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Cancer Chemotherapy: An Overview and Voice Implications

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INTRODUCTION

There are many treatment options for cancer, and the plethora of chemotherapeutic drugs and other agents continues to grow. Although the current agents possess effective antitumor activity, they come with a multitude of potentially voice impairing side effects with which singing teachers should be familiar. These side effects vary in severity and can affect each individual to different degrees. It is therefore very important to consider the known side effects of the chemotherapeutic agents in use today in regard to their potential to alter vocal characteristics. Successful cancer treatment must always be the paramount consideration; however, if effectiveness is equal, it is reasonable for voice professionals and their health care providers to seek out the treatment with the fewest adverse voice effects.

The concept of using chemotherapy to cure cancer dates back at least 1500 years. At the time of the Renaissance, many concoctions used for this purpose contained metals such as arsenic, silver, antimony, mercury, and bismuth. Although these mixtures had caustic or corrosive effects on skin tumors, they had no effect on malignant neoplasms derived from epithelial tissue such as breast, prostate, or lung. It was not until the introduction of nitrogen mustard and methotrexate in the 1940s that drugs were proven to have a real effect on tumor growth and remission. In the 1950s, a wide variety of alkylators, mustard derivatives, antimetabolites, and vinca alkaloids were introduced into clinical practice. In the 1960s, the anthracyclines and cisplatin were established. The use of cisplatin led the way for the development of further systemic agents for use on solid tumors. With the rapid advances in medicine today, the number of chemotherapeutic agents available has increased dramatically. The following will be a brief overview of the seven most common chemotherapeutic agents: antimetabolites, alkylating agents, antibiotics, plant alkaloids, endocrine agents, miscellaneous agents, and biologic response modifiers.

Cancer chemotherapy attempts to target malignant tumors by interfering with cellular processes involved in tumor growth and progression. Most often, these drugs try to cause cell death through cytotoxic lesions in metabolic pathways required for cell replication. For example, the purine and pyrimidine precursors for DNA and RNA synthesis are targeted. DNA and RNA are present in all eukaryotic cells (cells with a true nucleus) and are comprised of purine and pyrimidine nucleotides. DNA is genetic material replicated in the nucleus during the S-phase of the cell growth cycle by various enzymes prior to cell division, which directs all activities of the cell. RNA is made in the cytoplasm of the cell and directs the assembly of protein products required for cell growth and metabolism. Any agent that disrupts the functioning of the required enzymes in either of these processes, or inhibits the required precursor synthesis ultimately will lead to the death of the affected cell. Thus, many effective treatment modalities currently in use target various aspects of the above processes.

CHEMOTHERAPEUTIC AGENTS

The first class of chemotherapeutic agents, the antimetabolites, inhibit steps in DNA biosynthesis and are effective at killing cells during the time period when the cell's DNA is being replicated, or the S-phase of the cell growth cycle. Common agents in this class include methotrexate and fluorouracil. Methotrexate is a folic acid antagonist. It prevents the conversion of dihydrofolate to tetrahydrofolate, which is required for the synthesis of DNA, RNA, and some amino acids. Fluorouracil is a pyrimidine antimetabolite that interferes with the synthesis of DNA by blocking the methylation of deoxyuridylic acid. Both of these agents are commonly used to treat breast, colorectal, and lung carcinoma, as well as head and neck carcinomas.

The second class of chemotherapeutic agents are the DNA alkylating agents. This group includes cyclophosphamide and cisplatin, which are nonspecific agents that lead to DNA crosslinking, base-pair mismatching, or DNA breaks. Cyclophosphamide is a nitrogen mustard that is converted in the body to phosphoramidate mustard, which cross-links DNA and interrupts the progression of the target cancer. Cisplatin is a platinum coordination complex, which enters cells by diffusion.

Within the cells, it is converted to an electrophile that alkylates DNA and thus helps to stop tumor growth. Both of these agents are used to treat lung carcinoma. Cyclophosphamide is also used to treat lymphomas, breast carcinoma, and leukemia. Cisplatin is commonly used for head and neck, ovarian, and testicular carcinomas.

The third class, antibiotics, includes doxorubicin and daunorubicin. Both drugs are anthracycline antibiotics whose antitumor activity may be due to DNA intercalation (disruption of the DNA backbone), DNA breakage, inhibition of Topoisomerase II, or cell membrane disruption. These antitumor agents are common additions to chemotherapeutic regimens for breast, hepatic (liver), and thyroid carcinomas, as well as leukemia, and lymphomas.

The fourth class of antitumor agents is the plant alkaloids, which include etoposide, the vinca alkaloids (vincristine and vinblastine), camptothecans (irinotecan and topotecan), and the taxanes (paclitaxel and docetaxel). Etoposide stabilizes the DNA topoisomerase II-DNA complex, leading to breaks during DNA replication and subsequent cell death. Vincristine acts as a spindle poison and blocks the formation of the mitotic spindle required for proper chromosome assortment, thus inhibiting cell division. The taxanes stabilize the mitotic spindle and prevent chromosome assortment, thereby inhibiting cell division. The camptothecans inhibit Topoisomerase-I activity. Vincristine and etoposide are used in the treatment of lung carcinoma and childhood tumors such as Wilms's tumor. Etoposide is also commonly used to treat testicular tumors, while vincristine is also effective against leukemias and lymphomas. Vinblastine is used for testicular cancer and lymphomas. Paclitaxel and docetaxel are used for lung, breast, and ovarian carcinomas. Irinotecan is used for colon cancer. Finally, topotecan is used for lung and ovarian cancers.

The fifth class of chemotherapeutic agents is the endocrine (hormone) agents. These include antiestrogens (tamoxifen, Halotestin, and toremifene), aromatase inhibitors (anastrozole and letrozole), antiandrogens (bicalutamide, flutamide, and nilutamide), and luteinizing hormone-releasing hormone (LHRH) analogs (goserelin and leuprolide). The antiestrogens are nonsteroidal compounds that competitively block estrogen at

the estrogen receptor. The aromatase inhibitors block the aromatase enzyme involved with formation of estrone and estradiol. These agents are used in cases of breast carcinoma. The antiandrogens are nonsteroidal competitive antagonists at androgen receptors, commonly used to treat prostatic carcinoma. LHRH analogs suppress testosterone levels, and are also commonly used to treat prostate carcinoma.

The miscellaneous antineoplastic agents include a number of diverse drugs that do not fall into one of the other categories. Commonly used drugs in this class are hydroxyurea, which is used to treat chronic leukemias and sickle cell disease. Another is dacarbazine which is often used to treat lymphomas and melanomas.

Finally, a relatively new class of drugs is the biologic response modifiers, including the interferons and interleukins. These agents appear to act by modulation of the immune system. Interferons and interleukin-2 (aldesleukin) are commonly used to treat melanoma and renal carcinoma.

SIDE EFFECTS IN VOICE PROFESSIONALS

One of the most concerning side effects of chemotherapy to the professional voice user is neurotoxicity. Chemotherapeutic agents that are neurotoxic, such as paclitaxel, have the potential to damage the nerves that innervate the muscles of larynx or those involved in support of the voice, such as the nerves that innervate the diaphragm or intercostal muscles. Nerve damage can lead to irreversible changes in vocal range and power, as well as the inability to precisely control pitch required for performance. Other chemotherapeutic agents that are currently known to be neurotoxic include methotrexate, cyclophosphamide, etoposide, fluorouracil, interferon, nitrogen mustard, tamoxifen, vincristine, and vinblastine.

Ototoxicity is another side effect that has profound consequences for the professional voice user. Drugs that are ototoxic, such as cisplatin, can impair the ability to hear and are therefore a concern to the performer who needs to detect sound and pitch.

Side effects such as pulmonary toxicity or fibrosis (carmustine, lomustine, melphalan, busulfan, and bleomycin) can cause permanent changes in lung structure and function. Pulmonary damage can undermine the

ability to provide adequate breath support for the voice. Inadequate breath support can lead to vocal fold injury, scarring, and nodule formation. Rarely, methotrexate also can cause a pulmonary infiltration picture that may impede performance through a similar mechanism.

Diarrhea, nausea, vomiting, and decreased appetite often accompany chemotherapy and can result in temporary dehydration. Dehydration causes a thickening of the mucous secretions present in the larynx, which alters the vibratory characteristics of the vocal folds. This can lead to an increase in friction with subsequent voice fatigue and, potentially, vocal fold injury. Additionally, the acidic nature of vomitus can cause additive vocal fold injury. Diarrhea is often present with the use of fluorouracil (especially in combination with leucovorin), methotrexate, and irinotecan. Nausea and vomiting of varying severity are common with most antineoplastic agents; and when two or more agents are used in combination, the effect is usually additive or synergistic. Cisplatin, dacarbazine, and carmustine are among the most emetogenic agents in use today. During cancer treatment with these agents, effective anti-emetic therapy can be initiated with serotonin antagonists.

Stomatitis and esophagopharyngitis are common side effects associated with the use of fluorouracil and doxorubicin, which can alter mucous membranes. These drugs cause irritation, pain, and swelling of the mouth and throat, which result in changes in the resonance characteristics of the vocal apparatus. This can have a considerable impact on the ability to perform due not only to the discomfort, but also to narrowing of the airway, which occurs in some cases.

Additional gastrointestinal side effects such as bleeding, ulceration, intestinal perforations, and mucositis, threaten the professional voice user by undermining the performer's strength and ability to support his or her voice. This can result in the use of hyperfunctional singing techniques in an attempt to compensate for impaired support. Hyperfunctional singing techniques can lead to subsequent injury to the vocal folds.

Anemia, leukopenia, thrombocytopenia, and bone marrow suppression are common with almost all antineoplastic agents. Alterations in the blood quality leave an individual vulnerable to infection and impair the natural clotting abilities of the blood. This, accompanied by the associated weakness associated, can lead to the

use of improper singing techniques and subsequent vascular damage to the vocal folds. Vascular damage, bleeding and the resulting injuries can be very severe and possibly career ending. The use of growth factors including erythropoietin, filgrastim, sargramostim, and oprelvekin may help overcome the drug induced bone marrow suppression.

Nephrotoxicity and hepatotoxicity are generalized side effects of many chemotherapeutic agents but they are most prominently associated with cisplatin and methotrexate. Damage to the hepatorenal system affects the body's ability to metabolize certain drugs and, therefore, can lead to toxic levels of common over-the-counter medications used by performers. Impairment of liver function and kidney function also leaves the performer more susceptible to infection from simple laryngitis to more severe infectious processes. It is imperative for the healthcare provider to be aware of these potential side effects that remotely can affect voice quality.

Finally, many of the chemotherapeutic agents in use today alter hormone levels in the body, which can have deleterious effects on the voice. For example, the production of excess androgens, or the use of antiestrogen therapy with Halotestin, can cause physical changes in the larynx resulting in the lengthening and thickening of the vocal folds. This causes the voice to deepen, which can result in permanent loss of range and masculinization of quality.

CONCLUSION

The treatment of cancer, regardless of its location, can cause many unwanted voice changes in the voice. Side effects resulting from certain currently used chemotherapeutic agents can ultimately cause permanent changes in the vocal tract. These changes can impair the subtle features of the voice that are often critical to the professional voice user. The medical community must consider treatment options carefully before optimal recommendations of treatment protocols can be made to the professional voice user, and singing teachers should be certain that their students discuss voice risks with their doctors. Nevertheless, we must all appreciate the major advances that have been made in cancer therapy and must alter protocols for voice considerations only when cancer treatment success is not compromised.

Dominic A. Solimando Jr. is an Oncology Pharmacy Specialist, consultant and medical writer. From 2000 through 2019, he was President of Oncology Pharmacy Services, Inc., providing clinical, informational, educational, editorial, and consultative oncology pharmacy services for health care professionals, patients, and organizations. He also maintained a part time clinical practice as an oncology pharmacist at Walter Reed National Military Medical Center in Bethesda, MD.

Mr. Solimando received a Bachelor of Science in Pharmacy from the Philadelphia College of Pharmacy and Science, a Master of Arts in Management and Supervision, specializing in Health Care Administration, from Central Michigan University, and did graduate work in Clinical Pharmacy at Purdue University. A board certified oncology pharmacy specialist with more than 40 years of clinical experience, he has practiced in Washington, DC, San Francisco, Honolulu, and Philadelphia. His previous positions include Oncology Pharmacy Manager, Lombardi Cancer Center, Georgetown University Medical Center, Washington, DC; oncology pharmacist, Thomas Jefferson University Hospital, Philadelphia; Director, Hematology-Oncology Pharmacy and Oncology Pharmacy Residency Program, Walter Reed Army Medical Center, Washington, DC; Chief, Hematology Oncology Pharmacy Service, Letterman Army Medical Center, San Francisco; and Chief, Hematology-Oncology Pharmacy, Tripler Army Medical Center, Honolulu.

Dominic served as an adjunct clinical faculty member for Medical College of Virginia, LECOM College of Pharmacy, New England College of Pharmacy, Philadelphia College of Pharmacy, South Carolina College of Pharmacy, and the University of Maryland. He previously held adjunct clinical faculty positions at Butler University, Howard University, Bernard J. Dunn School of Pharmacy, Shenandoah University, Temple University, University of Arkansas and University of the Pacific. He was a Contributing Editor for *Hospital Pharmacy* from 1996–2017; and co-author of *Guide to Combination Cancer Therapy Regimens*. He served as a co-author and Senior Editor of Lexi-Comp's *Drug Information Handbook for Oncology* from 1999–2008. Dominic has also served on the editorial advisory boards of *Drug Intelligence and Clinical Pharmacy* (now *Annals of Pharmacotherapy*), the *Journal of the American Pharmaceutical Association* and *Pharmacy Today*.

An active member of numerous professional associations, Dominic has held elective and appointed offices at the local, state, national and international levels. He is a past Chairman of the Administrative Practice, Hospital and Institutional Practice, and Clinical/Pharmacotherapeutic Practice Sections of the Academy of Pharmacy Practice and Management. Dominic is a past president of the Hawaii Pharmaceutical Association and the Hawaii Society of Hospital Pharmacists. He is a Fellow of the American Pharmaceutical Association, and the American Society of Hospital Pharmacists. Dominic has served in the APhA House of Delegates 32 times; and has been a member of the Nominations Committee (2000, 2010), New Business Review Committee (1993, 1994, 1996, 1999) and Reference Committee on Educational Affairs (1995). He also served on the APhA Educational Affairs Policy Committee (1994–1995), Professional Affairs Policy Committee (1985–1986), and APhA Foundation Advisory Com-

mittee (2002–2010). Dominic is also a member of ASHP, AIHP, ACCP, FIP, VPhA, WMSHP, Hematology-Oncology Pharmacy Association and International Society of Oncology Pharmacy Practitioners.

His professional practice interests include safety precautions in handling parenteral medications, drug preparation and administration procedures, pain control, antiemetic therapy, and prevention and management of drug-induced toxicities.

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Dr. Opperman received a Fellowship in Laryngology and Disorders of the Voice at UCLA in Los Angeles where he studied under the direction of Gerald Berke, MD and performed research in laryngology, neurolaryngology, and care of the professional voice. He trained under George L. Adams at the University of Minnesota where he received his Master of Science in otolaryngology and received his Doctor of Medicine at Thomas Jefferson University.

He is also a presenter, author, and recognized expert in the field of voice care and repair and enjoys sharing his expertise with groups.

Dr. Jillian Mattioni is in private practice with Chester County Otolaryngology and Allergy Associates in West Chester, PA. She attended Penn State University–Schreyer Honors College for an undergraduate degree in Kinesiology and went on to earn her doctorate from Philadelphia College of Osteopathic Medicine. She completed her Otolaryngology–Head & Neck Surgery/Facial Plastic residency through Philadelphia College of Osteopathic Medicine as well.

Dr. Mattioni is a member of the American Osteopathic Association, the American Academy of Otolaryngology–Head and Neck Surgery, and the American Osteopathic Colleges of Ophthalmology and Otolaryngology. She has extensive research experience and is published in several otolaryngology journals. She also has many years of teaching experience, and has been an avid volunteer, spending time in Guayaquil, Ecuador, and Chimbote, Peru.

In her free time Dr. Mattioni enjoys spending time with her husband and two children, traveling, hiking, and swimming. She is also a Boston Marathon participant and Half Ironman World Championships qualifier.



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