest of the cell and ultimately causing apoptosis, or cell death (Silverman et al., 2013). Vinblastine targets cancer cells well because of their characteristic rapid cell division in comparison to normal cells. This antineoplastic agent is a vesicant, which causes significant damage to internal organs and body processes if it crosses out of the vein into the rest of the body, which is an uncommon but serious side-effect. Typical side-effects are myelosuppression, mucositis, fever, anemia, and alopecia (Dhyani et al., 2022). Vinblastine is

commonly used with other chemotherapeutic agents that are generally ototoxic, such as cisplatin. Vinblastine causes central neurotoxicity in 1% of patients (BC Cancer Agency, 2015), which can affect the auditory system, including the eighth cranial nerve and the auditory pathway to the brain (Magge & DeAngelis, 2015). This neurotoxicity manifests itself with more vestibular side effects, in addition to hearing loss. Test of auditory functions, like ABRs and OAEs, may show the potential for a hearing loss due to damage to the system before pure-tone audiometry shows a hearing loss or before a person notices a change in their perception of sound. Ototoxicity to the cochlea or vestibular system from only vinblastine chemotherapy in humans is seldom reported in the literature; however, this could potentially be attributed to its low cochlear toxicity when used on its own.

Historical evidence suggests vinblastine is ototoxic to the cochlear hair cells in zebrafish (Ton & Parng, 2005), and rabbits (Serafy & Hashash, 1981), but current literature does not discuss the pathophysiologic effects of vinblastine on the human auditory system. However, there are isolated case study reports of hearing loss in patients treated with vinblastine in the literature. In one case study of a 26-year-old male in Morocco with nodular sclerosing Hodgkin's lymphoma, the patient was treated using vinblastine in combination with adriamycin, bleomycin, and dacarbazine. A sudden bilateral hearing loss occurred over the course of two days of treatment. Once treatment with these potentially ototoxic agents ceased and treatment with another agent began, hearing sensitivity returned to normal. The authors of this case study noted that the hearing loss was accompanied with aural fullness, tinnitus, and dizziness, symptoms that are not common with vinblastine treatment (Tazi et al., 2014). Another case of a 36-year-old man with evidence of ototoxicity showed an improvement in hearing abilities after cessation of vinblastine for treatment of Hodgkin's lymphoma (Kapoor et al., 2015). A third case reported on

a 29-year-old man treated with multiple chemotherapeutics, including vinblastine and no other known ototoxic agents, who had a mild sensorineural hearing loss in the high frequencies, but there was no mention of improvement after the end of treatment (Moss et al., 1999). These three case studies suggest that when utilized with other chemotherapeutics, vinblastine can contribute to ototoxic effects, even if the other agents are not known ototoxins.

Vincristine. This type of vinka alkaloid is most commonly used to treat malignant melanoma in combination with cisplatin (Hansson, 1997). Vincristine is administered to children with leukemia or other cancers of the blood (Riga et al., 2006), as well as adults with breast, head, and neck cancers, non-lymphoma Hodgkin's and Hodgkin's lymphoma (Dhyani et al., 2022) and ovarian cancer (Škubník et al., 2021). Vincristine works to attack cancer cells in the body by the same mechanisms as vinblastine; however, vincristine has a different chemical structure. The two drugs vary by one chemical group in composition, and this affects their antineoplastic effects (Moss et al., 1999), especially when used in combination with other chemotherapeutic agents. Vincristine is emerging in combination therapy with monoclonal antibody agents like rituximab, and in a combination chemotherapy regimen known as CHOP: cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine (Oncovin), and prednisone. The CHOP regimen with a monoclonal antibody agent increases the patient's potential for a positive treatment outcome and is more efficient at treating cancers than just utilizing vincristine on its own or with another combination of chemotherapeutics (Škubník et al., 2021).

Vincristine-induced neurotoxicity is widely reported in the literature, affecting motor-sensory, motor, and sensory nerves (Chauvenet et al., 2003; Gomber et al., 2010; Hatzl et al., 2021). Very few reports show neurotoxicity of the auditory system, but higher dosage levels can

have this effect. Vincristine has been shown to penetrate the blood-brain barrier, and therefore can affect the central auditory nervous system, inducing a peripheral auditory neuropathy. When vincristine crosses the blood-brain barrier, it tends to affect the spiral ganglion nerve bundles of the auditory nerve. This causes central nerve issues, resulting in damage to auditory function without affecting the hair cells or other cochlear structures (Triarico et al., 2021). Riga et al. (2006) states that hearing sensitivity is not generally affected with low to moderate doses of vincristine as evidenced by normal behavioral pure-tone and speech audiometry responses, and normal transient-evoked and distortion-product otoacoustic emissions, but higher doses of vincristine can elevate hearing thresholds. Auditory damage might be evident on ABR or other tests of the auditory nerve if neurotoxicity occurs, while pure-tone audiometry thresholds may remain unaffected due to the location of the damage within the auditory pathway and the specificity of the auditory tests being used.

Difluoromethylornithine. Difluoromethylornithine (DFMO) is more commonly used as a chemoprotective agent, meaning its purpose is to protect healthy cell tissues from the effects of chemotherapeutics, than as a chemotherapeutic agent. However, it is considered a maintenance-chemotherapy drug, as well as a chemotherapeutic agent. DFMO can be used to reduce tumor incidence in those with a risk of melanoma, breast, prostate, colorectal cancer, and small-cell lung cancer (Bojarska et al., 2021). DFMO is commonly utilized as a long-term maintenance therapy in pediatric populations with high-risk neuroblastomas (Lewis et al., 2020). Maintenance therapy, chemoprotection, and chemoprevention works by inhibiting ornithine decarboxylase (ODC), which is a limiting enzyme in polyamine synthesis (Laukaitis & Gerner, 2011). Polyamines are essential for cell regulation, and without them, cancer cells cannot proliferate (Nowotarski et al., 2013).

DFMO is not widely studied, and animal studies produce conflicting outcomes regarding what auditory structures and functions may be affected by this agent. One article from 1991 by Marks et al. states that DFMO may interfere with polyamine synthesis in the inner ear, but current research still does not demonstrate the physiological purpose of polyamines in the inner ear. A more recent study from 2005 states that the endocochlear potential is affected by the decrease of polyamines in the cochlea, causing a flat hearing loss configuration across all conventional test frequencies (Nie et al., 2005). Although limited, animal research suggests that IHCs are affected to a higher degree than OHCs in guinea pig cochlea, however there is no mention of polyamines in the cochlea (Salzer et al., 1990).

There are two different forms of DFMO, each of which has a different amount of enzyme-inhibition and levels of chemotherapeutic effect. D-DFMO has higher enzyme-inhibition and chemotherapeutic effect than L-DFMO or a combination of D/L-DFMO. D-DFMO has a decreased overall normal tissue toxicity in comparison to L-DFMO and is more widely used (Qu et al., 2003). In guinea pig models studied by McWilliams in 2000, D/L-DFMO doses of 500mg-1g/kg/day showed a loss of the compound action potential. However, the dosage did not affect the cochlear microphonic amplitude. These results indicate that inner hair cells are more affected than outer hair cells, specifically in the basal turn of the cochlea where the higher frequencies are encoded for. Histological evidence confirmed these findings. The evidence showed that 1g/kg/day of D-DFMO did not produce auditory damage in the guinea pigs via ABRs, but the same dose of L-DFMO caused a threshold shift that was worse than the same dose of D/L-DFMO, suggesting that D-DFMO has a higher otoprotective property and L-DFMO has an ototoxic property (McWilliams, 2000).

DFMO is not an effective chemotherapeutic on its own, so it is often used in conjunction with other chemotherapeutic agents to minimize side effects in patients or to increase chemotherapeutic effects. However, DFMO is associated with a risk of hearing loss for patients treated with this drug. McWilliams (2000) states that DFMO is known to cause vertigo-like dizziness and hearing loss in patients, but that these side-effects are often reversible after cessation of treatment. However, the temporary nature of the hearing loss induced by DMFO is not well-studied (Doyle, 2001). More research is needed to conduct a more thorough review of DFMO and its effects on the auditory system.

Summary

Chemotherapeutic agents that are ototoxic can cause detrimental peripheral and central pathologic changes to the auditory system resulting in hearing loss, auditory neuropathy, and central auditory disorders. It is important that patients receiving ototoxic chemotherapeutic agents be monitored for ototoxicity damage at all levels of the auditory system by audiologists. Each chemotherapeutic agent affects different areas of the auditory system; therefore, utilizing tests that are specific and sensitive to the anatomical areas of potential auditory damage is necessary for the early detection of hearing loss. This helps to avoid negative sequelae that may affect quality of life and communication abilities of the patients receiving potentially ototoxic chemotherapy.

CHAPTER II

OTOTOXICITY MONITORING

Ototoxicity monitoring programs are designed and implemented by an audiologist for patients undergoing chemotherapy treatments that have previously been shown to be toxic to the inner ear or auditory neural pathway. Ototoxicity monitoring of cancer patients provides an opportunity for early identification of hearing loss/auditory damage due to the cancer treatment and allows for early intervention and rehabilitation.

Several organizations recommend that adult patients receiving ototoxic chemotherapeutics be monitored for auditory and vestibular toxicity. These include the American Academy of Audiology (AAA) (Durrant et al., 2009) and the American Speech-Language-Hearing Association (ASHA) (Fausti et al., 1993). Ototoxic monitoring, performed by an audiologist, helps to provide the oncologist with information regarding the ototoxic side effects of the cancer treatment(s) and better informs them when changes to the treatment regime may need to be considered. When healthcare professionals work together as a team, better care is provided for the patient (Lord, 2019). Early identification of a hearing loss caused by ototoxic chemotherapeutics helps to facilitate intervention and set realistic goals for the patient and provides an opportunity to address any communication issues they may have during or after treatment (Konrad-Martin et al., 2005b). There are a variety of tests that have been investigated to evaluate their usefulness in monitoring ototoxicity.

Behavioral and Objective Test Methods Used for Monitoring Ototoxicity

There are objective (requiring no behavioral response from the patient) and subjective (requiring a behavioral response from the patient) tests that give reliable results and can detect a significant change in hearing sensitivity or auditory function. Utilizing a combination of objective and behavioral tests, an audiologist can detect changes in hearing sensitivity at frequencies that are first affected by the ototoxic chemotherapeutics before they affect thresholds at speech frequencies, and the tests are proven to be reliable over time with great test-retest reliability (Konrad-Martin et al., 2005b).

The American Speech-Language-Hearing Association (ASHA) and American Academy of Audiology (AAA) have published guidelines on how to properly monitor for ototoxicity, and organizations such as the Veterans Affairs (Konrad-Martin et al., 2005a, 2014), as well as private clinics have adopted these recommended guidelines. This overview utilizes recommendations from a variety of guideline sources, but mainly following recommendations from ASHA (Fausti et al., 1993), AAA (Durrant et al., 2009), and the Veteran's Affairs (Konrad-Martin et al., 2005a).

Conventional Pure-tone Air and Bone Conduction Audiometry

Pure-tone air and bone conduction thresholds are used to rule out or document the type and degree of hearing loss prior to cancer treatment, as hearing loss caused by chemotherapeutics is usually sensorineural and oftentimes permanent. Hearing thresholds are defined as the softest level of sound that a person can hear and respond to at least 50% of the time, and the standardized and best-practice way to test this is to use the Hughson-Westlake threshold method (American Speech-Language-Hearing Association, 2005). With the Hughson-Westlake method, a frequency-specific pure tone is presented to the patient in 10 dB increasing steps until they

respond that they hear it. Once they hear the pure tone, the intensity is decreased by 10 dB until the patient stops responding. Once the patient does not respond, an increase is made in 5 dB increments until the patient responds. This is repeated until the patient responds to the same level at least 50% of the time, or at least two out of three stimulus presentations. This intensity level becomes the patient's hearing threshold for that specific frequency. Conventional air conduction thresholds are generally recommended to be obtained at 0.25 kHz, 0.5 kHz, 1 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz, and 8 kHz, and bone conduction thresholds at 0.25 kHz, 0.5 kHz, 1 kHz, 2 kHz, and 4 kHz, with 3 kHz as needed (American Speech-Language-Hearing Association, 2005). Some monitoring recommendations do not include 0.25 kHz, as it is less common for ototoxic agents to affect that low of a frequency (Brooks & Knight, 2017).

Extended High Frequency Audiometry

Extended high frequency audiometry (EHFA) allows audiologists to detect changes in frequencies that are affected by ototoxic agents that affect the basal end of the cochlea first but are not tested utilizing conventional audiometry. van der Hulst et al. (1988) examined the ototoxicity of platinum-based chemotherapeutics and investigated whether EHFA could detect ototoxicity sooner than conventional audiometric testing. Results showed that there is a difference in patterns of ototoxicity between cisplatin and carboplatin, and that damage began in the high-frequency range and continued to affect hearing sensitivity in the conventional audiometric range (0.25-8 kHz). The authors recommended reconsidering treatment regimens if ototoxicity was detected in the EHF range and began progressing toward 8 kHz (van der Hulst et al., 1988). Beahan et al. (2012) and John and Kreisman (2017) reported that test-retest-reliability of EHFA is high with no significant differences in mean hearing thresholds between test and retest conditions. Extended high frequency audiometry would be less helpful of a measure of

auditory damage when a patient is being treated with a chemotherapeutic agent that does not cause damage to the inner or outer hair cells of the basal region of the cochlea. However, it is still important to test this range for thresholds in case a change in hearing sensitivity occurs, especially in cases of combination drugs or treatments.

Sensitive Range for Ototoxicity

One specific way of increasing the efficacy of detecting ototoxicity is through testing a limited behavioral range, which may include EHFA thresholds and/or conventional audiometric thresholds. This specialized way of detecting ototoxicity is called the Sensitive Range for Ototoxicity (SRO). It is a testing procedure in which a set of frequencies, individualized for each patient, are tested throughout the chemotherapy treatment regime. The upper-most screening frequency is the highest frequency with a threshold less than or equal to 100 dB SPL and extends to the next six lower consecutive frequencies in 1/6 octave increments. The American Speech-Language-Hearing Association (Fausti et al., 1993) and the American Academy of Audiology (Durrant et al., 2009), defines a significant change when one of the following criteria is met: "(a) ≥20 dB decrease at any one test frequency, (b) ≥10 dB decrease at any two adjacent frequencies, or (c) loss of response at three consecutive frequencies where responses were previously obtained" (Durrant et al., 2009). Hearing thresholds are always compared to baseline responses, and if a significant change is detected in the SRO, the change must be confirmed with repeat testing within 24 hours and the change must be reported to the referring physician (Durrant et al., 2009). The SRO method is able to identify 90% of all ototoxicity cases and decreases testing time (Baguley & Prayuenyong, 2019). This method also allows for a limited range of frequencies to be tested, increasing efficiency for the audiologist, and decreasing test fatigue in the patients.

Speech Testing in Quiet

Speech recognition threshold and word recognition scores are obtained to provide a baseline for comparison for how well a person can communicate prior to treatment or any otologic pathologies caused by the chemotherapeutic treatment. Speech recognition testing is not utilized in detecting ototoxic changes to hearing sensitivity, but rather can inform audiological treatment options after chemotherapy is completed if there is a change in hearing sensitivity. Speech scores should be re-tested if a person shows a significant change in hearing thresholds to determine if communication abilities are being affected and to determine if the audiologist needs to recommend rehabilitation options during or post-treatment. There is no standard for what a significant change in speech understanding is, but it is generally accepted that if there was a significant change in threshold and the patient complains of communication issues, rehabilitation needs to be recommended to the patient (Konrad-Martin et al., 2005a).

Speech Testing in Noise

Speech understanding is tested in the sound booth as part of the initial test battery. It is used as an indicator for word recognition abilities when speech is at a sensation level that is comfortable for the listener when listening in quiet situations. However, speech understanding, measured in quiet in a sound-controlled booth, is not well-representative of complex communication situations (Kuehne, 2019). As many real-world listening environments are more complex than a quiet sound-controlled booth, Speech in Noise (SIN) testing has been found to be more representative of real-world situations and provide better prediction of the success of patients' word recognition abilities across multiple listening environments (Hadley et al., 2021; Jorgensen & Wu Inyong Choi, 2021). Word recognition performed in background noise is proven to be significantly harder for persons with hearing loss when compared to those with

normal hearing, even when measured with the same background noise and presented at the individualized sensation level (Kenyon et al., 1998). SIN testing is not commonly used in ototoxicity monitoring; however, Baguley and Prayuenyong (2019) state that SIN results can aid in aural rehabilitation decision-making and should be included in all comprehensive ototoxic monitoring programs. SIN testing could also be an earlier indicator of damage to the SGNs or damage causing auditory neuropathies due to the higher-level auditory processing required during testing. Patients could have normal pure-tone hearing thresholds if hair cells are not yet affected, but have disproportionately worse SIN scores, indicating an issue with sending the signal through the auditory pathway to the cortex (Narne et al., 2015).

Otoacoustic Emissions

Otoacoustic emissions (OAEs) are a repeatable objective test that can detect the functionality of OHCs via energetic movements in response to acoustic stimuli (Reavis et al., 2008). There are two different types of OAEs used clinically and the difference is in how the emissions are elicited. The first type of OAE to be used clinically was a transient-evoked OAE, or TEOAE. However, TEOAEs are not efficient at measuring OHC responses in the high frequencies, which is required for ototoxic monitoring of chemotherapeutics that affect those higher frequencies first (Brooks & Knight, 2017). The frequency range that TEOAEs are the most robust at testing in adults are 1 – 4 kHz (Kemp, 2002). The second type of OAE, distortion-product otoacoustic emissions (DPOAEs), is better at measuring responses from high-frequency regions of the cochlea and can provide more frequency specific information than TEOAEs (Brooks & Knight, 2017). Traditional or conventional DPOAEs tend to evaluate distortion product frequencies that correspond with traditional behavioral audiometry, 0.5-8 kHz. With DPOAEs, two pure-tone sound stimuli are presented to the cochlea and the OHCs react to the

stimuli. Their electromotility, or movement in response to the stimuli amplifies the efferent signal to the brain, but also emits an acoustic distortion response that travels back through the middle ear and can be measured by a probe with a sensitive microphone in the ear canal (Reavis et al., 2008). The probe in the ear canal measures the ambient noise level of the ear canal and the amplitude of the distortion product (DP) created by the OHCs in response to the two pure tones. A value is calculated based on the two measurements and is given in a signal-to-noise ratio format. Reduction in DP amplitudes, or a reduced SNR, is what indicates that OHCs could be affected by the chemotherapeutic regimen (Dreisbach et al., 2017). A reduced SNR, or absent DPOAE response, is indicative of at least a 40 dB HL threshold. A reduced SNR could occur due to a number of other reasons, such as recent excessive noise exposure, a middle-ear pathology such as otitis media, or anything that affects the functionality of the OHCs other than the chemotherapeutic being used. It is important to rule this out. However, there is no current guideline that states what a significant change would be based on DPOAE responses. This interpretation is left up to the audiologist and treating physician.

As discussed earlier, platinum-based chemotherapeutics tend to have an early effect on the amplitude of OAEs due to damaged OHCs and loss of function. OAEs can detect significant changes in OHC function suggestive of ototoxicity before changes in hearing threshold become evident in either the conventional or EHF ranges (Reavis et al., 2008). Stavroulaki et al. (2001) measured DPOAEs in children treated with cisplatin. The authors detected a change in DP amplitude at 4, 6, and 8 kHz that corresponded with a change in behaviorally measured hearing thresholds, even if it was not significant. OAEs are an objective and reliable test, and they are especially useful in detecting changes in outer hair cell function in those who cannot reliably participate in a behavioral measure of hearing. DPOAEs should be utilized for cochleotoxicity

monitoring when the auditory damage the chemotherapeutic is causing is at the level of the OHCs, such as cisplatin and carboplatin. If the chemotherapeutic is not generally known to cause OHC damage, such as vinblastine and DFMO, other objective measures such as ABR should be used instead.

High Frequency DPOAEs

Traditional DPOAEs are most often measured clinically at 1-10 kHz; however, there is also the ability to measure DPOAEs at frequencies in a similar range to what is measured by EHFA. The frequencies measured with high-frequency DPOAEs are generally 10-16 kHz (Poling et al., 2019). High-frequency DPOAEs are important for detecting changes in hearing before ototoxicity can impact frequencies that are important for speech understanding. It is recommended by Reavis et al. (2008) that OAEs be measured at the highest one octave range where DPOAEs are measurable at baseline testing with fine-frequency steps of $1/12^{th}$ to $1/24^{th}$ of an octave in order to detect any fine changes in cochlear function, potentially indicating changes in hearing function. High-frequency DPOAEs are especially important in measuring any changes to OHC functionality, even after one dose of cisplatin or other platinum-based agents. High-frequency DPOAEs have been shown to be repeatable in normal hearing adults and hearing-impaired adults and children over multiple trials (Dreisbach et al., 2006; 2018). This repeatability demonstrates that high-frequency OAEs are reliable and accurately measure OHC responses (Dreisbach et al., 2006).

Auditory Brainstem Response

Auditory Brainstem Responses (ABRs) are commonly used to estimate hearing thresholds in populations that cannot participate in behavioral testing, as it is an objective measure of auditory nerve and brainstem function in response to an acoustic stimulus (Lord, 2019). ABRs are elicited using a sound stimulus, usually a frequency-specific tone-burst, or most

recently frequency specific narrowband noise chirps. Depending on equipment three or four electrodes are placed on the patient's head using the 10-20 International electrode montage, with one ground electrode, one or two reference electrodes, and one measuring electrode. Electrical responses to the sound stimulus are recorded with specific filter settings to show the brainstem's response. Each peak of the response, or wave, is thought to show responses from different areas along the auditory pathway. Wave I of the ABR is thought to arise from the IHC synapse with the SGNs of the auditory nerve (Lavinsky et al., 2021), making it a good predictor for whether or not the cochlear amplification and functionality of the OHCs is being affected, as well as IHC functionality. Waves II-V measure structures further along the auditory pathway, making these measurements useful for detecting damage due to chemotherapeutics that cause neuropathies, such as vinblastine. ABRs are also a good indicator of auditory neuropathy in patients being treated with neuropathic chemotherapeutics, such as vincristine, vinblastine, nedaplatin, oxaliplatin, and DFMO.

For ototoxic monitoring, tone-burst elicited ABRs are measured at high frequencies and should include 8-14 kHz (Fausti et al., 1994), or the frequencies within the SRO. The use of frequency-specific stimuli, such as tone-bursts or narrowband CE-CHIRPs (Dzulkarnain et al., 2022), is pertinent for objectively estimating hearing thresholds at frequencies that correspond to regions of the cochlea that may first be affected by chemotherapeutics (Lord, 2019). The reliability of frequency-specific stimuli is low when it is used to estimate hearing thresholds at the higher frequencies, making it less appealing for ototoxicity monitoring than other objective tests, such as DPOAEs (Lord, 2019), and the measurement failure rate is high, bringing down the overall reliability of the ABR's ability to detect ototoxicity on their own (Dille et al., 2013). However, ABR testing is still clinically useful when estimating hearing sensitivity in those who

cannot accurately respond to behavioral methods of testing, as there are no other tests that will objectively monitor auditory function of the full auditory pathway (past the OHCs) at high frequencies in patients who are unable to respond behaviorally. When utilizing ABRs with DPOAEs, sensitivity to changes in structure function can be increased in those populations that cannot behaviorally respond to pure-tone testing.

ABRs and DPOAE Combination Testing

When used together, ABRs and DPOAEs can be a more reliable and accurate test of functionality than when used independently. In a study by Chen et al. (2021), the correspondence between ABR and DPOAE responses was shown to be consistent for cisplatin-induced ototoxicity in mice. The authors gave one round of a cisplatin-based chemotherapy treatment protocol designed to create a minimal but progressive threshold shift in mice (100mg/ml for four days, injected at 4mg/kg per day, followed by a 10-day rest period), and saline to a control group of mice. After one round of treatment, the authors found that there was no damage to the structure of the IHCs, OHCs, or the synaptic ribbon count in the cochlea of the mice, and there was no difference in ABRs between the cisplatin- and saline-treated mice. However, the researchers found damage to the mitochondria of SGNs in the basal region of the cochlea that continued to worsen with additional treatments, indicating an early identification of cisplatin ototoxicity before it showed up on any objective testing. After the second round of cisplatin treatment, there was a difference for ABR results between the experimental and control groups at 28 kHz and 10 kHz, and these differences corresponded with the high-frequency DPOAE responses in both groups (Chen et al., 2021). This indicates that high-frequency DPOAEs and ABRs used together are reliable and accurate indicators of early ototoxicity in the cochlea,

especially with regards to cisplatin. One limitation to this study is that known ototoxic chemotherapeutics other than cisplatin were not included.

Early Detection of Ototoxicity

Chemotherapeutic agents that are ototoxic to the cochlea tend to affect the base of the cochlea first, which is where the higher pitches, or frequencies, are encoded. According to Konrad-Martin et al. (2005b), accurate monitoring requires tests that are specific enough (have a low false-positive rate) and sensitive enough (have a high hit rate) to hearing changes that occur due to cochleotoxicity. In platinum-based chemotherapeutic agents such as cisplatin and carboplatin, cochleotoxicity is generally observed first in higher frequencies, as the damage tends to occur at the basal end of the cochlea before affecting more apical structures. Conventional audiological testing occurs in the frequencies where speech occurs (0.25-8 kHz); however, it is possible to test frequencies that are higher and detect hearing changes in the extended high frequency range before speech understanding is affected (Konrad-Martin et al., 2005a). For vincristine, vinblastine, and DFMO, the best way to monitor changes to hearing sensitivity and changes in responsiveness of the auditory system to sound stimuli is through EHF audiometry in combination with ABR testing. If significant changes in hearing sensitivity are identified during ototoxic monitoring, results are reported to the oncologist or physician in charge of the cancer treatment. Criteria for what constitutes a significant change by professional organizations in the audiology field are discussed later in this manuscript.

Overview of Ototoxicity Monitoring Guidelines by Professional Organizations

The previous section described the audiological test battery and reviewed literature on effectiveness of different tests for ototoxicity monitoring. This next section includes a table

(Table 2) that reviews differences in recommendations between the two audiology professional organizations: ASHA and AAA.

American Speech-Language-Hearing Association (ASHA)

ASHA is a professional organization consisting of 218,000 Speech-Language Pathologists, Audiologists, and Speech-Language-Hearing Scientists. The organization was established in 1925 and has since created an academic accreditation board (Council on Academic Accreditation in Audiology and Speech-Language Pathology, or CAA) for university programs related to the field, provides certification for clinical competency in professionals, and produces guidelines for clinical practice in various areas of speech-language pathology and audiology. An Ad Hoc (or temporary) committee chosen by ASHA leaders released guidelines titled "Audiologic Management of Individuals Receiving Cochleotoxic Drug Therapy" in 1993 (Fausti et al., 1993). These recommendations have not been updated since that time.

American Academy of Audiology (AAA)

AAA is a professional organization consisting of more than 14,000 Audiologists across the United States. The organization was established in 1988 and has since established many different suborganizations, such as the American Board of Audiology, the Student Academy of Audiology, the American Academy of Audiology Foundation, and the Accreditation Commission for Audiology Education, providing deeper involvement in the field, educational accreditation, and clinical/specialty certification in audiology. AAA also produces clinical practice guidelines via position statements. The guidelines relating to ototoxic medications is entitled "Ototoxicity Monitoring" and was released in October 2009 and has not been updated since that time (Durrant et al., 2009).

Table 2

Summary Comparison of ASHA and AAA Guidelines for Ototoxicity Monitoring

Category	ASHA (Fausti et al., 1993)	AAA (Durrant et al., 2009)
Objectives of Ototoxicity Monitoring Protocols	Detection of ototoxic damage before patient is aware of any symptoms. Consideration of treatment alternatives (modification of drug dosage or type).	Early detection of changes to sensitivity of hearing, thought to be due to a drug regimen or treatment, so changes in the regimen or treatment can be considered. Allow for audiologic intervention if hearing sensitivity affects daily life or quality of life.
Audiological Methods of Value	Basic Monitoring Evaluations (otoscopy, air-conduction thresholds from 0.25-8kHz). High-Frequency Threshold Evaluation (9-20kHz) to detect changes in which cochleotoxic change initially occurs utilizing high-frequency audiometers with specialized circumaural or insert earphones.` Otoacoustic Emissions (OAEs) for use in evaluation of unresponsive patients, as they are an objective measure. Electrocochleography (EcochG) can be useful but not for routine objective auditory monitoring, as it is time-consuming and not frequency specific. Auditory Brainstem Response (ABRs) is also time-consuming and not frequency specific. High-frequency tone-burst stimuli is the best option for objective monitoring of ototoxicity.	Basic Audiologic Assessment Extended High Frequency Audiometry (EHFA) (9-20kHz) to detect changes that occur in the basal end of the cochlea first. Otoacoustic Emissions (OAEs) are sensitive to OHC dysfunction, which toxicities tend to first be expressed as. Research shows that DPOAEs detect changes in hearing before TEOAEs, so DPOAEs are the preferred method. Auditory Brainstem Response (ABRs) obtained in-office or via bedside testing are useful objective measures for those who cannot reliably respond behaviorally, either due to pre-treatment cognitive issues or fatigue from treatment. High-Frequency ABRs, if equipment and test environment allow.

Table 2 (continued)

Category	**ASHA (Fausti et al., 1993)**	**AAA (Durrant et al., 2009)**
Frequency of Monitoring	Patient Identification: Patients receiving therapeutic drugs known or suspected of having side effects that are ototoxic. Pretreatment Counseling: Informing of potential effects of treatment on the auditory system. Baseline: Prior to treatment, if possible, otherwise within one week of initial treatment; comprehensive, including word discrimination; utilized for comparison to any potential changes through and following the treatment regimen; SRO is determined; reliability of behavioral responses should be assessed; cisplatin treatment can cause hearing loss quickly, so a baseline prior to treatment is pertinent. Monitoring tests (during treatment): Scheduled to enable earliest possible detection of cochleotoxic effects; Platinum-based treatments warrant monitoring within 24 hours prior to each course of treatment. Frequency should be increased if subjective or behaviorally-monitored decrease in hearing sensitivity is observed. Follow-ups (post-treatment): Immediately after treatment, and at 3- and 6-months post-treatment. If a decrease in hearing sensitivity is noted, weekly monitoring should occur until sensitivity stabilizes.	Baseline: Prior to treatment; comprehensive, including all tests that might be needed in subsequent testing; utilized for comparison to any potential changes through and following the treatment regimen; SRO is determined; a baseline prior to beginning treatment is especially important for those receiving cisplatin. Monitoring tests (during treatment): Occur just prior to each course of platinum-based chemotherapy, after any temporary threshold shift has had time to recover, and before the patient is connected to IV lines or monitoring equipment. Follow-ups (post-treatment): With platinum-based chemotherapy, follow-ups should occur a few months after treatment regimes are ceased. If head and neck radiation was part of the treatment, recommendation of monitoring for the next year or two is advisable.

Table 2 (continued)

Category	ASHA (Fausti et al., 1993)	AAA (Durrant et al., 2009)
Sensitive Range for Ototoxicity (SRO)	"The highest frequency with a threshold at or below 100dB SPL followed by the next six lower adjacent frequencies in 1/6th-octave steps, or the one octave range near the highest audible frequency" (Fausti et al., 1993).	"The highest frequency with a threshold at or below 100dB SPL followed by the next six lower adjacent frequencies in 1/6th-octave steps, or the one octave range near the highest audible frequency" (Fausti et al., 1993). Determined during the baseline assessment. Reported High Sensitivity. 90% of all initial ototoxic hearing changes occur in the seven frequency SRO.
Significant Change Criteria	No significant change criteria specified in the guidelines, but criteria is specified elsewhere: (1) ≥20dB decrease at any one test frequency within the SRO (2) ≥10dB decrease at any two adjacent frequencies within the SRO (3) Loss of response at three consecutive frequencies where responses were previously obtained.	National Cancer Institute Common Terminology Criteria for Adverse Events Ototoxicity Grades (National Institutes of Health, 2017) Brock's Hearing Loss Grades (Brock et al., 1991) Use of ASHA's Criteria: (1) ≥20dB decrease at any one test frequency within the SRO (2) ≥10dB decrease at any two adjacent frequencies within the SRO (3) Loss of response at three consecutive frequencies where responses were previously obtained. (4) Changes are computed relative to baseline measures and must be confirmed by repeat testing, within 24 hours if possible.

Table 2 (continued)

Category	ASHA (Fausti et al., 1993)	AAA (Durrant et al., 2009)
Next Steps (After a Significant Change Occurs)	Retest within 24 hours for confirmation of change. Physicians should be informed of validated change. Immittance and/or Bone-Conduction testing to differentiate from conductive pathologies.	More complete evaluation is necessary to (1) Verify changes in hearing sensitivity, (2) Rule out other possible disorders (including otitis media or other middle ear issues), and (3) Determine possible effect on speech understanding and quality of life moving forward. After verification: (1) Inform referring physician about change in hearing, and (2) Suggest a change in treatment regimen to alleviate ototoxic effects, if possible.
Special Considerations	Limited Responsive Patients: provide reliable behavioral responses for short periods of time. Unresponsive Patients: cannot provide reliable behavioral responses, can only be evaluated using objective measures. Testing Environments: Ideally should be in a sound-treated booth. Patients who cannot leave their bed may need bedside testing. Ambient noise is not a problem at higher frequencies, and reliability for EHFA has been routinely demonstrated in normal-hearing patients. Ambient noise levels should be assessed with a sound level meter and utilized in assessing response reliability between sessions.	Bedside testing: Patients undergoing active chemotherapy treatment may not be able to leave their bed and may need bedside testing in a quiet hospital room. Pre-Treatment Hearing Loss in Speech Frequencies: Elderly patients may have hearing loss that already affects frequencies tested with conventional audiometry, rendering EHFA useless. SRO may be lower. Objective Measurements of Hearing Sensitivity: Pediatrics and other populations who may not be able to reliably respond to behavioral measures need objective tests, such as OAEs and ABR. Otitis Media: Common among pediatrics and infectious disease patients, especially those immuno-suppressed by chemotherapeutics.

Table 2 (continued)

Category	**ASHA (Fausti et al., 1993)**	**AAA (Durrant et al., 2009)**
Pediatrics	Considerations are included in the guidelines but are not summarized here. This manuscript focuses on adult monitoring.	Considerations are included in the guidelines but are not summarized here. This manuscript focuses on adult monitoring.
Audiologist Responsibilities	Design and implementation of an auditory monitoring program for ototoxicity. Implementation and continuation of a program is a collaborative effort between audiologists and medical center personnel. Audiologic rehabilitation and management.	Audiologists are the only professionals with adequate training to achieve *both* objectives of ototoxicity monitoring protocols, therefore they should be the one to develop monitoring protocols. Audiologic rehabilitation and management.
Limitations of OAEs	Not well studied or clinically adapted at this time.	Sensitivity and specificity has yet to be documented on large-scale patient populations and confirmed. Responses may be limited or absent in the elderly population due to lifelong noise exposure or age-related hearing loss. Results are affected by middle ear pathologies and are less reliable in the presence of conductive hearing losses and middle ear pathologies, like otitis media.
Tinnitus	Not specified in the guidelines.	Common side effect of many ototoxic drugs, especially cisplatin. Assessments are not commonly used. Research needs to be done regarding the common assumption that tinnitus is an early indicator of ototoxicity.

Table 2 (continued)

Category	**ASHA (Fausti et al., 1993)**	**AAA (Durrant et al., 2009)**
Noise Exposure Bias	Undergoing chemotherapy treatments while also being exposed to excessive noise levels could possibly increase the risk of ototoxicity.	Prior Noise Exposure: No known research showing potentiation of ototoxicity. Concomitant Noise Exposure: Increases risk for ototoxicity of cisplatin.
Audiologic Rehabilitation and/or Management	It is the audiologist's responsibility to begin or recommend aural rehabilitation. Intervention should begin as soon as possible after identification of a hearing loss to give the patient the most access to sound and speech understanding during treatment.	Audiologic management may be overlooked initially as the patient is going through other serious health conditions. Use of hearing aids or assistive listening devices, and which type, varies on a case-by-case basis.
Vestibulotoxicity Monitoring	The guidelines do not discuss monitoring for vestibulotoxicity.	This manuscript does not discuss the vestibulotoxic effects of chemotherapeutics; however, the guidelines recommend routine monitoring of patients undergoing treatment with known or suspected vestibulotoxins, or if a patient reports signs of vestibular pathology. Further research on this should be conducted.

Note. Adapted from ASHA (Fausti et al., 1993) and AAA (Durrant et al., 2009) Ototoxicity Monitoring Position Statements and Guidelines. American Academy of Audiology (AAA), Auditory Brainstem Response (ABRs), American Speech-Language-Hearing Association (ASHA), decibel (dB), Electrocochleography (EcochG), Extended High Frequency Audiometry (EHFA), Otoacoustic Emissions (OAEs), Sound Pressure Level (SPL), and Sensitive Range for Ototoxicity (SRO).

Differences Between the Guidelines

The ASHA guidelines are fifteen years older than AAA's guidelines, so some information was not known about or as widely studied or used clinically as they are in AAA's guidelines. For example, AAA's guidelines discuss the effects of tinnitus on testing abilities, as well as it being an early indicator of ototoxicity due to chemotherapy. This is also supported by other recent research, such as Dille et al. (2010), El Charif et al. (2019), and Patatt et al. (2021). AAA also discusses the use of high-frequency ABRs (Durrant et al., 2009), which were not as widely studied when ASHA released guidelines in 1993 (Fausti et al., 1993) and describes more specific limitations to OAEs than ASHA. AAA also has more specific next steps for after a change is detected than ASHA. However, ASHA discusses the ramifications of a louder testing environment and what the preferred testing environment should be with regards to noise levels. ASHA also outlines patient identification strategies and pre-monitoring counseling strategies to set patient expectations, which AAA does not outline.

Other Considerations for Monitoring

Patients should first have a baseline hearing test completed before the beginning of their chemotherapeutic treatments, during treatment to monitor auditory status between therapy sessions, and following cessation of treatment. Ototoxic monitoring after cessation is suggested at intervals of one week, one month, six months, and a year after cessation of treatment (Durrant et al., 2009; Fausti et al., 1993). In addition, when cisplatin therapy is used at the same time as radiation therapy, audiological monitoring should continue for two to five years post-therapy, as the agents can remain in the body and continue to affect the auditory pathway even after completion of treatment (Campbell, 2011; Durrant et al., 2009; Konrad-Martin et al., 2005a). Other chemotherapy agents, such as nedaplatin, can also be more damaging to the auditory

system when used in combination with cranial-radiotherapy (Tang et al., 2021), and should be monitored with such considerations in mind.

Regardless of which potentially ototoxic chemotherapeutic agents are being used for treatment, the initial test battery should always include any tests that may be needed later on for monitoring. This battery generally includes a conventional audiometric examination consisting of immittance testing, pure-tone air-conduction thresholds, pure-tone bone-conduction thresholds, speech recognition thresholds, word recognition scores, EHF audiometry, otoacoustic emissions (including high-frequency OAEs) (Baguley & Prayuenyong, 2019; Konrad-Martin et al., 2005a; Paken et al., 2020; Santucci et al., 2021), and occasionally an auditory brainstem response in special cases or those who cannot behaviorally respond, such as infants (Brooks & Knight, 2017). Testing should always be conducted bilaterally, as chemotherapeutics are shown to affect both ears, but can affect only one ear in rare cases.

Other researchers, such as Campbell (2011) and some agencies, such as the Veterans Affairs, recommend or request that a tinnitus screening questionnaire also be included (Konrad-Martin et al., 2014). Speech-in-noise testing is recommended if the patient is showing difficulty understanding speech in quiet and is also recommended for assessment of hearing aid and rehabilitation effectiveness (Einarsson et al., 2011). It is helpful for comparative purposes to have a baseline speech-in-noise test for pre-treatment comparisons, especially if a patient begins to develop sensorineural hearing loss or auditory neuropathies with poor word understanding. Informal case-history questions about tinnitus, dizziness, decreased hearing ability, aural fullness, noise exposure, or the beginning of radiation or other ototoxic agents are also recommended to be asked prior to each monitoring appointment (Konrad-Martin et al., 2005a).

Recommended Protocols

Based on the review of literature and how each individual chemotherapeutic agent affects the auditory system, in the appendix are flowcharts of recommendations for ototoxicity monitoring protocols based on the chemotherapeutic regimen, and whether the patient can reliably respond to behavioral testing. These recommendations build off the AAA/ASHA guidelines and are extended to include drugs that are used to treat the five most common adult cancer types in the U.S. Recommendations for responsive and unresponsive patients can be found in the appendices.

Interventions for Ototoxicity

Role of Medical Professionals

Management of a patient undergoing cancer treatment requires a multidisciplinary care team and a multidisciplinary approach. The medical professionals involved in the auditory side of the care team include oncologists, audiologists, pharmacists, physician assistants and nurse practitioners or medical assistants.

Role of the Oncologist

Oncologists are responsible for choosing a drug regimen, determining the effective dosage, as well as timelines for administration of the regimen. Oncologists make the decision to use an ototoxic drug or another drug depending on the needs of the patient and the type of cancer. Ototoxicity may not even be a factor in choice of chemotherapeutic if the oncologist determines that a specific drug is needed to treat the cancer. The oncologist may not be the first person on the patient's care team to notice a change in a patient's hearing abilities and may not recommend monitoring. However, it may be that the patient is routinely enrolled in an ototoxicity monitoring program when specific chemotherapeutic regimes are initiated. If a

significant change to hearing occurs, the oncologist is notified of the change. It is also suspected that the change will grow over time if the chemotherapy treatment continues as-is. Lord (2019) states that the oncologist may change the drug regimen from an ototoxic agent to a chemotherapeutic agent that is less damaging to the auditory system. Although, in some cases, the tumor may be too big or too far progressed that the oncologist believes the original treatment regimen needs to remain the same, regardless of how it is affecting the hearing of the patient. Baguley and Prayuenyong (2019) state that even if a significant change is detected while utilizing EHFA, some oncologists may still choose not to change a patient's regimen until the ototoxicity affects 8kHz and below and threatens speech understanding, or the oncologist may choose not to change the drug regimen at all.

The treating oncologist utilizes guidelines that are generally drafted by a protocol writing committee for potential treatment changes based on audiological results. These guidelines typically contain grading scales for tumors and audiological changes that provide insight into possible treatment changes (Brock, 2021). There are some cancer types that have evidence-based alternatives to ototoxic chemotherapeutics, or evidence-based guidelines on the amount the treatment can be reduced to ameliorate ototoxic effects. For example, a study by Bielefeld et al. (2021) demonstrated that a longer rest period between cisplatin treatments can cause less ototoxicity in mice, but platinum from the cisplatin can still remain in the cochlea even after treatment ceases, making it hard to tell if this has a long-term effect on ototoxicity. Some people who have more aggressive cancers may not be able to extend the rest periods between treatments, so it is not an approach that can help every patient who shows early signs of ototoxicity (Bielefeld et al., 2021).

Role of the Audiologist

The audiologist's role in ototoxicity monitoring is to establish a monitoring program that will reliably and effectively catch a change in auditory function and inform the referring oncologist of such a change. It is also the role of the audiologist to provide intervention if the patient does have an irreversible change in hearing sensitivity.

Counseling on Realistic Expectations. It is important for the audiologist to initially establish realistic expectations with the patient prior to beginning ototoxicity monitoring. This is important to inform the patient of the importance of the monitoring and continued follow-ups; the importance of paying attention to changes in hearing sensitivity, tinnitus, and balance; and to assure them audiologists are there to help with rehabilitation if a permanent change does occur (Khoza-Shangase & Masondo, 2021; Konrad-Martin et al., 2014). If a chemotherapy patient presents with a hearing loss, and it is confirmed to be permanent, it is the audiologist's job to counsel the patient and help set realistic expectations surrounding what the patient can expect moving forward.

Audiologic Intervention. Regardless of pharmacological intervention strategies, when a hearing loss is present that affects the patient's ability to communicate, an audiologist must provide adequate and proper intervention in the form of amplification and aural rehabilitation (Lord, 2019). The audiologist must consider how much the hearing loss is affecting the individual and their ability to communicate before recommending interventions. For adults, audiologic intervention usually comes in the form of utilizing hearing aids along with specific communication strategies that they can take part in with their loved ones to greatly improve their quality of life, both during treatment and post-treatment. This requires multiple visits to the audiologist to not only monitor for ototoxicity, but to also reprogram the hearing aids as changes

occur. It is important to counsel the patient and their family on potential further progression of ototoxicity and hearing loss and how it affects communication ability. Providing intervention strategies for both the patient and their communication partners is also key in ensuring that quality of life increases (Lord, 2019).

Role of the Oncology Nurse Practitioner/Medical Assistant

Due to the intensity of the daily caseload and workload of an oncologist, the treating physician may not have the ability to explain all pertinent information regarding treatment to the patient. A nurse practitioner or medical assistant may be appointed by the oncologist to explain the treatment regimen, any potential side-effects of the treatment (i.e., ototoxicity), ways to monitor side-effects (i.e., ototoxic monitoring by an audiologist or other hearing specialist), and, later, what will happen with the treatment when the side-effects occur. The nurse practitioner and oncologist will both make referrals to audiology or ENT/otology offices for monitoring of ototoxicity in cancer patients if the chemotherapeutic agent is known to be ototoxic, or if a not-known ototoxic agent begins to show auditory side-effects (Paken et al., 2020).

Role of the Pharmacist

The pharmacist has a large role in an ototoxicity monitoring program. It is their job to ensure, when warranted, that the treating oncologist and the patient understands the side effects of ototoxic chemotherapeutics. It is also important for pharmacists to identify anybody who may be receiving an ototoxic drug. Professors and doctors in South Africa at the Sefako Makgatho Health Sciences University train their students in both audiology and pharmacology in an attempt to bridge the gap between the two disciplines. The curriculum implements an ototoxicity monitoring program with a service-learning approach that promotes interdisciplinary communication between the pharmacists, treating physicians, nurses, and audiologists. The

pharmacists know the drugs that are ototoxic and inform the physicians and patients of the possibility of ototoxicity. They are also included in the monitoring report that is written by the audiologists to track the progress of the patient. This is an example of an efficient way for treating physicians and audiologists to include pharmacists into their monitoring programs (Schellack et al., 2015). An overview of these roles is summarized in Table 3.

Table 3

Role of Medical Professionals Summary

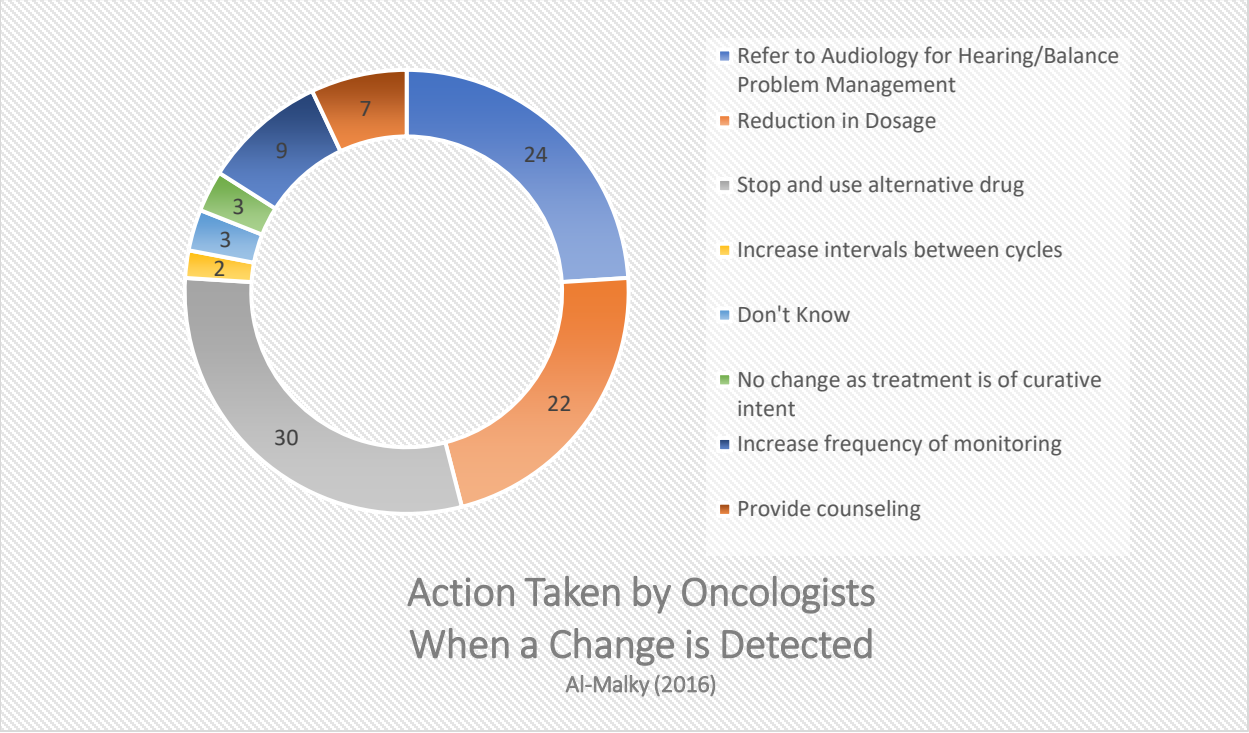
Provider	Drug Choice/ Treatment	Determine Ototoxicity Monitoring Need	Ototoxicity Monitoring Involvement	Action if Change in Auditory Function	After Treatment Considerations
Treating Physician/ Oncologist	Choose initial treatment regimen, and whether it includes an ototoxic chemo-therapeutic.	May initially refer to audiology if drug has a widely-known ototoxic effect, such as cisplatin.	Receive updates regarding patient's auditory function status.	Continue treatment as is, change type of cancer treatment, or reduce dosage of ototoxic drug.	No involvement.
Audiologist	No involvement.	No involvement.	Conduct baseline and monitoring testing. Determine if a significant change occurs.	Inform treating physician/ oncologist or NP/MA of changes and severity of changes.	Provide aural rehab efforts, such as hearing aids or cochlear implants, and aural rehab classes/ therapy.
Nurse Practitioner/ Medical Assistant/ Physician's Assistant	Counsels the patient on side-effects of the regimen, including potential ototoxicity.	May hear initial complaints from the patient about not being able to understand speech and decide to refer to audiology.	Receive updates regarding patient's auditory function status.	Continue counseling efforts to mitigate patient's realistic expectations for re-habilitation.	No involvement.
Pharmacist	Assist oncologist with treatment regimen, to ensure no adverse drug interactions occur.	Educate NPs/MAs/PAs or oncologist on ototoxicity of certain drugs before monitoring can occur.	No involvement.	Assist oncologist in choosing a new treatment regimen that is less ototoxic or include otoprotectants in the regimen.	No involvement unless there is an otoprotectant that works post-treatment.

Pharmacological Intervention

Once cisplatin and carboplatin reach the inner ear, where it can affect hearing, the platinum-based drug creates a toxic environment in the cochlea that contributes to its ototoxic effect. Neuropathy-inducing chemotherapeutics, such as vincristine, vinblastine, or DFMO, can cause ototoxic damage to the auditory neural pathway beyond the cochlea. There are ways to pharmacologically mitigate and minimize the amount of ototoxicity, which are discussed in the following section. These can include a modification of the treatment regimen or utilizing otoprotectants during the treatment or shortly after. However, it is important to note that not all oncologists or treating physicians will make any changes. Some oncologists might refer out to audiology for management of symptoms, as the physician looks at the chemotherapy as a curative treatment only and that the side effects are manageable. Others only increase the monitoring frequency. What the treating physician does depends on the aggressiveness of the cancer and the previous knowledge and education of the physician on the effects of hearing loss on a person's daily life. Figure 1 is a graphic illustrating what oncologists reported they do when a change in the SRO is detected, based off research in the UK by Al-Malky (2016). The three most common actions taken are (1) stop and use alternative drug (30%), (2) to refer to audiology for hearing or balance management (24%), and (3) a reduction in drug dosage (22%) (Al-Malky, 2016).

Figure 1

Action Taken by Oncologists When a Change is Detected



Note. Adapted from Al-Malky, G. (2016). Audiological monitoring in ototoxicity – Are we doing enough? *ENT and Audiology News.* Retrieved from https://www.entandaudiologynews.com/features/audiology-features/post/audiological-monitoring-in-ototoxicity-are-we-doing-enough.

Modification of Treatment Regimen

When significant changes to the SRO are found by an audiologist, the next step is to inform the oncologist in order to explore the options if any of changing the drug treatment regimen to something less ototoxic (Al-Malky, 2016). The ramifications of ototoxicity and the possibility of hearing loss affecting the patient's quality of life are explained to the oncologist or treating physician in detail with a recommendation for change, if possible, but the ultimate

decision to change a treatment regimen lies with the treating physician. Some oncologists will always want to change a regimen if it is possible, but this is dependent upon the aggressiveness of the cancer and thus the required aggressiveness of the treatment regimen. Other oncologists will increase the amount of time between treatments (Al-Malky, 2016) so the chemotherapeutic agent cannot build up in the system as intensely, and hopefully mitigate the ototoxic properties of the agent in that way.

Otoprotectants

The ototoxic mechanisms of chemotherapeutics include an imbalance of the antioxidant defense system within the cochlea and an inflammatory reaction to cytokines, causing ROS; apoptosis; autophagy; and nitrative stress. Based on the mechanisms of ototoxicity, researchers have hypothesized that other drugs, such as antioxidants, anti-inflammation drugs, and anti-apoptosis drugs could be an efficient way to combat ototoxicity or other toxicities of the platinum-based chemotherapeutics (D. Yu et al., 2020). These drugs are known as otoprotectants. There are many different otoprotectants that are currently being researched in animal models and human models, and this topic will be further discussed in Chapter 3 of this manuscript for further research considerations. Otoprotectants can be utilized alongside chemotherapy treatment to ameliorate the toxicities of chemotherapeutics on the auditory system and will possibly have more widespread use with further research.

Audiological Management

If the oncologist or treating physician decides that the risks of ototoxicity and its effects outweigh the benefits of the chemotherapy treatment, a hearing loss may occur. Or, even with a pharmacological change in the treatment regimen, there may still be a permanent hearing loss. There are multiple steps that an audiologist can take regarding hearing loss management and

intervention in these cases, and it is often left up to the audiologist to make the best recommendations in terms of hearing management for the patient. Chemotherapy patients undergo many different treatments and see many doctors. It is important that the monitoring audiologist follow-up with these patients to ensure continuum and quality of care to ensure the patient has the best quality of life possible both during treatment and post-treatment.

Presenting all possible options for rehabilitation to the patient is key to their success and quality of life. Many people with hearing loss who have never utilized amplification expect that rehabilitation options such as a hearing aid or cochlear implant will return their hearing to normal, and they will not have to work hard to communicate anymore. This is not entirely the case, so letting them know that with a hearing loss, it is important to utilize amplification devices and work on aural rehabilitation skills will save them from further frustration.

Amplification

Based on the severity and audiological configuration of the hearing loss acquired during chemotherapy treatment, an audiologist will recommend the proper type of amplification (Durrant et al., 2009; Fausti et al., 1993). Amplification may be as simple as providing assistive listening devices, such as a microphone with headphones for patients with mild hearing loss and some situations where they cannot hear well. Sometimes all that is initially needed is an assistive listening device, such as a PockeTalker (Tran & Manchaiah, 2018) or other personal amplifier, that works for the patient while they are receiving treatment. The patient still needs to hear pertinent information and instructions regarding their treatment, and a personal amplifier may be all that is necessary at the time of treatment. The patient may pursue other options, such as hearing aids once they are less fatigued and may need a more permanent option.

It may be helpful for patients whose hearing loss is affecting their day-to-day communication abilities to have properly selected and fit hearing aids. Hearing aids are devices that amplify sound and send that amplified sound through a damaged auditory system, hoping that the brain can pick up the information if it is made loud enough. The ability for one to hear well in noisy situations, such as restaurants or board meetings, is much more difficult for those utilizing hearing aids than normal hearing individuals, so counseling and utilization of active listening skills and assistive devices are important for success and a better quality of life (Bass et al., 2016). Hearing assistance technologies, such as remote microphones that directly stream to the hearing aid(s) may be especially helpful in more complex listening situations, or places where there is quite a distance between the speaker and hearing aid user, such as a worship service ((Khoza-Shangase & Masondo, 2021) and (AAA Guidelines for the Audiologic Management of Adult Hearing Impairment).

Cochlear Implantation

If hearing aids are not sufficient, and the patient's hearing loss is severe enough and the neural pathways past the cochlea are shown to be intact, the audiologist may recommend cochlear implants (CI) (Nader & Gidley, 2019). Cochlear implants are an attempt to bypass the damaged sensory organs of the auditory system and send an electrical impulse directly to the nerves and the brain. It involves an outpatient surgery to put an electrode array inside the cochlea, which is done by an otolaryngology surgeon, and follow-up care with the audiologist to include programming of the implant and aural rehabilitation efforts. The sound quality of a CI is generally described as noisy at first and does not sound like natural listening initially, and patients require copious amounts of counseling and active listening practice to succeed with these devices (Ryu et al., 2015). Patients who have had damage outside of their cochlea, for

example to the SGNs, may not see as much benefit from a cochlear implant as a patient who has purely cochlear damage from chemotherapy. This is evidenced in an article by Harris et al. (2011) in which a loss of cochlear implant benefit occurred after cisplatin treatment in a pre-treatment implantation case.

There are several other considerations that need to be taken when recommending cochlear implantation. Patients who have undergone chemotherapy and radiotherapy, especially in the head and neck region, have temporal bone and auditory pathway damage that may affect the outcomes of surgery and use of CIs (Biggs & Ramsden, 2001). Nader and Gidley (2019) state that chronic middle ear disease and mastoid diseases due to radiation complications need treatment before considering cochlear implantation and the surgical technique may need to be adapted to work around these diseases and temporal bone softening. Patients will also need magnetic resonance imaging (MRI) compatible implants and processors to continue ongoing monitoring for new tumors (Biggs & Ramsden, 2001).

Aural Rehabilitation Therapy

Aural rehabilitation therapy is a type of training that is typically performed by audiologists, and sometimes speech-language pathologists. The purpose of aural rehabilitation is to address any communication disruptions in real-life situations and provide resources and communication strategies to better communicate in the real world, reducing stress or other psychosocial consequences of hearing loss (Hickson et al., 2007). Aural rehabilitation can be conducted in a group or individualized setting, and can include anything surrounding amplification, speech-reading therapy, family counseling and communication strategies, internet-based aural rehabilitation. Some well-known programs include Active Communication Education (ACE) (Hickson et al., 2007) and Listening and Communication Enhancement

(LACE) (Sweetow & Sabes, 2006), although many audiologists and other hearing health professionals should utilize the basics of a “best practices" aural rehabilitation program to form their own group or individualized programs.

Summary

The best first step to ensuring quality of life in cancer patients undergoing potentially ototoxic chemotherapy treatments, such as cisplatin or DFMO, is to change the treatment regimen to a different drug that is not ototoxic. This may not be a possibility in all cancer patients, based on the type of cancer, and so reducing the dosage utilized for the treatment, or switching to a less ototoxic drug (i.e., switching from cisplatin, which is highly ototoxic but effective at treating the cancer, to carboplatin, which is still ototoxic but to a lesser degree) may be the route of choice for the oncologist or treating physician. If the chemotherapeutic cannot be changed, it is best to look into utilizing researched otoprotectants, such as dexamethasone or atorvastatin, to best mitigate any potential hearing loss that may occur due to the ototoxicity of the chemotherapeutic being used. If the treatment regimen cannot be changed and there is a permanent hearing loss throughout the course of treatment and/or at the end of treatment, it is the audiologist’s role to provide amplification and rehabilitation/communication strategies to improve the patient’s quality of life.

CHAPTER III

LIMITATIONS IN THE LITERATURE AND FUTURE DIRECTIONS

Limited Research on the Ototoxicity of Chemotherapeutics

Cisplatin is the most researched ototoxic chemotherapeutic agent. This is most likely because it is the most common ototoxic chemotherapeutic and causes damage to the auditory pathway that is well studied in animals (Chiu et al., 2008; Febles et al., 2022; Hellberg et al., 2013; Rybak et al., 2007; Thomas et al., 2013; van Ruijven et al., 2005) and humans (Coradini et al., 2007; Generotti et al., 2022). Cisplatin and carboplatin are utilized more often and are more widely studied in terms of ototoxicity, and this likely influenced the focus of AAA (Durrant et al., 2009) and ASHA (Fausti et al., 1993) when drafting ototoxicity monitoring protocols specific to these chemotherapeutics.

As detailed earlier in this manuscript, DFMO, vincristine, vinblastine, nedaplatin and oxaliplatin are not widely studied in terms of ototoxicity. This could be because they are not used as often, or when they are, they are used in combination with substances that are generally known to be more ototoxic. An example of such combination therapy would be vinblastine and carboplatin to treat small gliomas (Jakacki et al., 2011) or DFMO and cisplatin to treat epithelial ovarian cancer (El Naggar et al., 2022; Hwang et al., 2021). There is some research to describe the known or possible sites of generalized lesions, such as nephrotoxicity or neurotoxicity, but very little research on actual ototoxic effects and patient complaints related to potential ototoxicity. One example of limitations to current research is that the physiological role and

purpose of polyamines in the inner ear are unknown, rendering the knowledge of DFMO's effects on polyamines somewhat useless when considering the specific effects on the inner ear. Patient reports and case studies are also few and far between, especially for vincristine, vinblastine, and DFMO. The quantity of research that suggests the ototoxicity of these agents is low; however, this points to the need for more research to be conducted in these areas.

The other challenge with research on ototoxicity is the diversity of patient populations receiving the treatments, the differences in treatment regimens and control of other factors such as pre-existing hearing loss, medications, and/or other systemic medical conditions that affect the auditory system. Without large, similar patient populations and control of all the other factors, it is difficult to assess the ototoxic effects of a specific drug. More case reports are needed and more patients with baseline audiograms prior to treatment would be helpful towards strengthening the literature.

Limitations of ASHA and AAA's Ototoxicity Monitoring Guidelines

The guidelines recommended by ASHA (Fausti et al., 1993) and AAA (Durrant et al., 2009) only apply to drugs that affect the basal end of the cochlea and the OHCs, specifically cisplatin and carboplatin. The guidelines are limited in the context of drugs that affect IHC function, IHC ribbon synapses, SGNs, and the central auditory pathway. The SRO also does not apply to damage that occurs outside of the basal end of the cochlea. Carboplatin, nedaplatin, oxaliplatin, vincristine, vinblastine, and DFMO all affect the auditory pathway beyond the basal end of the cochlea and OHCs, and thus require more sensitive tests for the auditory areas that they will potentially damage. This leaves applicability of the existing guidelines by ASHA (Fausti et al., 1993) and AAA (Durrant et al., 2009) up to the discretion of the audiologist in charge of monitoring patients being treated with drugs other than cisplatin or carboplatin for

ototoxicity. The guidelines also do not address tinnitus, of which research surrounding tinnitus and ototoxicity has developed since these guidelines were released and research on tinnitus in relation to chemotherapeutic treatments is needed both in terms of early detection and prevention, but also information on effective tinnitus management options for this unique population.

The audiologist must make clinical decisions based on research regarding how best to monitor ototoxicity inpatients' undergoing chemotherapy. Position statements and clinical practice guidelines from ASHA and AAA help the audiologist to make the best decision for implementing an ototoxicity monitoring protocol in a clinic utilizing "best practices". There are other clinical practice guidelines, such as those put forth by Konrad-Martin et al. (2005a), who, at that time, conducted research for the Veterans Affairs Rehabilitation Research and Development Service and worked at the Oregon Health & Science University in the Department of Otolaryngology. These other guidelines may also help an audiologist decide how to implement a best practices ototoxicity monitoring protocol. More research is needed in terms of how audiologists select and implement ototoxicity monitoring in the field.

Limitations of the Paper

Number of Chemotherapy Agents Discussed

There are many types of chemotherapeutics that are considered ototoxic. The ones chosen for this manuscript were more commonly used than others, treated the top five most common cancers in the United States, and had relevant and timely research on their ototoxic effects. There is a need to develop ototoxicity monitoring protocols for a wider range of drugs.

Further Research for Vestibulotoxicity

This manuscript only considered the cochleotoxic effects of some chemotherapeutics in adults. However, some of these same chemotherapeutics, such as cisplatin and vincristine, and others such as methotrexate and docetaxel (Ramma et al., 2019), cause vestibulotoxicity. Further research should discuss the vestibulotoxic effects of chemotherapeutic agents and identify the best ways to monitor for vestibulotoxicity. There is a gap in the literature regarding potential vestibular after-effects when cessation of chemotherapeutic treatment occurs and how to treat or manage vestibular symptoms in cancer patients.

Ototoxicity Monitoring Protocols for Children

The manuscript discussed ototoxicity in the scope of chemotherapy treatment for five of the most common cancers, and monitoring protocols for adults. Future research on the differing effects for children can bridge a gap and identify areas for more in-depth research regarding monitoring for ototoxicity in children undergoing chemotherapy. There are many publications that discuss ototoxicity in children (e.g., Cohen-Cutler et al., 2021; Fetoni et al., 2016; Romano et al., 2020, 2023), but this information needs to be compiled and reviewed in order to create specific protocols for ototoxicity monitoring in children.

Bedside Ototoxicity Monitoring

This manuscript also does not discuss protocols for bedside ototoxicity monitoring. If a patient is bedridden in the hospital or cannot physically be present in a sound booth, audiologists are able to do most monitoring tests at the bedside (Stumpf, 2019). It would be helpful for further research to include the best protocols and procedures for bedside monitoring for ototoxicity of

common chemotherapeutics. Advances in new boothless audiometry techniques may offer new solutions in the future (Gates et al., 2021).

Practical Implementation Limitations

Equipment & Noise Control

Most of the testing for monitoring requires very specific equipment that must be calibrated properly. For example, if an audiologist is not equipped to conduct portable ABRs or DPOAEs, they will not be able to test an unresponsive or unreliably responsive patient. Audiologists also need audiometers and circumaural headphones or inserts allowing for EHFA. Proper noise control (i.e., a calibrated sound booth or utilizing a sound level meter and ambient noise level standards) must be implemented prior to testing behavioral thresholds, ABRs, or DPOAEs, and monitored during testing, or results may not be considered accurate and reliable, especially if completing bedside monitoring.

Time

Time is a factor in whether certain monitoring protocols may be implemented in certain clinics. The SRO method combined with DPOAEs is a quick way to monitor for ototoxicity in the basal end of the cochlea (Vaughan et al., 2002), however, not all damage from chemotherapeutics occurs in that area of the inner ear. Other monitoring tests that may be more effective at detecting damage in the auditory pathway unrelated to the OHCs at the basal end of the cochlea may take longer. For example, it takes about one hour to effectively estimate hearing thresholds based on ABRs (Sininger et al., 2018), and the amount of time depends on the degree of hearing loss present and cooperation of the patient. Patients and busy clinics may not have the time to implement tests that take longer, like ABRs. It may be more difficult to work new

ototoxic monitoring patients into a busy clinic schedule on short notice, which is required for this patient population.

Summary

To better serve this special population of patients, an office might have specific time blocks in the schedule to accommodate baseline testing for new ototoxicity monitoring patients and monitoring appointments. An office might also ensure that all of the required equipment for baseline and monitoring appointments for these common chemotherapeutics are calibrated and in proper working conditions prior to scheduling and accepting ototoxicity monitoring patients into an ototoxicity monitoring program.

Current Research on Otoprotectants

Otoprotectants were briefly mentioned in Chapter 2 and are used to decrease the risk of ototoxicity during chemotherapeutic treatments. These drugs are given before, during, or after chemotherapy treatment, and are chosen by the treating oncologist or recommended by the pharmacist with the goal of preventing or minimizing ototoxic effects. Some examples of more commonly used otoprotectants include sodium thiosulfate, dexamethasone, D-methionine, N-acetylcysteine, and atorvostatin. Some otoprotectants are given systemically, while others are more localized via intratympanic injection, or injection through the tympanic membrane to the round window of the cochlea (Nader & Gidley, 2019).

Sodium Thiosulfate

Sodium thiosulfate is an antioxidant that is commonly used to treat cyanide poisoning, but due to its antioxidant properties it has been evaluated as an otoprotectant against cisplatin-induced ototoxicity, especially in the pediatric population. Hesitancy surrounding the use of antioxidants as an otoprotectant during chemotherapy stems from its possible protective

mechanisms for the cancer cells, rendering chemotherapy treatment useless (Laurell, 2019). A study conducted in 2021 in the Netherlands by Duinkerken et al. included twelve subjects who were undergoing cisplatin treatment. The participants were given a 0.1M intratympanic injection of sodium thiosulfate gel in one ear, and a placebo injection in the other ear. The primary outcome was safety and feasibility. The authors found that the transtympanic application of sodium thiosulfate was safe, feasible, and did not interfere with the systemic absorption of cisplatin. Of the twelve participants, four patients did not develop a cisplatin-induced hearing loss. The pure tone average in the twelve sodium thiosulfate treated ears was 18.4 dB less compared to the untreated ears. The results of this study provide preliminary evidence that transtympanic sodium thiosulfate may be a useful otoprotectant against cisplatin-induced hearing loss. The use of sodium thiosulfate as an otoprotectant has been well-studied by Brock et al., with results published in 2018. Their outcomes support the otoprotective theory, reporting a 48% lower incidence of hearing loss in those who were treated six hours after cisplatin infusion with sodium thiosulfate without jeopardizing rate of survival (Brock et al., 2018). Another clinical trial by Freyer et al., published in 2017, showed protection in patients treated with cisplatin and sodium thiosulfate, but differences were not statistically significant. The small number of studies and non-clinically significant results warrant further research on sodium thiosulfate as an effective otoprotectant.

Dexamethasone

Dexamethasone is a corticosteroid commonly accepted to be used for the treatment of inflammatory diseases, including lupus, arthritis, and ulcerative colitis. Dexamethasone has been used for the treatment of idiopathic SSNHL (Chandrasekhar, 2001), and has been hypothesized to be effective in otoprotection during ototoxic chemotherapy treatment. Hill et al., (2008)

studied the use of dexamethasone in guinea pigs and evaluated its otoprotective properties against cisplatin. Using ABRs and an intratympanic injection of dexamethasone, the authors showed dexamethasone is protective in a frequency-dependent manner for both the frequency of administration of the chemotherapeutic and otoprotectant, and it does not interfere with the chemotherapeutic actions of cisplatin. The effects of dexamethasone and vitamin E on otoprotection in cisplatin-treated rats was studied by Paksoy et al. (2011) and these researchers found that the two in combination may minimize the ototoxicity of cisplatin with no adverse side effects.

D-methionine

D-methionine (D-met) has previously been shown to work as an otoprotectant against aminoglycosides, noise-induced hearing loss, and chemotherapeutics in animal models and in some human models. The otoprotectant properties of D-met were first shown in human models for cisplatin treatment in 2010 in India (Hamstra et al., 2010). A 2021 randomized clinical trial conducted in India by Campbell et al. shows that D-met administered orally is protective against cisplatin-induced hearing loss in humans. D-met is consumed through food by humans and is an important amino acid in the normal daily function of a human body. Hamstra et al., (2010) reports that D-met is routinely used in Europe and India to treat and prevent acetaminophen overdose and dermatitis.

N-acetylcysteine

N-acetylcysteine (NAC) is a drug currently used to protect the liver from large amounts of acetaminophen (Tylenol) and has been shown to have otoprotective effects for aminoglycoside-induced ototoxicity (Kranzer et al., 2015). The effects on the auditory system are currently being studied by Orgel and colleagues at the Children’s Hospital Los Angeles on

children undergoing cisplatin chemotherapy to determine the proper dosage needed for NAC treatment for preventing ototoxicity. NAC is different from other antioxidants because it increases the production of glutathione in the inner ear and is important for tissue repair within the body and could help with its otoprotective effect (National Library of Medicine, NCT02094625, 2016). In 2020, Somdaş et al., in Brazil used ABR and OAEs to evaluate rats treated with cisplatin (an untreated group) and a combination of cisplatin and NAC (a treated group). The researchers found that the animal group treated with NAC had better ABR and OAE values than the untreated group, and that histopathological samples of the rats with NAC had milder irregularities and degeneration of the auditory pathway, as well as milder stereocilia loss than the untreated group. The authors concluded that NAC has a potential otoprotective effect and should be used in clinical trials in humans (Somdaş et al., 2020).

Atorvastatin

Atorvastatin is a drug that is part of the hydroxymethylglutaryl-CoA reductase inhibitors. This class of drugs could be helpful to protecting the inner ear from ototoxicity because they have been shown to improve endothelial function, as well as microcirculation, reduce oxidative stress, and decrease overall inflammation. Atorvastatin has previously been shown to be effective in protecting hearing in mice from hazardous noise (Jahani et al., 2016), aging (Syka et al., 2007), and aminoglycoside ototoxicity (Brand et al., 2011), and may also reduce tinnitus in these populations, as well (Sutbas et al., 2007). Fernandez et al. (2021) found that the use of atorvastatin in human subjects undergoing cisplatin treatment reduced the incidence and severity of hearing loss when compared to those with other otoprotectants or without statin treatment. The incidence of hearing loss in patients treated with cisplatin was reduced by 17.6% in those treated with atorvastatin in relation to those not treated with a statin. An individual utilizing

atorvastatin with cisplatin therapy is 53% less likely to have a clinically significant hearing loss than those who were not treated with a statin during cisplatin chemotherapy. The researchers also found that the three-year overall survival and health outcomes following cessation of cisplatin treatment did not differ between those who took atorvastatin and those who did not during their treatment, suggesting atorvastatin is a viable and ethical otoprotectant (Fernandez et al., 2021).

Emerging Role of the Audiologist

As otoprotectants become more commonly used in the field of oncology, audiologists will not only be in charge of monitoring for the ototoxicity of the chemotherapeutic but also will have to monitor the effectiveness of otoprotectants. Moving forward, audiologists should have a general understanding of how otoprotectants work, why they are commonly used, which chemotherapeutics they are most effective with, and how to report the effectiveness of the otoprotectant to the treating oncologist.

Summary

Audiologists are only one part of the multidisciplinary team when it comes to treating cancer patients with ototoxic chemotherapeutics. It is important for the audiologist to be familiar with best practice guidelines and recommendations for ototoxic monitoring for all commonly used ototoxic chemotherapeutics, including cisplatin, carboplatin, oxaliplatin, nedaplatin, vincristine, vinblastine, and DFMO. The different ways in which these chemotherapeutics affect the auditory pathway play an important role in how an audiologist should be monitoring for ototoxicity. Ototoxic monitoring plays an important role in hearing conservation, and programs must be properly equipped and implemented properly to be fully effective. Limitations in the literature lead to gaps in knowledge surrounding the exact mechanisms and exact site of lesions of ototoxicity from each of these drugs, and more research needs to be completed to fill these

gaps that have been identified. Audiologists will need to continue to monitor the literature for updates on drug ototoxicities and the future for otoprotectants.

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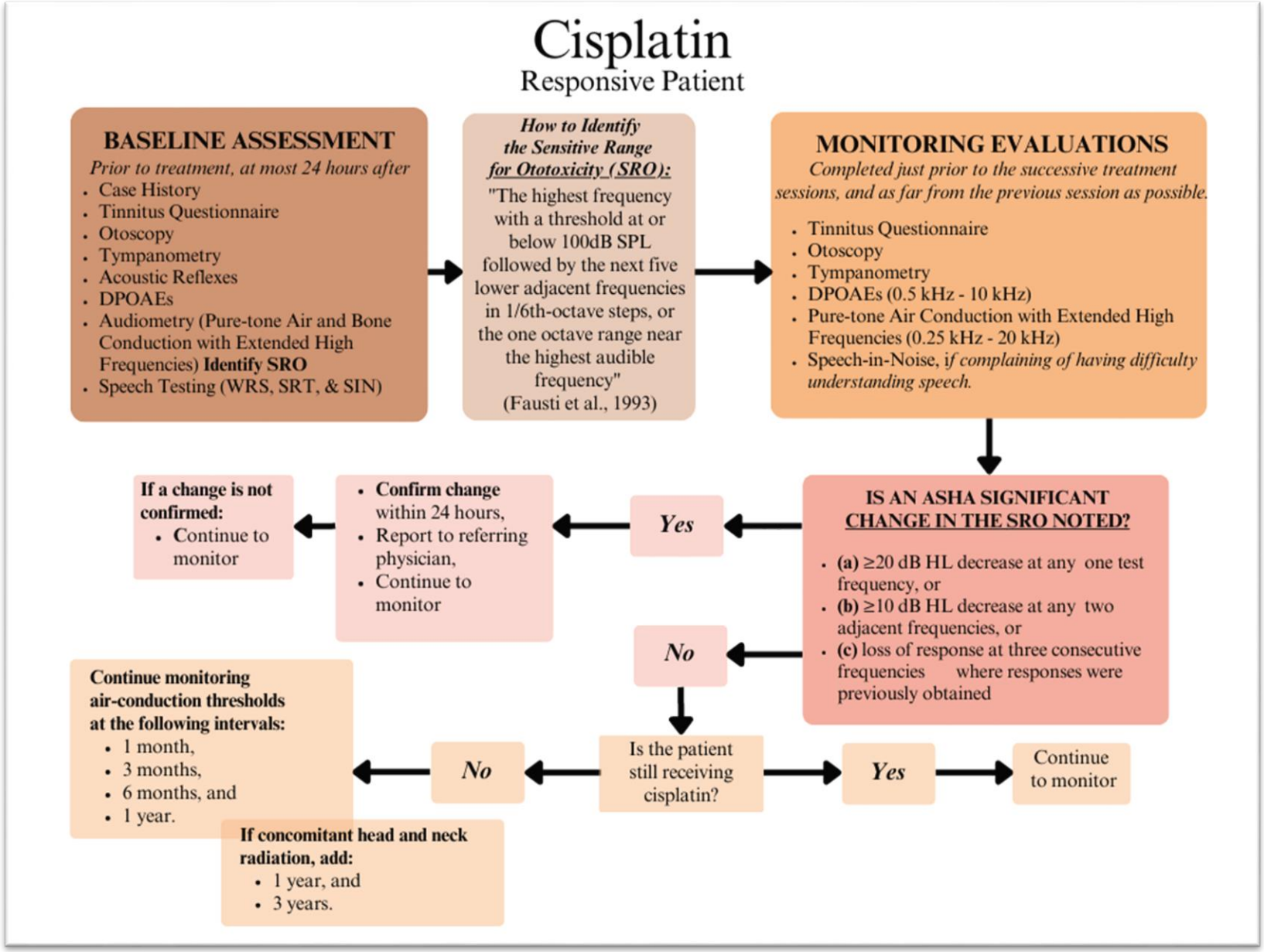
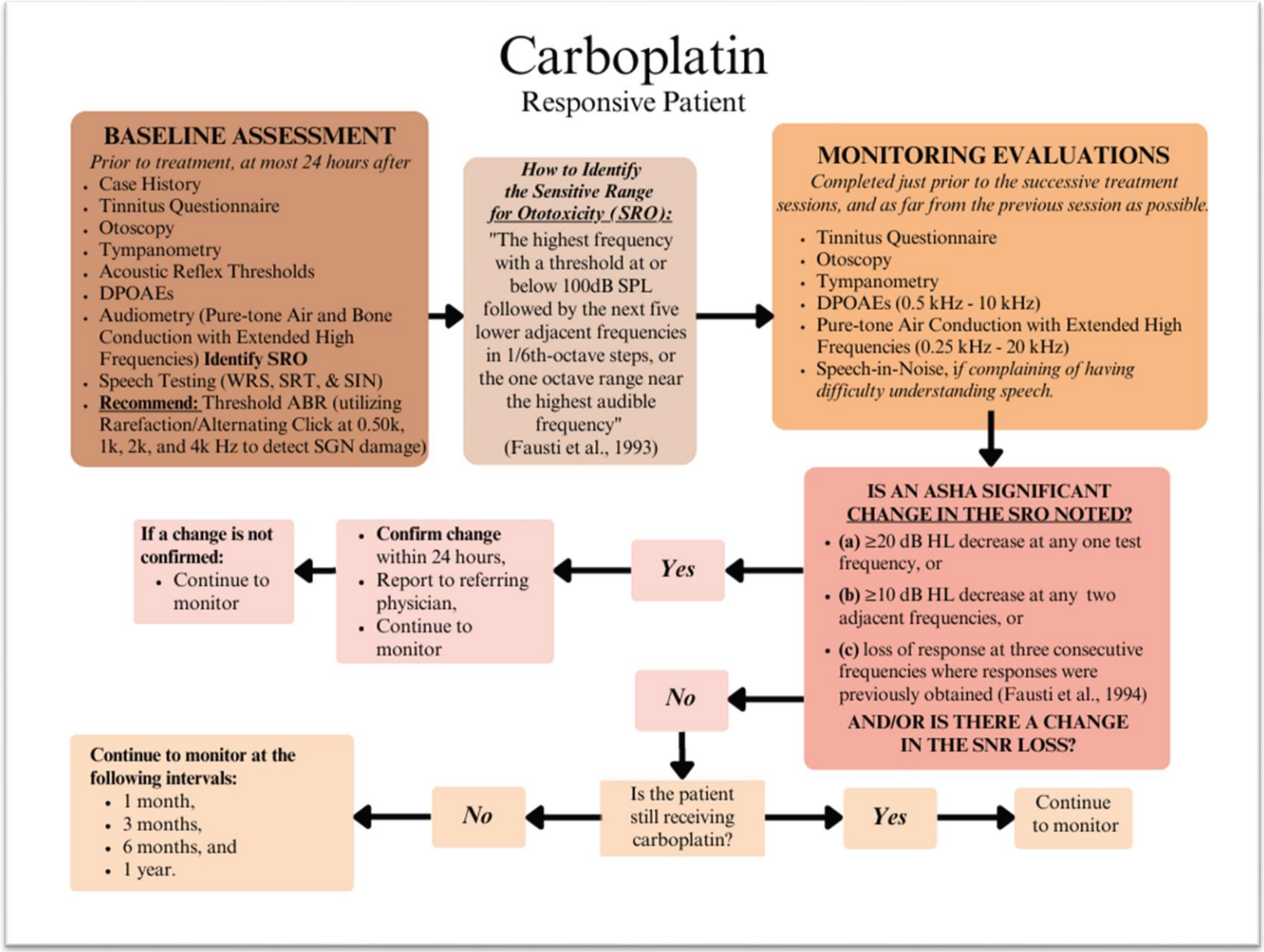
APPENDIX A

RECOMMENDED PROTOCOLS FOR RESPONSIVE PATIENTS RECEIVING CISPLATIN


Cisplatin
Responsive Patient
BASELINE ASSESSMENT
Prior to treatment, at most 24 hours after
Case History
Tinnitus Questionnaire
Otoscopy
Tympanometry
Acoustic Reflexes
DPOAEs
Audiometry (Pure-tone Air and Bone Conduction with Extended High Frequencies) Identify SRO
Speech Testing (WRS, SRT, & SIN)
How to Identify the Sensitive Range for Ototoxicity (SRO):
"The highest frequency with a threshold at or below 100dB SPL followed by the next five lower adjacent frequencies in 1/6th-octave steps, or the one octave range near the highest audible frequency"
(Fausti et al., 1993)
MONITORING EVALUATIONS
Completed just prior to the successive treatment sessions, and as far from the previous session as possible.
Tinnitus Questionnaire
Otoscopy
Tympanometry
DPOAEs (0.5 kHz - 10 kHz)
Pure-tone Air Conduction with Extended High Frequencies (0.25 kHz - 20 kHz)
Speech-in-Noise, if complaining of having difficulty understanding speech.
IS AN ASHA SIGNIFICANT CHANGE IN THE SRO NOTED?
(a) ≥20 dB HL decrease at any one test frequency, or
(b) ≥10 dB HL decrease at any two adjacent frequencies, or
(c) loss of response at three consecutive frequencies where responses were previously obtained
Yes
Confirm change within 24 hours,
Report to referring physician,
Continue to monitor
If a change is not confirmed:
Continue to monitor
No
Is the patient still receiving cisplatin?
Yes
Continue to monitor
No
Continue monitoring air-conduction thresholds at the following intervals:
1 month,
3 months,
6 months, and
1 year.
If concomitant head and neck radiation, add:
1 year, and
3 years.

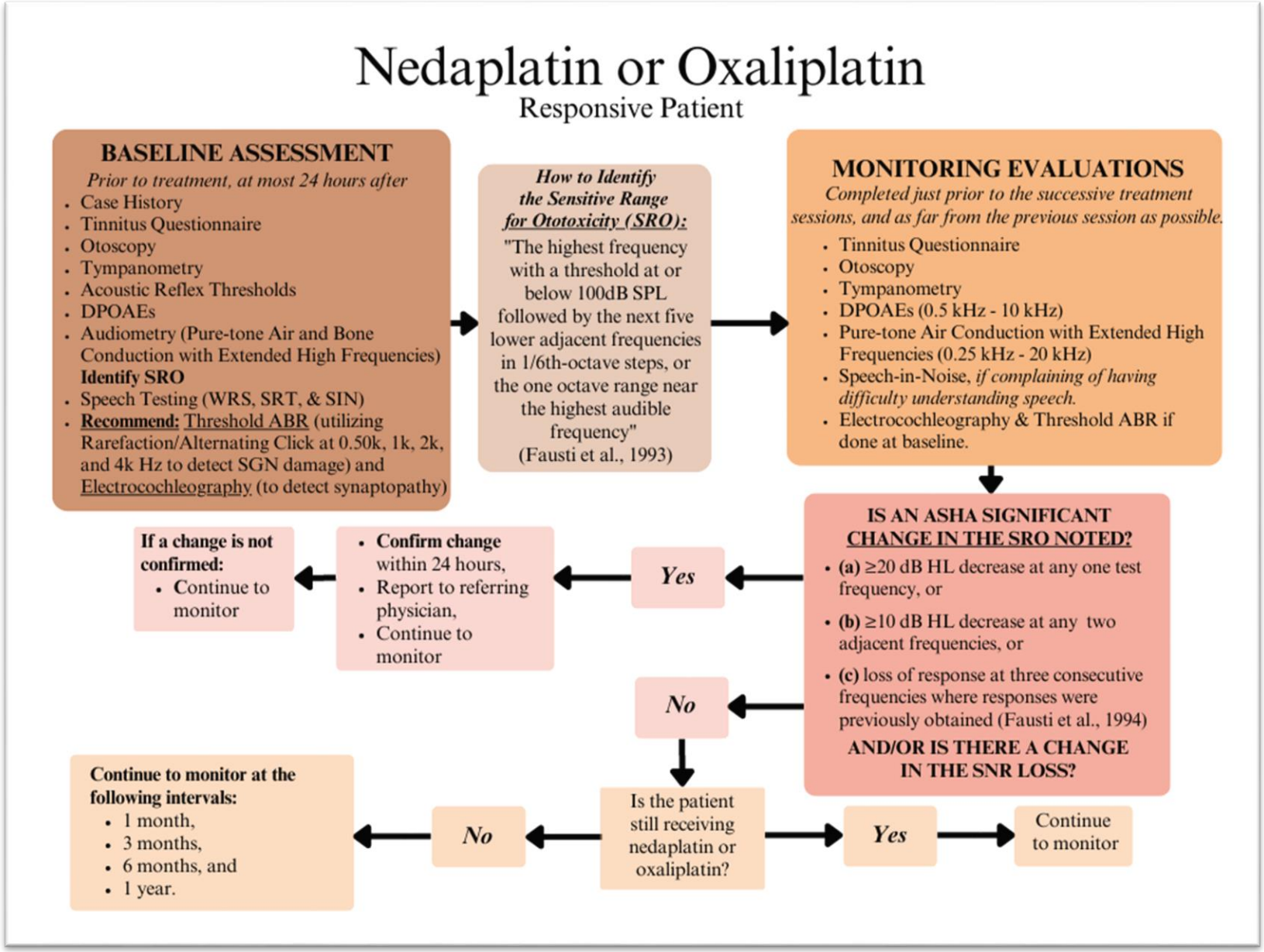
APPENDIX B

RECOMMENDED PROTOCOLS FOR RESPONSIVE PATIENTS RECEIVING CARBOPLATIN


Carboplatin
Responsive Patient
BASELINE ASSESSMENT
Prior to treatment, at most 24 hours after
Case History
Tinnitus Questionnaire
Otoscopy
Tympanometry
Acoustic Reflex Thresholds
DPOAEs
Audiometry (Pure-tone Air and Bone Conduction with Extended High Frequencies) Identify SRO
Speech Testing (WRS, SRT, & SIN)
Recommend: Threshold ABR (utilizing Rarefaction/Alternating Click at 0.50k, 1k, 2k, and 4k Hz to detect SGN damage)
How to Identify the Sensitive Range for Ototoxicity (SRO):
"The highest frequency with a threshold at or below 100dB SPL followed by the next five lower adjacent frequencies in 1/6th-octave steps, or the one octave range near the highest audible frequency"
(Fausti et al., 1993)
MONITORING EVALUATIONS
Completed just prior to the successive treatment sessions, and as far from the previous session as possible.
Tinnitus Questionnaire
Otoscopy
Tympanometry
DPOAEs (0.5 kHz - 10 kHz)
Pure-tone Air Conduction with Extended High Frequencies (0.25 kHz - 20 kHz)
Speech-in-Noise, if complaining of having difficulty understanding speech.
IS AN ASHA SIGNIFICANT CHANGE IN THE SRO NOTED?
(a) ≥20 dB HL decrease at any one test frequency, or
(b) ≥10 dB HL decrease at any two adjacent frequencies, or
(c) loss of response at three consecutive frequencies where responses were previously obtained (Fausti et al., 1994)
AND/OR IS THERE A CHANGE IN THE SNR LOSS?
Yes
Confirm change within 24 hours,
Report to referring physician,
Continue to monitor
If a change is not confirmed:
Continue to monitor
No
Is the patient still receiving carboplatin?
Yes
Continue to monitor
No
Continue to monitor at the following intervals:
1 month,
3 months,
6 months, and
1 year.

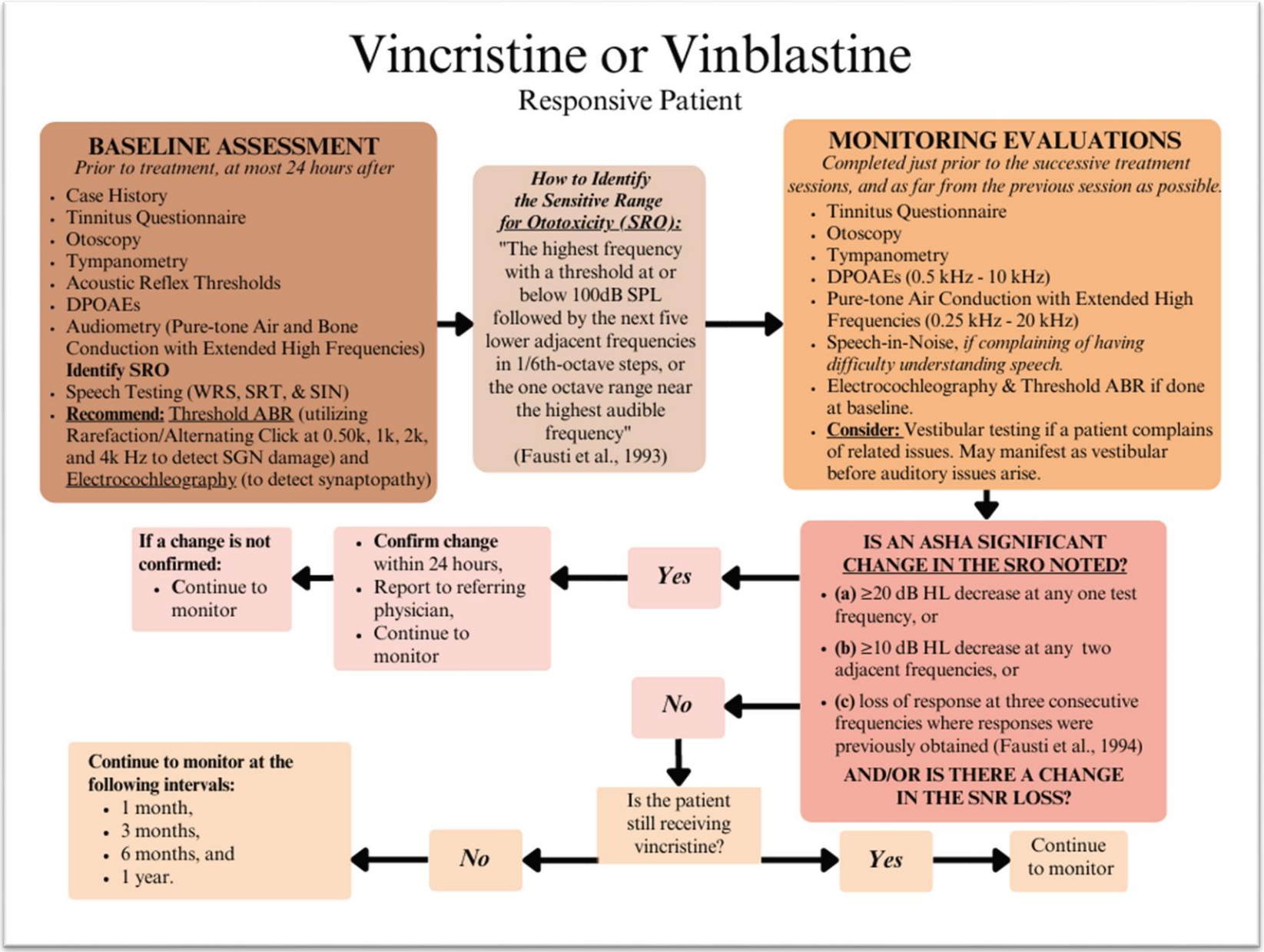
APPENDIX C

RECOMMENDED PROTOCOLS FOR RESPONSIVE PATIENTS RECEIVING OXALIPLATIN OR NEDAPLATIN


Nedaplatin or Oxaliplatin
Responsive Patient
BASELINE ASSESSMENT
Prior to treatment, at most 24 hours after
Case History
Tinnitus Questionnaire
Otoscopy
Tympanometry
Acoustic Reflex Thresholds
DPOAEs
Audiometry (Pure-tone Air and Bone Conduction with Extended High Frequencies)
Identify SRO
Speech Testing (WRS, SRT, & SIN)
Recommend: Threshold ABR (utilizing Rarefaction/Alternating Click at 0.50k, 1k, 2k, and 4k Hz to detect SGN damage) and Electrocochleography (to detect synaptopathy)
How to Identify the Sensitive Range for Ototoxicity (SRO):
"The highest frequency with a threshold at or below 100dB SPL followed by the next five lower adjacent frequencies in 1/6th-octave steps, or the one octave range near the highest audible frequency"
(Fausti et al., 1993)
MONITORING EVALUATIONS
Completed just prior to the successive treatment sessions, and as far from the previous session as possible.
Tinnitus Questionnaire
Otoscopy
Tympanometry
DPOAEs (0.5 kHz - 10 kHz)
Pure-tone Air Conduction with Extended High Frequencies (0.25 kHz - 20 kHz)
Speech-in-Noise, if complaining of having difficulty understanding speech.
Electrocochleography & Threshold ABR if done at baseline.
IS AN ASHA SIGNIFICANT CHANGE IN THE SRO NOTED?
(a) ≥20 dB HL decrease at any one test frequency, or
(b) ≥10 dB HL decrease at any two adjacent frequencies, or
(c) loss of response at three consecutive frequencies where responses were previously obtained (Fausti et al., 1994)
AND/OR IS THERE A CHANGE IN THE SNR LOSS?
Yes
Confirm change within 24 hours,
Report to referring physician,
Continue to monitor
If a change is not confirmed:
Continue to monitor
No
Is the patient still receiving nedaplatin or oxaliplatin?
Yes
Continue to monitor
No
Continue to monitor at the following intervals:
1 month,
3 months,
6 months, and
1 year.

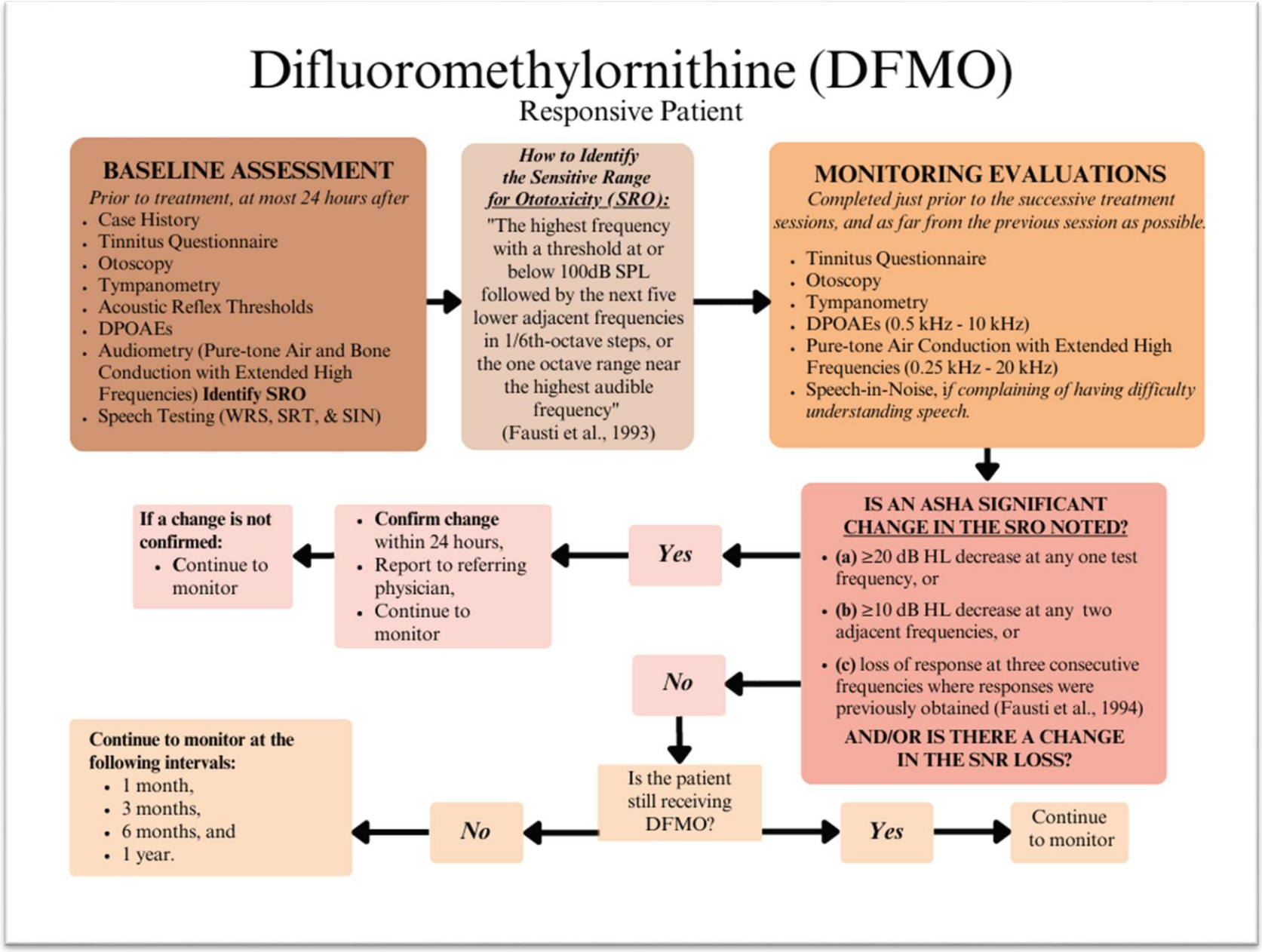
APPENDIX D

RECOMMENDED PROTOCOLS FOR RESPONSIVE PATIENTS RECEIVING VINCRISTINE OR VINBLASTINE


Vincristine or Vinblastine
Responsive Patient
BASELINE ASSESSMENT
Prior to treatment, at most 24 hours after
Case History
Tinnitus Questionnaire
Otoscopy
Tympanometry
Acoustic Reflex Thresholds
DPOAEs
Audiometry (Pure-tone Air and Bone Conduction with Extended High Frequencies)
Identify SRO
Speech Testing (WRS, SRT, & SIN)
Recommend: Threshold ABR (utilizing Rarefaction/Alternating Click at 0.50k, 1k, 2k, and 4k Hz to detect SGN damage) and Electrocochleography (to detect synaptopathy)
How to Identify the Sensitive Range for Ototoxicity (SRO):
"The highest frequency with a threshold at or below 100dB SPL followed by the next five lower adjacent frequencies in 1/6th-octave steps, or the one octave range near the highest audible frequency"
(Fausti et al., 1993)
MONITORING EVALUATIONS
Completed just prior to the successive treatment sessions, and as far from the previous session as possible.
Tinnitus Questionnaire
Otoscopy
Tympanometry
DPOAEs (0.5 kHz - 10 kHz)
Pure-tone Air Conduction with Extended High Frequencies (0.25 kHz - 20 kHz)
Speech-in-Noise, if complaining of having difficulty understanding speech.
Electrocochleography & Threshold ABR if done at baseline.
Consider: Vestibular testing if a patient complains of related issues. May manifest as vestibular before auditory issues arise.
IS AN ASHA SIGNIFICANT CHANGE IN THE SRO NOTED?
(a) ≥20 dB HL decrease at any one test frequency, or
(b) ≥10 dB HL decrease at any two adjacent frequencies, or
(c) loss of response at three consecutive frequencies where responses were previously obtained (Fausti et al., 1994)
AND/OR IS THERE A CHANGE IN THE SNR LOSS?
Yes
Confirm change within 24 hours,
Report to referring physician,
Continue to monitor
If a change is not confirmed:
Continue to monitor
No
Is the patient still receiving vincristine?
Yes
Continue to monitor
No
Continue to monitor at the following intervals:
1 month,
3 months,
6 months, and
1 year.

APPENDIX E

RECOMMENDED PROTOCOLS FOR RESPONSIVE PATIENTS RECEIVING DIFLUOROMETHYLORNITHINE


Difluoromethylornithine (DFMO)
Responsive Patient
BASELINE ASSESSMENT
Prior to treatment, at most 24 hours after
Case History
Tinnitus Questionnaire
Otoscopy
Tympanometry
Acoustic Reflex Thresholds
DPOAEs
Audiometry (Pure-tone Air and Bone Conduction with Extended High Frequencies) Identify SRO
Speech Testing (WRS, SRT, & SIN)
How to Identify the Sensitive Range for Ototoxicity (SRO):
"The highest frequency with a threshold at or below 100dB SPL followed by the next five lower adjacent frequencies in 1/6th-octave steps, or the one octave range near the highest audible frequency"
(Fausti et al., 1993)
MONITORING EVALUATIONS
Completed just prior to the successive treatment sessions, and as far from the previous session as possible.
Tinnitus Questionnaire
Otoscopy
Tympanometry
DPOAEs (0.5 kHz - 10 kHz)
Pure-tone Air Conduction with Extended High Frequencies (0.25 kHz - 20 kHz)
Speech-in-Noise, if complaining of having difficulty understanding speech.
IS AN ASHA SIGNIFICANT CHANGE IN THE SRO NOTED?
(a) ≥20 dB HL decrease at any one test frequency, or
(b) ≥10 dB HL decrease at any two adjacent frequencies, or
(c) loss of response at three consecutive frequencies where responses were previously obtained (Fausti et al., 1994)
AND/OR IS THERE A CHANGE IN THE SNR LOSS?
Yes
Confirm change within 24 hours,
Report to referring physician,
Continue to monitor
If a change is not confirmed:
Continue to monitor
No
Is the patient still receiving DFMO?
Yes
Continue to monitor
No
Continue to monitor at the following intervals:
1 month,
3 months,
6 months, and
1 year.