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Association of Pediatric
Hematology/Oncology Nurses

PEDIATRIC **CHEMOTHERAPY** AND **BIOTHERAPY** PROVIDER RENEWAL

Updated Information Packet

2021–2023

Pediatric Chemotherapy and Biotherapy Provider Renewal

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Acknowledgments

Since October 2004, the Association of Pediatric Hematology/Oncology Nurses (APHON) has trained more than 30,000 nurses as chemotherapy and biotherapy providers using *The Pediatric Chemotherapy and Biotherapy Curriculum*. In addition, APHON has trained more than 600 nurses as instructors to teach the material. The most recent edition of the curriculum (the fourth edition) contains updates on chemotherapy and biotherapy agents, safe handling of chemotherapy and biotherapy, and special considerations pertinent to chemotherapy and biotherapy administration. We are grateful to our colleagues who have dedicated their time and expertise to this project. We commend the nurses who have achieved and maintained the Pediatric Chemotherapy and Biotherapy Provider status in order to provide the best care for the children, adolescents, and families they serve.

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Chemotherapy and Biotherapy Administration Standards for Practice and Education

Safe and consistent administration of chemotherapy and biotherapy to children and adolescents requires specific knowledge and specialized skills.

- Chemotherapy and biotherapy administered to children and adolescents should be provided by registered nurses who have completed APHON's Pediatric Chemotherapy and Biotherapy Provider Program.

- *The Pediatric Chemotherapy and Biotherapy Curriculum,* Fourth Edition, offers the specific knowledge required through a didactic course and an online renewal examination.

- A clinical practicum by the employer of the nurse is recommended to validate the clinical skills used in the administration of chemotherapy and biotherapy.

A Pediatric Chemotherapy and Biotherapy Provider is a registered nurse who has successfully completed APHON's Pediatric Chemotherapy and Biotherapy Provider Course and maintained provider status.

- Pediatric Chemotherapy and Biotherapy Provider status is maintained by renewal every 3 years.

- Renewal is obtained by successfully completing an online exam.

- Annual education specific to administration of chemotherapy and biotherapy and skills validation by employers are recommended.

The Pediatric Chemotherapy and Biotherapy Curriculum, Fourth Edition

Some of the questions in the posttest refer to general chemotherapy/biotherapy information that can be found in *The Pediatric Chemotherapy and Biotherapy Curriculum,* Fourth Edition. If you do not have the fourth edition available, you may use previous editions as a resource. However, please note that previous editions will not have the most up-to-date information.

Drug Shortages

Mary E. Newman, MSN RN NE-BC CPON©

Learner Outcomes

Upon completion of this Pediatric Chemotherapy and Biotherapy Provider Program learning activity

1. the learner will be able to identify the root causes of drug shortages in the United States
2. the learner will be able to describe the impact of drug shortages in pediatric oncology and the ethical considerations related to them
3. the learner will be able to list available resources with the most up-to-date information on current drug shortages in the United States
4. the learner will be able to summarize the positions and recommendations of the Association of Pediatric Hematology/Oncology Nurses on drug shortages in pediatric hematology and oncology.

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The APHON Position Paper on Drug Shortages (Bunnell et al., 2020) opens with this statement:

> The Association of Pediatric Hematology/Oncology Nurses (APHON) affirms that all children have a right to the highest standard of physical and mental health and the right to treatment that maximizes their survival and well-being.

> Shortages of essential drugs compromise the health and well-being of all children, especially those diagnosed with cancer and blood disorders, who are among the most vulnerable members of society and require added protection.

Background

Shortages of medications and other essential healthcare resources have a long-standing history. One of the first drugs to be involved in a large-scale shortage was insulin in the 1920s, followed by penicillin in the 1940s. Both drug shortages were attributed to the manufacturers' inability to produce an adequate supply. At that time, decisions about prioritizing allocations were arbitrary; they were influenced by politics and emotions and were made without public comment.

Since 2001, the number of drug shortages in the United States has risen, and over the past decade, shortages of drugs, including chemotherapy drugs and those used in supportive care treatments, have become more common and are lasting longer. The American Society of Health-System Pharmacists (2021) has reported between 174 and 282 active drug shortages each quarter since 2015.

The causes of drug shortages are multifactorial. The U.S. Food and Drug Administration (2019) reports that economic forces are the root cause of drug shortages in the United States. These economic factors include the falling prices of the drugs, declining revenues from sales and the minimal contribution of certain drugs to the company's overall revenue. A manufacturer has little incentive to invest considerable time and money to produce a drug that will not bring sufficient income to the company to justify that investment. Another contributing factor is the limited availability of raw materials. In 2018, 88% of pharmaceutical ingredients came from non-U.S. sources. Obtaining pharmaceutical ingredients from sources overseas may be cost effective for pharmaceutical manufacturers, but it may also hinder the manufacturer's timely response to an increase in demand. Additional causes include quality-control problems in manufacturing that create production delays; a limited number of manufacturing companies; and manufacturers' business decisions, restricted distribution methods, inventory practices, and to a lesser degree, regulatory issues.

Impact

Drug shortages have a high impact on health, and in pediatric oncology, they have a particularly serious impact. As Bunnell and colleagues (2020, p. 2) note, "Childhood cancer treatment relies on the use of sterile injectable generic agents, which make up the majority of scarce medications and which manufacturers have limited economic incentives to produce." Pediatric hematologist/oncologist Yoram Unguru reinforced this point in a 2020 APHON webinar, *A Dearth of Lifesaving Medications: Scarcity and Shortage in Childhood Cancer*: "Costly chemotherapy agents with limited efficacy are rarely, if ever, in short supply, while inexpensive, older, curative drugs are."

Clinical trials have led to a dramatic improvement in childhood cancer survival over the past 5 decades, but drug shortages may negatively affect enrollment in those trials. Furthermore, many of the scarcest drugs have served as the backbone of childhood cancer clinical trials that have led to proven, lifesaving regimens. No adequate substitutes or alternative drugs are available to treat these pediatric patients during a shortage.

In 2019, a critical shortage of the drug vincristine had a significant impact on the childhood cancer population because of its widespread use in the treatment of many different childhood cancers. In the case of acute lymphoblastic leukemia (the most common childhood cancer, which accounts for nearly one-quarter of all children with cancer), a shortage of a critically important drug like vincristine means that the current 90% 5-year event-free survival rate for 3,000 U.S. children affected each year may be compromised.

Manufacturing of medical devices has also had an impact on drug shortages. For example, Puerto Rico is responsible for $40 billion of the pharmaceuticals market, more than any other state or territory. More than 100 companies that produce pharmaceuticals or medical devices have manufacturing sites in Puerto Rico. Puerto Rico was devastated by Hurricane Maria in 2017. However, the shortage of sterile normal saline that occurred during that time was not actually a

shortage of normal saline; it was rather a shortage of the sterile minibags that were manufactured in Puerto Rico (Unguru, 2020).

Those in the field of pediatric oncology have received little guidance for dealing with drug shortages. **Figure 1** graphs the percentage of Children's Oncology Group (COG) principal investigators and pharmacists who indicated that a shortage of chemotherapy agents had affected clinical trials in the period 2013–2015 (Salazar et al., 2015).
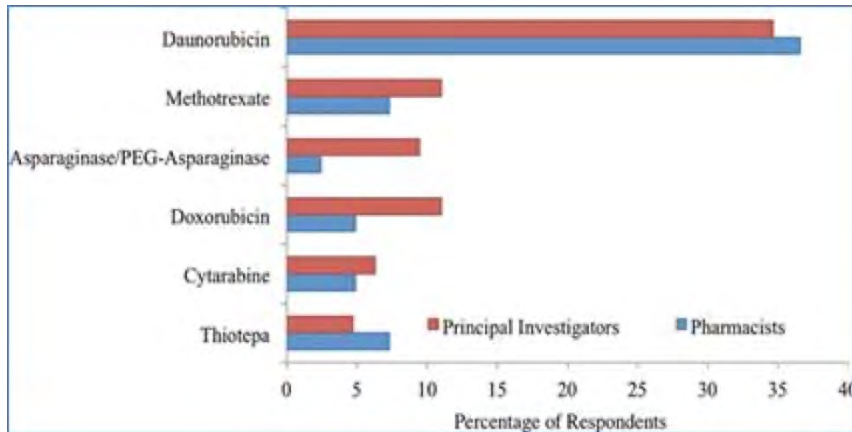

Figure 1. Impact of Drug Shortages on Clinical Trials
From "The Impact of Chemotherapy Shortages on COG and Local Clinical Trials: A Report from the Children's Oncology Group," by E. G. Salazar, M. B. Bernhardt, Y. Li, R. Aplenc, and P. C. Adamson, 2015, *Pediatric Blood and Cancer*, *62*(6), p. 942 (https://doi.org/10.1002/pbc.25445). Copyright 2015 by Wiley Periodicals, Inc.

Ethical Considerations

Children with cancer are particularly vulnerable to the impact of drug shortages, so the shortages present significant ethical challenges (Decamp et al., 2014). Substitute regimens need to be carefully examined before they are adopted because they can result in inferior patient outcomes.

APHON does not support unethical practices (such as drug hoarding or discrimination based on patients' age, developmental level, race, ethnicity, disability, immigration status, or ability to pay) that violate the principle of justice. Unsafe strategies of waste reduction, such as those that violate infection prevention protocols (e.g., reusing drugs, administering expired drugs) or compromise the quality of care are also unethical (Bunnell et al., 2020).

It is essential that decision making on drug allocation be founded on ethical principles. Moreover, the healthcare team must ensure that communication with patients and families about drug shortages is explicit and transparent. Ethical issues that may arise in the event of drug shortages may be related to decisions in these areas: delays in treatment, the skipping of a

dose or administration of a lower dose, which patients should receive a scarce drug, what constitutes an adequate reserve, and who makes these decisions.

According to Decamp and colleagues (2014), the imperative to prevent and to manage drug shortages is based on two fundamental values: (1) the need to maximize the benefits of highly effective drugs and (2) the obligation to ensure equitable access across patients and patient groups. Decamp et al. (2014, p. e718) made the following recommendations grounded on ethical rationales, and those recommendations were published in a consensus statement in the *Journal of the American Academy of Pediatrics*:

1. Optimize and efficiently use supplies to reduce the likelihood of future shortages and mitigate their effects.
2. Develop explicit policies that give equal priority during a drug shortage to evidence-based use of chemotherapy agents whether patients are receiving treatment within or outside a clinical trial.
3. Create an improved, centralized clearinghouse for sharing information about drug availability and shortages.
4. Explore voluntary sharing of drugs at state, regional, and national levels.
5. Develop a strategy for ongoing stakeholder engagement regarding managing drug shortages, with specific emphasis on patients and patient advocacy groups.

Positions and Recommendations

APHON supports the following efforts, as stated in its 2020 position paper on drug shortages (Bunnell et al., 2020, pp. 2–3):

- promoting awareness of drug shortages through reliable information sharing

- advocating for strategies that minimize the impact of drug shortages on the quality of care

- cooperating and collaborating with healthcare institutions, consortiums, professional organizations, policy makers, and stakeholders in prioritizing the prevention and management of drug shortages

- advocating for federal, local, and institutional policy changes that address drug shortages and reduce their frequency and impact on patients and families

- developing institutional policies that
  - describe the institution's approach to the management of drug shortages
  - include ethical principles of decision making on drug allocation

- ensure explicit and transparent communication with patients and families about drug shortages
- using evidence-based strategies to minimize the impact of drug shortages by maximizing efficiency and eliminating waste through interventions such as
  - grouping patients receiving the same therapy into cohorts to share vials during drug preparation
  - reducing advance preparation of drugs that may lead to waste
  - using safe dose-rounding practices to eliminate waste
  - evaluating drugs' expiration times and shelf life to extend the period of safe drug use
- developing institutional interdisciplinary drug allocation committees that
  - include physicians, pharmacists, nurses, social workers, members of institutional ethics committees, and patient representatives
  - apply ethical decision-making principles
  - explore reasonable therapeutic drug alternatives
  - make prioritization decisions that are applied equitably to patients affected by drug shortages
  - provide an appeal process for patients and families who have been affected by drug allocation decisions
- showing respect for patients and caregivers by informing them about drug shortages and the process by which allocation decisions are made.

APHON's position paper (Bunnell et al., 2020, p. 3) continues by offering these recommendations: that nurses

- become informed both about the causes and impact of drug shortages and about current recommendations to prevent or reduce the impact of drug shortages on public health
- advocate for and participate in institutional drug shortage and allocation committees
- ensure that families receive current and reliable information about drug shortages and the subsequent management plan for their child's care
- refrain from implementing individual strategies (e.g., drug hoarding) that, although well-intentioned, may compromise the delivery of safe, ethical, and high-quality care

- acknowledge the distress that clinicians experience when forced to implement drug allocation decisions that negatively affect individual patients and families
- provide support and therapeutic communication to patients and families whose treatment is altered because of an insufficient drug supply
- become involved in public policy advocacy that strives to minimize drug shortages.

Resources on Current Drug Shortages

More information is available from the American Society of Health-System Pharmacists (www.ashp.org) and the U.S. Food and Drug Administration (https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages).

Mitigation and Allocation Strategies

A 2017 survey that used the membership list of the American Society of Pediatric Hematology/Oncology (ASPHO) was conducted to assess what personnel were involved in scarce drug prioritization and distribution and what criteria were used to inform decisions about the distribution of scarce drugs (Beck et al., 2017). The survey results revealed a significant disparity between respondents' judgments about how decisions were currently being made and their views on who should be making them (**Table 1**).

Table 1. Survey of 191 ASPHO Physicians About Their Experiences of Drug Shortages	
How have drug shortages affected patient care?	
Physicians who were not able to prescribe a needed medication because of a shortage	65%
Physicians who knew of drug shortages at their institutions but had not yet been directly affected	79%
Who provided you with information about drug shortages?	
Pharmacist	98%
Another physician	41%
A website	38%
Nurses	7%
Does your institution have a drug shortage policy?	
Yes	62%
No	4%
Unsure	33%
At your institution, who makes decisions on the allocation of drugs during a shortage?	
Pharmacist	70%
Physician	60%
Hospital administration	23%
Panel	18%
Ethics committee	4%
Do not know	25%

Who *should* make decisions on the allocation of drugs during a shortage?	
Pharmacist	80%
Physician	83%
Hospital administration	19%
Panel	42%
Ethics committee	19%
Nurse	4%
Parent	3%
Not sure	7%
Adapted from "Physician Approaches to Drug Shortages: Results of a National Survey of Pediatric Hematologist/Oncologists," by J. C. Beck, B. Chen, and B. G. Gordon, 2017, *World Journal of Clinical Oncology*, *8*(4), 336–342; table 2, p. 338 (https://doi.org/10.5306/wjco.v8.i4.336). Copyright 2017 by the authors. Licensed under CC-BY-NC 4.0, https://creativecommons.org/licenses/by-nc/4.0/legalcode.	

Summary

Drug shortages prevent clinicians from providing a reasonable standard of care. Drugs that are critical in pediatric oncology and that have contributed to a dramatic improvement in childhood cancer survival over the past 5 decades are among the scarcest drugs. It is essential that those making decisions on drug allocation be guided by established ethical principles and that institutions establish interdisciplinary drug allocation committees. Pediatric hematology/oncology nurses play a key role in advocating for and participating in such committees as well as ensuring that families receive current and reliable information about drug shortages and the subsequent plans for managing their child's care.

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Fertility Preservation

AnnMarie Martinez, MSN RN CPN CPHON®

Learner Outcomes

Upon completion of this Pediatric Chemotherapy and Biotherapy Provider Program learning activity

1. the learner will be able to distinguish methods of fertility preservation according to pubertal status
2. the learner will be able to list six high-risk gonadotoxic chemotherapies.

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Advances in the treatment of childhood cancers have been on the rise, resulting in a remarkable 5-year overall survival rate of 85.1% for children diagnosed with cancer from 0 to 19 years of age, based on Surveillance, Epidemiology, and End Results (SEER) data from November 2020 (Howlader et al., 2021). Although this statistic is very promising, cancer treatments can result in subfertility, infertility, or sterility. Fertility preservation for pediatric patients should be discussed as soon as possible after the cancer diagnosis, regardless of the patient's reproductive age. This section will cover normal reproductive physiology; the indications for fertility preservation; methods of fertility preservation, which are determined by the patient's pubertal status; and counseling needs, barriers, and ethical and cultural considerations related to fertility preservation.

Normal Reproductive Physiology

The differences in male and female reproductive physiology determine the methods of fertility preservation available, and the options available for prepubertal boys and girls are minimal. In boys, spermatogenesis, though it occurs before puberty, does not lead to the production of mature sperm, or spermatozoa. *Spermarche*, or release of the spermatozoa, occurs in early to mid-puberty (ages 13 to 18 years). In girls, oogenesis occurs during fetal development. Mature oocyte development begins with menarche and occurs with each ovulation cycle (Klipstein et al., 2020).

Indications for Fertility Preservation

It is estimated that one in three people will get cancer at some point. Because survival rates are improving, the number of survivors whose reproductive future is in question is significant. For most cancers, the treatment involves a combination of two or more modalities, including chemotherapy, radiotherapy, surgical intervention, and immunotherapy. With the exception of immunotherapy, for which effects on fertility are now yet known, all these modalities can cause permanent infertility. The effects of chemotherapy and radiotherapy on the gonads are dose

dependent; **Table 1** presents the risks associated with various doses of radiation given in various locations.

Table 1. Risk of Infertility Associated with Radiation Therapy Doses and Sites	
High Risk	Intermediate Risk
Total body irradiation for bone marrow transplant or stem cell transplant	Testicular radiation dose 1–6 Gy from scattered pelvic or abdominal radiation
Testicular radiation dose >2.5 Gy in adult men	Pelvic or whole-abdominal radiation dose 5–10 Gy in postpubertal girls
Testicular radiation dose ≥6 Gy in prepubertal boys	Pelvic or whole-abdominal radiation dose 10–15 Gy in prepubertal girls
Pelvic or whole-abdominal radiation dose ≥6 Gy in adult women	Craniospinal radiotherapy dose ≥25 Gy
Pelvic or whole-abdominal radiation dose ≥10 Gy in postpubertal girls	
Pelvic or whole-abdominal radiation dose ≥15 Gy in prepubertal girls	
Adapted from "Fertility Preservation for Young Adults, Adolescents, and Children with Cancer," by K. A. Rodriguez-Wallberg, A. Anastacio, E. Vonheim, S. Deen, J. Malmros, and B. Borgström, 2020, *Upsala Journal of Medical Sciences, 125*(2), 112–120; table 1, p. 114. https://doi.org/10.1080/03009734.2020.1737601. Copyright 2020 by the authors. Licensed under CC-BY-NC 4.0, https://creativecommons.org/licenses/by-nc/4.0/legalcode.	

Although the connection between the radiotherapy dose and risks to fertility is clear, the connection is less clear for chemotherapy drugs. With chemotherapy, it is difficult to quantify the specific effects of individual drugs when they are given as part of a treatment regimen over time. **Table 2** presents what we currently know about gonadotoxicity related to chemotherapy drugs for both males and females (Rodriguez-Wallberg et al., 2020). With females, gonadotoxicity is age-dependent because females are born with a finite quantity of oocytes that declines over time until menopause is reached, whereas spermatogenesis continues throughout a male's lifespan. Pediatric diagnoses that have the highest risk of permanent sterility are testicular cancer, leukemia, and Ewing sarcoma (Del-Pozo-Lérida et al., 2019).

Table 2. Risk of Infertility Related to Chemotherapy Agents			
High Risk	**Intermediate Risk**	**Low Risk**	**Unknown Risk**
Busulfan Chlorambucil Cyclophosphamide Ifosfamide Melphalan Nitrogen mustard Procarbazine	Carboplatin with low cumulative dose Cisplatin with low cumulative dose Doxorubicin	Treatment protocols for Hodgkin lymphoma without alkylating agents Actinomycin D Bleomycin 5-Fluorouracil Methotrexate Radioiodine treatment for thyroid cancer Vincristine	Bevacizumab Erlotinib Imatinib Irinotecan Paclitaxel and docetaxel for treatment of breast cancer Trastuzumab
Adapted from "Fertility Preservation Young Adults, Adolescents, and Children with Cancer: Medical and Ethical Considerations," by K. A. Rodriguez-Wallberg, A. Anastacio, E. Vonheim, S. Deen, J. Malmros, and B. Borgström, 2020, *Upsala Journal of Medical Sciences, 125*(2), 112–120; table 2, p. 115. https://doi.org/10.1080/03009734.2020.1737601. Copyright 2020 by the authors. Licensed under CC-BY-NC 4.0, https://creativecommons.org/licenses/by-nc/4.0/legalcode.			

Methods for Preservation of Male Fertility

Prepubertal

Gonadal and gamete preservation in prepubertal males is challenging because many proposed treatment modalities (with the exceptions of shielding the testes or moving them out of the radiation field) are currently experimental. Most experimental methods include hormone manipulation or preserving a sample of testicular tissue. Studies in animals suggest that cryopreservation of testicular tissue, autotransplantation, xenotransplantation, and in vitro maturation have the potential to be successful; however, these methods still need to be tested in humans. Effective pharmacological interventions have yet to be identified (Klipstein et al., 2020).

Postpubertal

Once postpubertal males start producing mature sperm, the options for fertility preservation change. The current options are sperm cryopreservation and testicular tissue cryopreservation, with sperm cryopreservation from masturbation being the most effective (Klipstein et al., 2020). The procedure for sperm collection should be performed before the initiation of treatment. Ideally, the collection would consist of at least 3 semen samples with a period of abstinence for 48 hours between each sample. In some cases, collection of the samples must occur within the

same day because of the nature of the diagnosis and in order to prevent a delay in treatment (Del-Pozo-Lérida et al., 2019). Alternative methods of semen collection besides masturbation include testicular aspiration, electroejaculation under sedation, or retrieval from a urine sample post masturbation (Klipstein et al., 2020). Gonadal shielding is an option for those receiving radiotherapy and in which sperm collection is not possible. At the current time, testicular tissue cryopreservation should only be performed as part of a clinical trial or approved experimental protocols (Oktay et al., 2018).

Methods for Preservation of Female Fertility

Prepubertal

As with fertility preservation for prepubertal males, fertility preservation for prepubertal females (with the exception of gonadal shielding and oophoropexy) is primarily experimental. For patients who will receive radiation therapy to the pelvis, the ovaries can be transposed (surgically relocated out of the field of radiation therapy). However, oocytes are very sensitive to radiation, and only 15% of patients who choose to undergo transposition of their ovaries will achieve the goal of becoming pregnant. Gonadal shielding is another option for ovarian protection during radiation therapy; however, it is less effective if the patient receives gonadotoxic chemotherapy in addition to radiotherapy (Klipstein et al., 2020). In the United States, an open trial is being held to assess the safety and efficacy of cryopreservation of ovarian tissue in prepubertal females. Thus far we have no evidence that use of the autotransplanted tissue can lead to pregnancy and delivery. In addition, tissue harvested from a patient at diagnosis could potentially be contaminated with leukemia cells, and this tissue could reintroduce leukemia cells into the patient's body during a future autotransplant.

Postpubertal

Fertility preservation options for postpubertal females include oocyte or embryo cryopreservation. Although embryo preservation had previously been the only available option, oocyte cryopreservation has shifted from being considered an experimental method to being recommended in 2012 by the American Society of Reproductive Medicine (Klipstein et al., 2020). In embryo cryopreservation, the oocytes are fertilized with the sperm of a partner or an anonymous donor. This practice involves a larger number of social, emotional, and ethical considerations, which require a certain level of maturity. Now that oocyte cryopreservation has been recommended and proven successful, embryo cryopreservation is recommended for use only in rare circumstances. The oocyte cryopreservation is an invasive and lengthy process. It requires 10 days of transvaginal ultrasonography and blood tests, followed by a surgically performed transvaginal oocyte retrieval. Depending on the diagnosis and clinical status of the patient, the delay of a treatment regimen for 10 days or more may not be possible (Klipstein et al., 2020). Of note, even though contradictory evidence exists for the use of gonadotropin-releasing hormone (GnRH) or ovarian suppression, the 2018 American Society of Clinical Oncology (ASCO) guidelines suggest that in situations in which established fertility preservation methods (i.e. cryopreservation of oocytes, embryos, or ovarian tissue) are not possible, "GnRH

may be offered to patients with the hope of reducing chemotherapy-induced ovarian insufficiency" (Oktay et al., 2018).

Counseling Needs

According to ASCO guidelines, all patients with a cancer diagnosis should be counseled about the impact that their disease and treatment regimen may have on their future fertility (Lee et al., 2006). Such counseling is best done immediately after diagnosis (which is admittedly a very stressful moment in the patient's life) but before initiation of the treatment regimen. For preadolescent patients, it is recommended that the conversation involve one or both parents. However, for adolescent patients, it may be best to have the conversations without a parent present. Such conversations may be embarrassing, but the goal is to help patients understand their options, allow them to ask questions, gain their assent, and allow them to take an active role in their care. This counseling should start with their provider, who can then make referrals to specialists in fertility preservation: reproductive endocrinologists, surgeons, mental health professionals, urologists, and child life personnel (Klipstein et al., 2020).

Barriers

Providers and Timing

The single most critical barrier to fertility preservation is the first consultation. The emotional stress, anxiety, and fear that accompany a new cancer diagnosis often provoke the desire to start the treatment regimen right away. However, beginning treatment before addressing fertility concerns may impair reproduction or limit reproduction options (Klipstein et al., 2020). A review of studies shows that providers do not hold these conversations with patients and families for a number of reasons. The barriers reported include providers' lack of knowledge about treatment-induced fertility impairments and fertility preservation procedures, the perceived need to begin the patient's treatment immediately, estimates of the patient's likelihood of survival, discomfort discussing fertility, and sometimes even assumptions about their patients' preferences (Lampic & Wettergren, 2019). The consequence of these barriers is a significant information gap for the patients. In one study, only half of the parents surveyed recalled receiving fertility information, and approximately one third expected normal fertility following the cancer treatment (van den Berg & Langeveld, 2008). Another study of adolescents with cancer revealed that 81% would want to proceed with investigational or research-based alternatives in an attempt to maintain their fertility (Burns et al., 2006).

Economic Factors

Cryopreservation can cost hundreds of dollars a year, and that is added to the cost of the collection process, depending on the option chosen (Klipstein et al., 2020). Fertility preservation is not covered by most insurance plans, so it is often an out-of-pocket expense for patients. This situation is changing in a number of states, where new legislation is mandating insurance coverage for fertility preservation (Halpern et al., 2020).

Ethical and Legal Considerations

Pediatric fertility preservation raises several ethical and legal concerns. First and foremost is the obtaining of consent (for older patients) or assent (for younger patients); the specified ages vary by state. Disagreements between the parent and the adolescent child are difficult to manage. The critical concern in this situation is the extent of involvement of the minor child. The patient's family and the medical team should work together to provide an open future for the patient. The principle of an open future rests on the moral duty to protect the rights of children, especially in relation to important decisions being made before the child reaches the age of consent.

For adolescent patients, it is recommended that their feelings about such decisions be solicited without a parent or guardian present. It is also important to have these conversations regardless of a child's sexual orientation. When conflict occurs, it is prudent to hold a consultation with an ethics professional or a mental health professional.

Any disposition of gametes should be delayed until the child reaches the age of consent. For children who do not survive into adulthood, their eggs and ovarian tissue or sperm and testicular tissue should be destroyed. This practice is consistent with recommendations made by the American Society for Reproductive Medicine (Ethics Committee of the American Society for Reproductive Medicine, 2013).

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Neurotoxicities of Chemotherapy and Biotherapy

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Learner Outcomes

Upon completion of this Pediatric Chemotherapy and Biotherapy Provider Program learning activity

1. the learner will be able to describe the two main components of the nervous system
2. the learner will be able to recognize commonly used chemotherapy agents that cause neurotoxicity in the pediatric oncology patient population
3. the learner will be able to identify neurotoxicities caused by immunotherapy and targeted therapy agents used to treat pediatric oncology patients.

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Peripheral and Central Nervous Systems: An Overview

The nervous system controls our reflexes, movements, actions, and sensations, continuously controlling who we are and what we do. A complex collection of nerves that are connected to our brain and spinal cord, it is divided into two main parts: the central nervous system and the peripheral nervous system (**Figure 1**). Together the parts of the nervous system work to transmit signals between the brain and the rest of the body. These signals control our ability to move, breathe, see, and think, among many other daily activities.
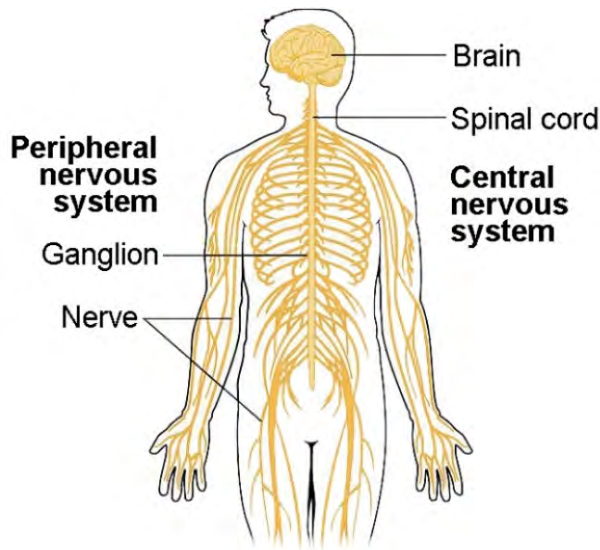
Figure 1. Central and Peripheral Nervous Systems
The central nervous system consists of the brain and the spinal cord. The peripheral nervous system is made up of nerves that branch off from the spinal cord and extend to all parts of the body.
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As with any other system or organ in our bodies, both the central and peripheral nervous systems are affected by chemotherapy and immunotherapy toxicities. Toxicities can be acute and may resolve as soon as the therapy is discontinued or completed, while other toxicities are chronic and may become long term effects of the chemotherapy or immunotherapy that was administered. This section will review some of the more common chemotherapies that have neurotoxic effects associated with them. Novel immunotherapies that have neurotoxic side effects will also be discussed.

Neurotoxicities of Chemotherapy

Antimetabolites
Cytarabine. Cytarabine is a cell-cycle-specific antimetabolite used for the treatment of hematologic malignancies; it can be administered intravenously, intrathecally, or subcutaneously. When cytabarine is administered in high doses, patients may develop acute cerebellar syndrome. Symptoms include gait disturbance, seizures, and in some cases, death (Sioka & Kyritsis, 2009). Lower doses of cytarabine have also been associated with posterior reversible encephalopathic syndrome (PRES) (Peddi et al., 2014). Patients with PRES, formerly known as reversible posterior leukoencephalopathy, can present with headache, impaired level of consciousness, confusion, visual disturbances, seizure, nausea, vomiting, encephalopathy, and focal neurologic deficits (Gillard et al., 2019; Peddi et al., 2014). Hypertension has also been frequently observed in patients during the days or hours leading up to the PRES event. PRES can

be reversible when the cytarabine or agent contributing to the syndrome is discontinued; however, in some cases symptoms have persisted after discontinuation of the offending drug.

Methotrexate. Methotrexate is a mainstay antineoplastic for hematologic malignancies and solid tumors alike. It can be administered through a variety of routes: oral, subcutaneous, intramuscular, intravenous, and intrathecal (IT). Methotrexate neurotoxicity, however, is typically associated with doses that are administered intrathecally or high intravenous doses (Peddi et al., 2014). There are several neurotoxicities associated with intrathecal administration of methotrexate including aseptic meningitis and transverse myelopathy. Aseptic meningitis should be considered in the differential for a patient exhibiting symptoms such as headache, stiff neck, mild fever, nausea and vomiting several hours after an intrathecal dose of methotrexate (Verstappen et al., 2003). Symptoms of aseptic meningitis due to IT methotrexate administration can last anywhere between 12 and 72 hours (Verstappen et al., 2003). Transverse myelopathy may occur after several IT methotrexate injections and can include symptoms of back pain that may radiate to the legs, sensory loss, bowl and bladder dysfunction and paraplegia. Thankfully, this toxicity is not long lasting and will resolve on its own (Peddi et al., 2014). Delayed methotrexate neurotoxicity or encephalopathy can also be found in patients who have received high intravenous doses of methotrexate or those who have received IT doses of methotrexate. This delayed leukoencephalopathy may occur six months or more after methotrexate administration and can be chronic. Symptoms of delayed methotrexate neurotoxicity include: progressive dementia, gait disturbances, hemiparesis, aphasia seizure and death. Radiation therapy administered concurrently with methotrexate has been associated with increased risk for developing delayed leukoencephalopathy (Peddi et al., 2014). A rare but potential complication of intrathecal methotrexate therapy may also include changes in the white matter that can manifest as a transient or persistent neurologic dysfunction. This neurologic dysfunction can first appear as facial nerve weakness, speech disturbance, seizures, hemiparesis, or an obtunded level of consciousness. It usually occurs within 2 weeks of a patient's receiving intrathecal therapy (Bhojwani et al., 2014). The nurse caring for a patient exhibiting these signs and symptoms after receiving intrathecal methotrexate should advocate for further work-up and imaging to rule out white matter changes (Ramli et al., 2020; Yim et al., 1990).

5-fluorouracil. 5-fluorouracil (5-FU) is a cell-cycle-specific antimetabolite that is given to treat germ cell tumors and hepatoblastoma in the pediatric oncology setting, but it can also be used to treat gastrointestinal, head and neck, and breast cancers. Administration can be intravenous or by mouth. Patients with a deficiency of the dihydropyrimidine dehydrogenase enzyme are at greater risk for 5-FU-related toxicities, including neurotoxicities, because this enzyme is responsible for the metabolic clearance of 5-FU from the body. This drug does cross the blood-brain barrier, and high concentrations of 5-FU can be found in the cerebellum. As a result, cerebellar toxicity can be seen with this drug. Symptoms of cerebellar toxicity include ataxia, dysarthria, dysmetria, extraocular muscle abnormalities, optic nerve neuropathy, and extrapyramidal symptoms. Leukoencephalopathy, although rare, has also been reported with 5-FU administration (Peddi et al., 2014).

Fludarabine. Fludarabine is an antimetabolite given to treat acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) and as an agent in hematopoietic stem cell transplant (HSCT) preparative regimens. Neurotoxicity is rare when fludarabine is administered in standard doses. However, severe neurotoxicity syndrome has been described when the drug is administered at doses greater than 40 mg/m^2/day. Blindness, encephalopathy, and coma are symptoms of the diffuse, necrotizing leukoencephalopathy that is the severe neurotoxicity syndrome associated with high doses of fludarabine (Sioka & Kyritsis, 2009).

Nelarabine. Nelarabine, approved for use in treating T-cell ALL and T-cell lymphoma, is a prodrug of a purine antimetabolite, arabinofuranosylguanine (ara-G). It is metabolized in cells to the metabolite ara-G triphosphate (ara-GTP). Cell death results from the incorporation of ara-GTP into DNA. The cytotoxic effects of ara-GTP were found to have a 20 times greater effect on T cells than on B cells, and it was therefore approved by the U.S. Food and Drug Administration (FDA) for use in T-cell hematologic malignancies in 2005. It should be noted that nelarabine's package insert contains a black-box warning for severe neurotoxicity, including mental status changes, severe somnolence, headache, paresthesia, dysesthesia, dizziness, seizures, and peripheral neuropathy, which can range from numbness and paresthesias to motor weakness and paralysis. These neurotoxicities were noted in both pediatric and adult patients. Nursing considerations include frequent monitoring during treatment and up to 24 hours after treatment, because neurotoxicity can be dose limiting. Adverse reactions related to demyelination and ascending peripheral neuropathies similar in appearance to Guillain-Barré syndrome have been reported. It has also been noted that patients who have undergone intrathecal chemotherapy or are concurrently undergoing intrathecal chemotherapy or craniospinal radiation while receiving nelarabine may have increased severity of neurotoxic effects (Ngo et al., 2015). Neurotoxicity associated with nelarabine may be transient or may be long-lasting. Correlation between neurotoxicity and dose and/or concurrent intrathecal chemotherapy has also been found.

Alkylating Agents
Cyclophosphamide and ifosfamide. Cyclophosphamide and ifosfamide are both cell-cycle-nonspecific alkylating agents that are used for a variety of solid tumor malignancies. Cyclophosphamide is also used in treating hematologic malignancies and as an agent in preparative regimens for HSCT. Cyclophosphamide has been reported to have minimal neurotoxic effects. Blurred vision, dizziness, and confusion have all been reported but found to be reversible. Ifosfamide has been associated with an acute encephalopathy characterized by somnolence, hallucinations, agitation, and seizures that may lead to coma and even death. This encephalopathy, also referred to as ifosfamide neurotoxicity, can develop hours to days into a course of ifosfamide, and methylene blue can be used to treat the encephalopathy (Sioka & Kyritsis, 2009). Ifosfamide has also been linked to peripheral neuropathies in patients receiving the drug for bone and soft tissue sarcomas. This axonal peripheral neuropathy (arising from the axon of a nerve cell; **Figure 2**) can be quite painful and may discourage patients from ambulating on their own (Frisk et al., 2001).
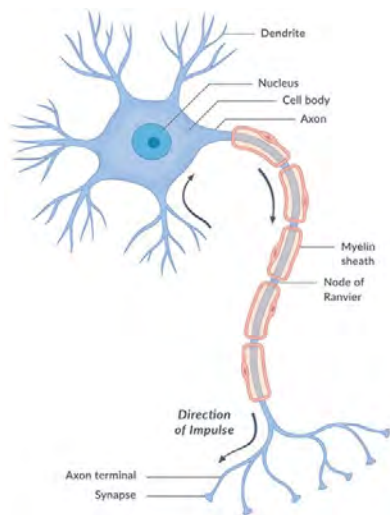
Figure 2. Nerve Cell or Neuron
Each neuron has a cell body that includes a nucleus, axons, and dendrites. Communication between neurons occurs via axons and dendrites, extensions found on the nerve cell. Used with permission.

Procarbazine. Procarbazine is a cell-cycle-nonspecific antineoplastic agent; its use is indicated in the treatment of central nervous system tumors and lymphomas. Procarbazine is administered by mouth (*per os,* PO) and should be given on an empty stomach for maximum absorption. Procarbazine readily crosses the blood-brain barrier. Neurotoxic effects of procarbazine include both central and peripheral nervous system toxicities. Toxicities can range from paresthesias, focal neurological deficits, and cognitive disturbances (e.g., depression, confusion, nightmares, and cerebral atrophy that can be detected via magnetic resonance imaging (MRI) (Verstappen et al., 2003). Peripheral nervous system toxicities can also include ataxia, orthostatic hypotension, weakness of intrinsic hand muscles, diminished reflexes, and peripheral neuropathy.

Cisplatin. Cisplatin, an alkylating agent used to treat a variety of solid tumors, is administered intravenously and crosses the blood-brain barrier only minimally. However, it is able to produce toxicities of the central nervous system, including PRES. The patient may experience headache, cortical blindness, focal deficits, stroke, and seizures related to PRES, but these symptoms have been reported to be reversible (Sioka & Kyritsis, 2009). Peripheral neuropathy and cranial nerve deficits have also been reported to accompany the administration of cisplatin and at dose-limiting toxicities. Ataxic gait, paresthesia, and numbness are toxicities that may surface after the completion of treatment with cisplatin and may be attributed to axonal changes caused by cisplatin secondary to neuronal damage (Verstappen et al., 2003). Perhaps the most recognized peripheral neurotoxicity associated with cisplatin is the high-frequency hearing loss that is commonly seen. This ototoxicity is found in patients after cumulative exposure to the drug and may result in permanent hearing loss. This is significant for the pediatric patient population

because hearing loss may influence patients' social and cognitive development, affecting their speech patterns, their learning, and their performance in school.

Carboplatin. Carboplatin, like cisplatin, can cause permanent hearing loss in patients receiving the drug. This vestibulotoxic effect results from high doses of carboplatin disrupting the mitochondria of hair cells, thus leading to damage of cranial nerve VIII, which is responsible for transmitting sound and equilibrium (balance) information from the inner ear to the brain (**Figure 3**).
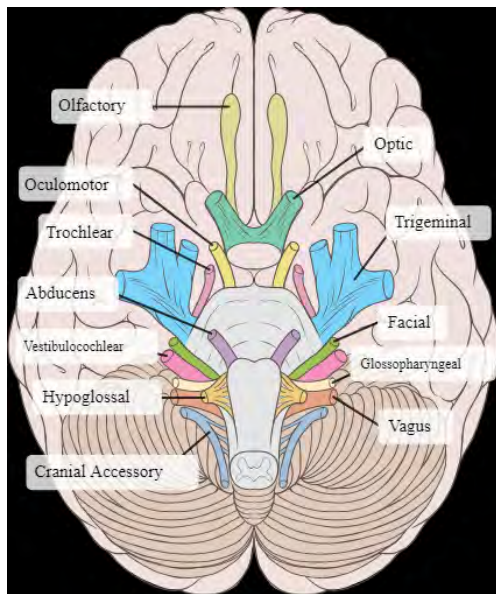
- The olfactory nerve (I): instrumental for the sense of smell, it is one of the few nerves that are capable of regeneration.

- The optic nerve (II): carries visual information from the retina of the eye to the brain.

- The oculomotor nerve (III): controls most of the eye's movements, the constriction of the pupil, and maintains an open eyelid.

- The trochlear nerve (IV): motor nerve that innervates the superior oblique muscle of the eye, which controls rotational movement.

- The trigeminal nerve (V): responsible for sensation and motor function in the face and mouth.

- The abducens nerve (VI): motor nerve that innervates the lateral rectus muscle of the eye, which controls lateral movement.

- The facial nerve (VII): controls the muscles of facial expression, and functions in the conveyance of taste sensations from the anterior two-thirds of the tongue and oral cavity.

- The vestibulocochlear nerve (VIII): responsible for transmitting sound and equilibrium (balance) information from the inner ear to the brain.

- The glossopharyngeal nerve (IX): receives sensory information from the tonsils, the pharynx, the middle ear, and the rest of the tongue.

- The vagus nerve (X): responsible for many tasks, including heart rate, gastrointestinal peristalsis, sweating, and muscle movements in the mouth, including speech and keeping the larynx open for breathing.

- The spinal accessory (XI): controls specific muscles of the shoulder and neck.

- The hypoglossal nerve (XII): controls the tongue movements of speech, food manipulation, and swallowing.

Figure 3. Cranial Nerves
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Oxaliplatin. Oxaliplatin is a platinum-based alkylating agent used to treat non-Hodgkin lymphoma as well as germ cell and solid tumors. It is administered intravenously and can cause acute sensory neuropathy. This neurotoxicity can occur within 30 to 60 minutes of the oxaliplatin infusion and consists of paresthesia, cold hypersensitivity, jaw and eye pain, ptosis, leg cramps, and visual and voice changes (Verstappen et al., 2003). Symptoms may last for several days after infusion, and the patient must be instructed to avoid cold food, drinks, and ambient temperatures during the infusion and for several days afterward. A chronic, cumulative neuropathy may also occur in patients who receive several courses of oxaliplatin. Symptoms include tingling, numbness, and even loss of sensation for touch or temperature. Chronic symptoms can last for weeks and may interfere with activities of daily living such as buttoning, writing, and walking. This cumulative neuropathy can be a dose-limiting toxicity.

Vinca Alkaloids

Vincristine. Vincristine, a cell-cycle-specific vinca alkaloid, arrests cell division by the inhibition of microtubule formation in the mitotic spindle; therefore, it is classified as a tubulin inhibitor. Vincristine has indications for use in protocols of treatment for hematologic malignancies and solid tumors such as leukemia, Ewing sarcoma, rhabdomyosarcoma, Wilms tumor, and retinoblastoma. The central nervous system toxicities associated with vincristine include encephalopathy and seizures. Seizure activity may come as a result of hyponatremia due to syndrome of inappropriate antidiuretic hormone, a rare but possible side effect of vincristine. The administering nurse and the nurse performing the double check must be cognizant of the dose of vincristine being given because accidental overdose with vincristine may cause a central nervous system toxicity that may lead to death. Fatal myeloencephalopathy may also occur if the vincristine is accidentally administered intrathecally. Vincristine is administered intravenously only. Although the central nervous system toxicities related to vincristine are quite serious, patients more frequently experience peripheral nervous system toxicities. These peripheral nervous system toxicities are thought to be caused by inhibition of fast axonal transport by microtubules (Verstappen et al., 2003) and include paresthesia in the fingers and toes and weakness in the extensor muscles of the wrist and dorsiflexors of the toes. An altered gait, difficulty walking, and numbness or tingling of the fingers and toes could help a healthcare provider recognize this neurotoxicity. Cranial nerve palsies such as vocal cord paresis, diplopia, facial nerve palsy, ophthalmoplegia, and sensorineural hearing loss have also been experienced. It is important to ensure that a thorough neurologic assessment is performed for any patient receiving vincristine therapy. Vincristine therapy can also cause autonomic neuropathies in the form of constipation, which may lead to paralytic ileus or megacolon; bladder atony, impotence, orthostatic hypotension, and disturbed heart rate may also occur. When assessing a patient receiving vincristine therapy, the nurse should ask questions about elimination to safeguard against the downstream complications of paralytic ileus and urinary retention.

Neurotoxicities of Biotherapy

Immunotherapy

Chimeric antigen receptor T cells (CAR T cells). CAR T cells are a type of adoptive cellular therapy that involves apheresis and genetic engineering of autologous T cells. These T cells have been engineered to express the intracellular domain of a T-cell receptor fused to the antigen-binding domain of a B-cell receptor. The T cells are then expanded in the lab and subsequently reinfused into the patient. The reprogrammed cells are then able to recognize and attack tumor cells that bear the tumor-specific antigen they were genetically engineered to seek out (Kennedy & Salama, 2020) (see **Figure 4**).
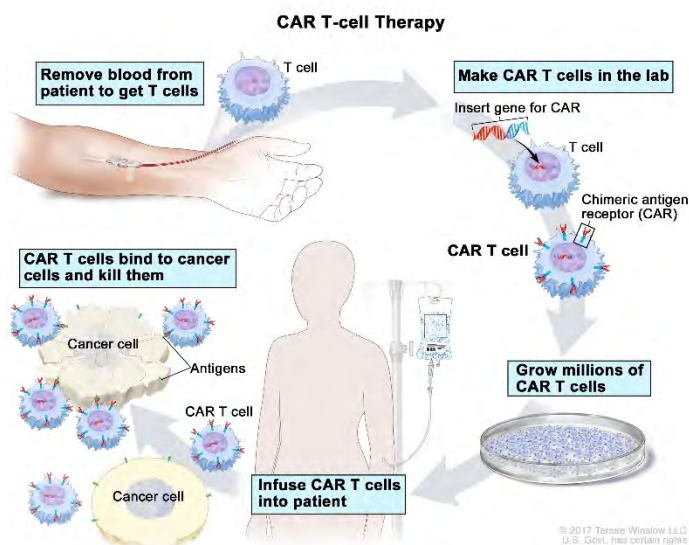

Figure 4. T-Cell Transfer Therapy
Cancer.gov, 2021. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/car-t-cell-therapy. Copyright 2017 Terese Winslow LLC; U.S. government has certain rights.

Immune effector cell-associated neurotoxicity syndrome (ICANS) is a neurotoxicity that can develop after a patient receives CAR T-cell therapy. Patients may develop neurologic symptoms as soon as 1 day after CAR T-cell infusion or onset may be delayed and occur 3 or 4 weeks after infusion. Initial neurologic symptoms include tremor, dysgraphia, mild expressive aphasia, apraxia, and impaired attention. As time passes, the symptoms can evolve in severity and a global aphasia can result, with patients presenting both expressive and receptive difficulty. As the patient's dysgraphia evolves, their ability to write intelligibly deteriorates, and patients may be found to be awake but mute and akinetic. Interestingly, this presentation may help the healthcare provider distinguish ICANS from other causes of encephalopathy (Kennedy & Salama, 2020). Neurotoxicity may progress to the point at which the patient develops subclinical or clinical seizures or even cerebral edema to the extent that the brain may herniate causing death—a rare but possible occurrence of which the nurse must be aware. Various risk factors

have been identified for the development of ICANS after CAR T-cell infusion, including the presence of B-ALL, high tumor burden, and a high CAR T-cell dose as well as younger age at time of infusion (Kennedy & Salama, 2020). There is also a correlation between cytokine release syndrome (CRS) and the development of ICANS. It has been found that patients with ICANS had CRS prior to the development of ICANS. Neurotoxicity after CAR T-cell infusion may arise from either the diffusion of cytokines into the central nervous system (high levels of IL-15, IL-6, IL-10, and IP-10 have been found in the serum of patients who develop ICANS) or the trafficking of CAR T cells into the central nervous system after CAR T-cell infusion. Tools for grading ICANS in pediatric patients and algorithms for treatment vary by institution; however, unlike with CRS, it has been found that neurotoxicity often does not respond to tocilizumab (Winter et al., 2020).

Immune checkpoint inhibitors. Immune checkpoint inhibitors (ICPIs) modulate immune responses by attaching to immune receptors or ligands. ICPIs were developed to overcome the immune escape mechanisms of cancer progression and metastatic cancer dissemination (Tian et al., 2020). Immune checkpoint inhibitors are monoclonal antibodies that target cytotoxic T lymphocyte–associated antigen 4 (CTLA4), programmed death-1 receptor (PD-1), and programmed death ligand 1 (PD-L1), all of which have been implicated in the evasion of tumor cells from the surveillance of the body's own immune system. Escaping immune system surveillance thereby allows the proliferation and dissemination of the cancerous cells (see **Figure 5**).
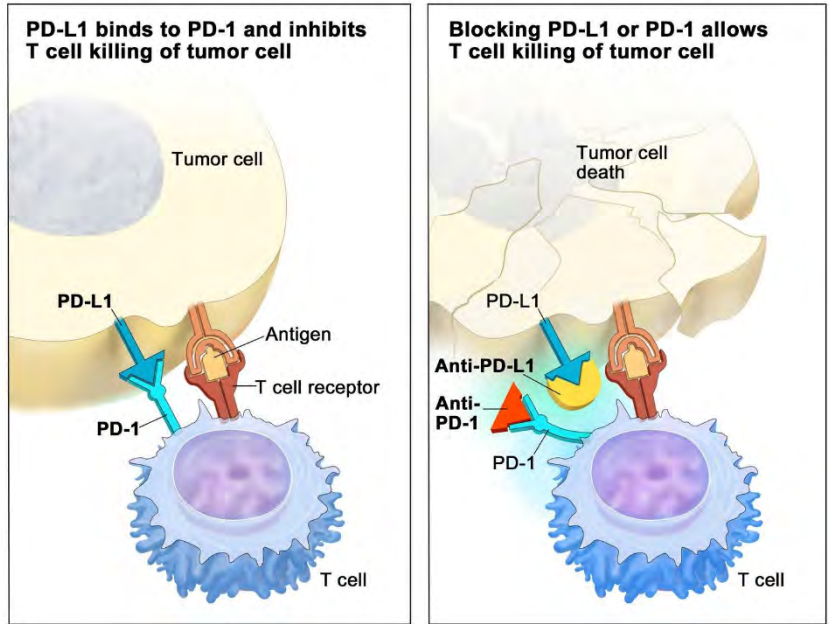
Figure 5: Immune Checkpoint Inhibitors

Checkpoint proteins, such as PD-L1 on tumor cells and PD-1 on T cells, help keep immune responses in check. The binding of PD-L1 to PD-1 keeps T cells from killing tumor cells in the body (left panel). Blocking the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor (anti–PD-L1 or anti–PD-1) allows the T cells to kill tumor cells (right panel). National Cancer Institute, 2019. https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/checkpoint-inhibitors. Copyright 2015 Terese Winslow LLC; U.S. government has certain rights.

Although ICPIs have not yet been widely utilized in the realm of pediatric cancer treatment, their successful use for adult cancers has increased interest in developing clinical trials to identify indications for their use in pediatric cancers. Commonly used ICPI drugs are featured in **Table 1**.

Table 1. Immune Checkpoint Inhibitors and Indications for Use		
Name of Immune Checkpoint Inhibitor Generic (Trade)	**Receptor/Ligand**	**Indication for Use**
Atezolizumab (Tecentriq)	Anti–PD-L1	Second-line metastatic non-small cell lung cancer, advanced or metastatic urothelial carcinoma
Avelumab (Bavencio)	Anti–PD-L1	Advanced or metastatic urothelial carcinoma, metastatic Merkel cell carcinoma
Durvalumab (Imfinzi)	Anti–PD-L1	Advanced or metastatic urothelial carcinoma
Ipilimumab (Yervoy)	Anti-CTLA4	Metastatic melanoma, stage III melanoma
Nivolumab (Opdivo)	Anti–PD-1	Metastatic melanoma, second-line metastatic non-small cell lung cancer, second-line metastatic renal cell carcinoma, refractory classical Hodgkin lymphoma, recurrent/metastatic squamous cell carcinoma of the head and neck Advanced/metastatic urothelial carcinoma
Pembrolizumab (Keytruda)	Anti–PD-1	Metastatic melanoma, second-line metastatic non-small cell lung cancer, first- and second-line metastatic renal cell carcinoma, refractory classical Hodgkin lymphoma, recurrent or metastatic squamous cell carcinoma of the head and neck Advanced or metastatic urothelial carcinoma Microsatellite instability–high or mismatch repair deficient metastatic solid tumors
Data from "Neurological Toxicities Associated with Immune-Checkpoint Inhibitors," by M. Touat, D. Talmasov, D. Ricard, and D. Psimaras, 2017, *Current Opinion in Neurology*, 30(6), 659–668. https://doi.org/10.1097/WCO.0000000000000503.		

Neurotoxicities related to these agents include immune-related adverse events (IRAEs) of both the central and peripheral nervous systems. Although they occur only rarely, it is important for the nurse to be able to recognize the IRAEs that ICPIs can cause in order to avoid complications or further deterioration of the patient's status (**Table 2**).

Table 2. Immune-Related Adverse Events Associated with Immune Checkpoint Inhibitors	
Immune-Related Adverse Event	**Name of Immune Checkpoint Inhibitor**
Acute immune demyelinating polyneuropathy	Nivolumab Pembrolizumab Ipilimumab
Aseptic meningitis	Ipilimumab

Cranial nerve neuropathies	Pembrolizumab Ipilimumab
Chronic immune demyelinating polyneuropathy	Nivolumab Pembrolizumab Nivolumab + ipilimumab
Encephalitis	Nivolumab Pembrolizumab Nivolumab + ipilimumab
Myasthenic syndromes	Ipilimumab Nivolumab Pembrolizumab Nivolumab + ipilimumab
Myositis	Ipilimumab Nivolumab Pembrolizumab Nivolumab + ipilimumab

Data from "Neurological Toxicities Associated with Immune-Checkpoint Inhibitors," by M. Touat, D, Talmasov, D. Ricard, and D. Psimaras, 2017, *Current Opinion in Neurology*, *30*(6), table 3. https://doi.org/10.1097/WCO.0000000000000503.

Encephalitis is typically characterized by seizure, confusion ataxia, abnormal behavior, and alterations in levels of consciousness.

Aseptic meningitis often presents with fever and headache and can occur anywhere from 1 to 7 weeks after initiation of the ICPI.

Myasthenia gravis and necrotizing myositis often present within 2 to 6 weeks of initiating treatment with ICPIs. Myasthenia gravis presents with acute motor symptoms, fatigue, diplopia, respiratory insufficiency, and distal weakness (Becuart et al., 2019). If not recognized and treated appropriately, this disease can become quite serious and lead to death. Necrotizing myositis closely resembles myasthenia gravis because the clinical presentation is quite similar. Patients with necrotizing myositis may experience bilateral proximal limb muscle weakness, myalgia, fever, dyspnea, ptosis, ophthalmoparesis, and bulbar weakness (Touat et al., 2017).

Cranial nerve palsies may involve the optic nerve, abducens, and facial nerves.

Immune demyelinating polyradiculoneuropathy is a rare but severe complication that may resemble Guillain-Barré syndrome; therefore, recognition of symptoms is important in making a proper diagnosis. Symptoms include paresthesias in the arms and legs, generalized weakening of the extremities bilaterally, loss of reflexes, loss of balance and altered gait, and loss of sensitivity to pinprick during neurologic exam.

Targeted Therapy

Brentuximab vedotin (Adcetris). Brentuximab vedotin is a conjugated monoclonal antibody that has been approved by the FDA for the treatment of relapsed Hodgkin lymphoma and systemic anaplastic large cell lymphoma. It is also used for the treatment of mycosis fungoides and peripheral T-cell lymphoma that expresses CD30. Brentuximab vedotin links a CD30 antibody to four molecules of the microtubule inhibitor monomethyl auristatin E (MMAE). The drug binds to the cells that express CD30 and forms a complex, which is taken into the CD30-positive cell where it releases its toxic payload of MMAE. MMAE binds to the tubules and disrupts the cellular microtubule network, inducing cell-cycle arrest and apoptosis. Peripheral neuropathy consisting of both motor and sensory neuropathy has been observed with brentuximab vedotin. Signs and symptoms of the peripheral neuropathy that is associated with this conjugated monoclonal antibody include hypesthesia, hyperesthesia, paresthesia, discomfort, burning sensation, and neuropathic pain. Brentuximab vedotin therapy has a black-box warning associated with progressive multifocal leukoencephalopathy. Nursing considerations include monitoring for new-onset signs and symptoms of central nervous system toxicity. These signs and symptoms would include changes in memory, behavior and cognition, motor coordination, and speech, as well as visual disturbances and muscle weakness. Any nurse caring for a patient exhibiting these symptoms should report the symptoms and be prepared to take prompt action following their evaluation by the medical team. Evaluation should include a consultation with the neurology team, along with a brain MRI and lumbar puncture, and possibly a brain biopsy (Corbin et al., 2017; Pastorelli et al., 2013).

Dinutuximab (Unituxin). Dinutuximab is a chimeric human-mouse monoclonal antibody used for treatment of high-risk neuroblastoma. It targets GD2, a tumor-associated antigen expressed on the surface of neuroblastoma cells as well as on many "normal" cells, including skin melanocytes, neurons, optic nerves, and peripheral pain fibers (McGinty & Kolesar, 2017). Dinutuximab induces cell death via antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity, because it binds to GD2 on the surface of neuroblastoma cells as well as the nonmalignant cells mentioned above. It is this action that causes the various neurotoxicities associated with this drug. A neurological ocular toxicity may occur as dinutuximab binds to the GD2 found on the surface of optic nerve cells, resulting in blurred vision, photophobia, mydriasis, fixed or unequal pupils, optic nerve disorder, eyelid ptosis, and papilledema. Nursing interventions for this toxicity include frequent and thorough assessments, including evaluation of the patient's pupillary response. Dose reduction, therapy interruption, or treatment discontinuation may be necessary to address this ocular neurotoxicity. Dinutuximab also presents more serious neurotoxicities, including severe neuropathic pain and peripheral neuropathy. Dinutuximab carries a black-box warning for neuropathic pain, which is quite serious. It occurs in more than 50% of patients receiving dinutuximab, and peripheral neuropathy occurs in 2%–9% of patients receiving the drug (McGinty & Kolesar, 2017). This pain may be described as generalized, abdominal, back, or musculoskeletal pain. Some patients report arthralgia, neuralgia, and pain in their extremities. Patients receiving dinutuximab are

treated prophylactically with opioid therapy prior to each dose of the drug, as continuous infusion throughout the dinutuximab infusion, and for 2 hours after the infusion is complete. If the patient's pain is severe, the rate of infusion of dinutuximab therapy may be reduced or the therapy may be discontinued altogether (Hoy, 2016; McGinty & Kolesar, 2017).

Blinatumomab (Blincyto). Blinatumomab is a bispecific CD-19-directed CD3 T-cell engager (BiTE). Blinatumomab binds to CD19 expressed on the surface of B cells and the CD3 epsilon subunit found on mature T cells. When blinatumomab binds to a CD3-positive T cell and a CD19-positive B cell, it brings both cells together in a cytolytic synapse, and cell death is induced on the malignant B cell by the cytotoxic T cell (Newman & Benani, 2016). Blinatumomab is used to treat CD19-positive B-cell precursor ALL in both pediatric and adult patients. Pediatric dosing and administration involve a 28-day continuous infusion with close monitoring both by the nursing staff while the patient is hospitalized for the first days of the infusion and by the caregivers for the remainder of the infusion. Patient and caregiver education are of supreme importance because blinatumomab carries two black-box warnings with it: cytokine release syndrome and neurotoxicity. The nurse should employ the "teach-back method" of patient and caregiver education to confirm that the caregivers understand the instructions provided and that the patient's safety will be ensured while the therapy is administered away from the hospital. Neurotoxicity associated with blinatumomab may be severe and can even result in the patient's death. Neurological symptoms include headache and tremor, encephalopathy, seizure, speech disorders, confusion, disorientation, disturbances in level of consciousness and coordination, and balance disorders (Stein et al., 2019). Routine prophylaxis for seizures is not typically recommended; however, labeling from the manufacturer recommends discontinuation of the drug should the patient experience more than one seizure while receiving blinatumomab. Although events meeting the Grade 3 and Grade 4 *Common Terminology Criteria for Adverse Events* are not typically seen, adverse events occurred in at least 50% of patients treated with blinatumomab while on clinical trial, making recognition of neurotoxicity crucial if neurotoxicity is to be quickly treated or resolved for the best possible patient outcomes (Newman & Benani, 2016).

Conclusion

Neurotoxicities from chemotherapy and biotherapy pose challenges for both the patient and the medical team. These toxicities can be severe and therapy-limiting for the patient. Short- and long-term sequelae from CNS and peripheral nervous system toxicities can affect the patient's quality of life for many years. CNS toxicities can prove challenging because the patient may develop encephalopathy, altered mental status, fatigue, headache, and seizures that can lead to a lifetime neurocognitive impairment, brain atrophy, progressive leukoencephalopathy, cerebrovascular disease, and more. It is incumbent on nurses to learn to recognize the neurotoxicities associated with both the chemotherapy and biotherapy their patients are receiving. This knowledge can lead to more thorough assessments and documentation, as well as

greater awareness of the measures necessary to alleviate and remedy the toxicities that do occur.

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Small Molecule Inhibitors

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Learner Outcomes

Upon completion of this Pediatric Chemotherapy and Biotherapy Provider Program learning activity

1. the learner will be able to identify four small molecule inhibitors that can be given as extemporaneous liquid preparations
2. the learner will be able to demonstrate proper safe handling practices for administering small molecule inhibitors
3. the learner will be able to name four medications or foods that could increase serum concentrations of small molecule inhibitors, resulting in the possibility of increased side effects

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Small molecule inhibitors are a class of targeted therapies that are becoming more common in pediatric oncology. Nurses can readily identify drugs in this category by their generic name, which ends in "-nib," "-imus," or "-stat." Most small molecule inhibitors are administered orally (notable exceptions are bortezomib and temsirolimus, which are given intravenously). Oral small molecule inhibitors have a short half-life, so they must be administered daily. Small molecule inhibitors are classified by the intracellular pathway that they target (this will be discussed below).

Pathophysiology

General Pathophysiology
Every cell in the human body has a set of internal regulatory pathways designed to control four cellular functions that are essential to the life of the cell: cell growth, cell proliferation, cell survival, and cell death. These basic functions are regulated by external signals sent from outside the cell. The external signal is a protein—a cytokine or a hormone, for example—and it carries a message that needs to be delivered to the nucleus within the cell. On the surface of the cell are receptors that are designed to receive specific signals. Once received, the signal is modified (transduced), and it unlocks a designated pathway in the interior of the cell that will transport the message to its destination. The signaling pathway includes a series of waypoints, like locked doors, that the message will need to pass through on the way to its destination in the nucleus of the cell. At each waypoint, the signal may be amplified or modified in a way that enhances its

message as it travels along the pathway. When the destination is reached, the message will be translated, and the cell will respond by performing the specific function that the signal initiated.

In malignancy, a disruption occurs along one or more of the signaling pathways, resulting in loss of control. One or more of the "doors" along a pathway malfunctions, resulting in uncontrolled proliferation and loss of programmed cell death–hallmarks of malignant cells.

Small molecule inhibitors can target specific malfunctioning doors along the signaling pathway. They block the aberrant signal that is keeping the door from opening and closing correctly, thereby restoring the normal signals that keep the door functioning properly. During the last few years, scientific research has identified many of the doors on signaling pathways and the specific cancers associated with the malfunctioning pathway. After these locations have been identified, further research can focus on finding small molecule inhibitors that will be effective against those targets. As Kuhlen and colleagues (2019, p. 2) expressed it, "These developments may ultimately break with the practice paradigms of 'one-size-fits-all' therapy and guide the development of precision/personalized treatment including immunotherapy and targeted (genomic) therapy to offer the 'right drug for the right patient at the right time,' even in children."

The following is a brief review of a few intracellular pathways that are important to cancer cells, along with examples of the small molecule inhibitors that can have an impact on those pathways.

Intracellular Signaling Kinase Pathways

Many of the signaling pathways are named for the protein kinases along that pathway. These protein kinases are the waypoints, or doors, that the signal will pass through as it travels along the pathway. "Protein kinases play a major role in cellular regulation including differentiation, survival, proliferation, metabolism, migrating, and signaling, as well as cell-cell interactions" (Kuhlen et al., 2019, p. 2). Cancer cells often take control of these signaling pathways in order to survive. For example, in the MAP kinase pathway, certain signals attach to the epidermal growth factor receptor (EGFR), and these communications are then transferred from protein to protein inside the cell. After those signals are passed on, they eventually reach the nucleus of the cell, activating genes that control cell division (Anderson et al., 2019). **Figure 1** illustrates this mechanism. Dabrafenib is an example of a small molecule inhibitor that targets BRAF kinase mutations along this pathway and the proteins inside the cell that transfer the cell division signals (Novartis, 2020).
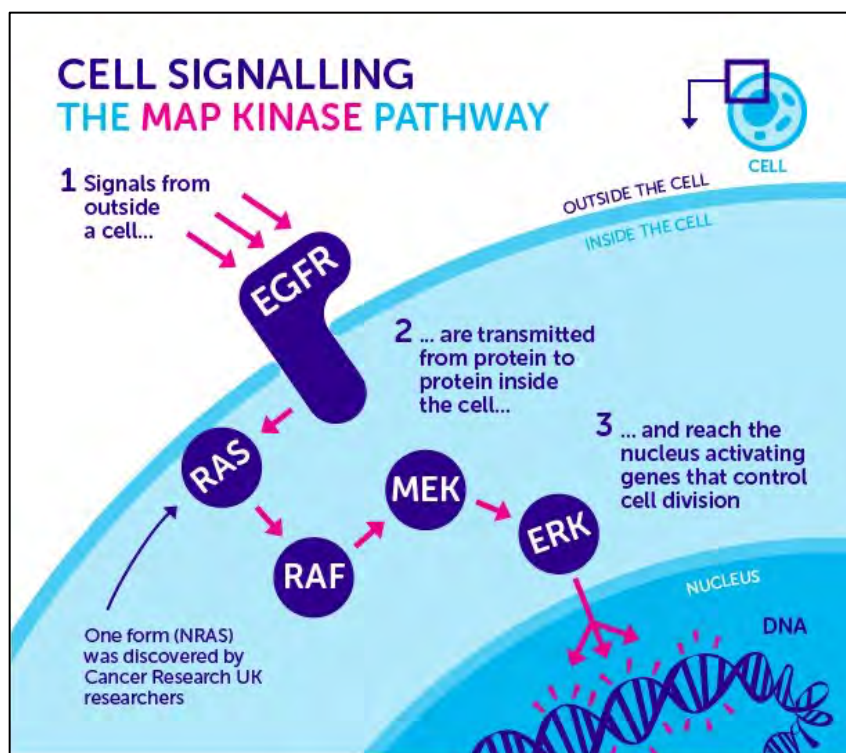
Figure 1: Example of Signal Transduction Pathway
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Another example of an intracellular signaling pathway is the PI3K/ATK/mTOR pathway. Many types of cancer take over this pathway to promote their abnormal cell growth. Temsirolimus is a small molecule inhibitor that affects the mTOR receptor in this pathway, causing "decreased expression of mRNAs necessary for cell cycle progression and arresting cells in the G_1 phase of the cell cycle" (National Center for Biotechnology Information, 2021, "Summary").

Tyrosine kinase inhibitors target signaling proteins that control cell growth and differentiation. Examples of tyrosine kinase inhibitors are imatinib, dasatinib, and nilotinib. This family of agents is most often used in the treatment of BCR-ABL1-positive leukemias.

The JAK/STAT pathway regulates cell growth, survival, and differentiation. Ruxolitinib is a small molecule inhibitor that targets this pathway and is currently being evaluated for use against pediatric leukemias that have a JAK mutation.

Ubiquitin-Proteasome System
The proteasome is a large multiprotein complex in the ubiquitin-proteasome system that is responsible for cell protein degradation, therefore playing a role in cell survival and signaling. Because cancer cells have a high protein turnover rate, they are particularly sensitive to proteasome inhibition. Bortezomib was the first proteasome inhibitor used in clinical trials; it has since been found to be more effective when used with additional chemotherapeutic agents (Kuhlen et al., 2019).

Epigenetic-Targeting Inhibitors

The category of epigenetic-targeting small molecule inhibitors involves a diverse set of pathways that control gene expression. One of the components of gene expression involves histone deacetylases (HDACs), the enzymes that are key in keeping DNA tightly coiled, which "results in a closed chromatin structure and consequently in suppressed transcription of many genes including tumor suppressor genes" (Kuhlen et al., 2019, p. 5). HDAC inhibitors block the HDAC enzymes, which results in decreased proliferation of malignant cells; this causes cell cycle arrest, leads to tumor cell apoptosis, and slows down cancer progression. With the pathway to malignant transformation blocked, the targeted gene can then turn on and make its specific protein, allowing cell differentiation to occur, and the cell can mature to its specific role, such as becoming a skin cell or liver cell. It is important to remember that tumor cells avoid the process of differentiation. Differentiation allows cells to progress through their natural processes, rather than the malignant ones. Although no HDAC inhibitors have been approved by the U.S. Food and Drug Administration for pediatric use at this time, the HDAC inhibitors panobinostat and vorinostat are currently being investigated in pediatric clinical trials.

Summary

Returning to the analogy that only certain keys fit in certain doors, and only certain doors open into certain rooms, we see that each small molecule inhibitor is the key to stopping a malignant cellular process. Each inhibitor affects only certain pathways and processes. Understanding the mechanism inside the cell will be essential to understanding the processes and uses for each of these new small molecule inhibitors.

Administration

Intravenous

Currently two small molecule inhibitors are given intravenously: bortezomib (a proteasome inhibitor) and temsirolimus (an mTOR inhibitor). Bortezomib should be administered as a rapid intravenous push over 3 to 5 seconds (Lexicomp). Temsirolimus is administered as a 30-minute infusion. Premedication with diphenhydramine is recommended before temsirolimus infusions because of the risk of hypersensitivity reactions. Temsirolimus should be administered through non-diethylhexylphthalate (DEHP) tubing using an inline filter (Lexicomp).

Subcutaneous

Bortezomib can be given subcutaneously. Studies have shown that when it is given by the subcutaneous route, the incidence of peripheral neuropathies is decreased. A survey by Martin and colleagues (2015) of the administration practices of nurses who often administered subcutaneous bortezomib offered these suggestions to minimize skin reactions at the site of injection:

- Change the needle after drawing the medication into the syringe and administer the medication through a fresh needle in order to decrease the chance of tissue irritation along the injection track.

- Use an abdominal site of administration.

- Use the air-bubble technique (adding a small air bubble to the syringe, 0.1 mL), to decrease the possibility of tracking medication along the injection track.

When calculating doses and administering bortezomib, the nurse should also be aware that the concentrations for the subcutaneous dose and the IV preparation are different.

Oral

Most small molecule inhibitors are available as capsules or tablets. The advantage of these oral preparations is that patients are able to receive their cancer treatments at home. Oral administration does, however, present some challenges for pediatric patients. Prescribing information for most oral small molecule inhibitors advises that they be taken whole, with specific instructions to not chew, break, or crush the capsule or tablet. Manipulation of these capsules or tablets may significantly affect absorption and potency. For example, disruption of the nilotinib capsule may result in increased absorption, causing the potential for increased toxicity. Studies have shown that when dasatinib is crushed and dispersed in liquid, its bioavailability is decreased by 36% (Lexicomp). Some small molecule inhibitors (e.g., imatinib, everolimus) are available as coated tablets because they are mucosal irritants. Absorption and potency of these small molecule inhibitors may also be affected by acidic environments (e.g., the stomach). Nurses can use the "Do Not Crush" list published by the Institute for Safe Medication Practices (www.ismp.org/recommendations/do-not-crush) as a quick reference tool to verify which small molecule inhibitors, and other medications, should not be crushed or otherwise manipulated (see also **Table 1**).

When it is not possible for the patient to swallow pills or capsules, nurses should check with their pharmacy colleagues regarding the possibility of alternative dosing formulations. A few small molecule inhibitors come in alternate forms for patients who cannot swallow tablets or capsules. For example, everolimus is commercially available as a dispersible tablet, and larotrectinib is commercially available as an oral solution. Some small molecule inhibitors are approved for extemporaneous solutions (see Table 1). These extemporaneous solutions should be prepared one dose at a time and administered as soon as possible after preparation to ensure maximum effectiveness. They also may develop a bitter taste if left standing for longer than recommended time. A study by Li and associates (2016) demonstrated that extemporaneous suspensions of erlotinib, lapatinib, and imatinib were stable for several days.

Table 1. Administration Guidelines for Oral Small Molecule Inhibitors		
Do not crush, break, or chew	**Alternative dose form available**	**Extemporaneous liquid preparations permissible (see Lexicomp or prescribing information for drug-specific instructions)**
Dabrafenib	Everolimus (dispersible tab commercially available)	Crizotinib
Erlotinib		Dasatinib
Olaparib	Larotrectinib (oral solution commercially available)	Imatinib
Palbociclib		Isotretinoin
Pazopanib	Trametinib powder for oral solution(investigational)	Lenvatinib
Ponatinib	Sirolimus (oral solution commercially available)	Nilotinib
Sorafenib		Ruxolitinib
Sunitinib	Veliparib oral solution (investigational)	Vandetanib
Vemurafenib		
Information from Lexicomp and drug monographs		

For patients enrolled on clinical trials, there may be protocol-specific instructions regarding whether the small molecule inhibitor can be made into an extemporaneous solution. When extemporaneous oral solutions are permissible, the prepared liquid medication should be given as soon as possible after preparation to avoid oxidation that could compromise the potency of the medication.

Additional considerations for oral administration pertain to foods or medications taken concurrently with the drugs. Some tablets (e.g., afatinib, sunitinib, venetoclax) should be taken on an empty stomach. High-fat meals can affect absorption for some (for example, nilotinib has increased bioavailability if it is taken after a high-fat meal). Some small molecule inhibitors should not be administered together with medications that affect gastric pH, such as proton pump inhibitors or H2 blockers. Increased gastric pH may reduce the bioavailability of dasatinib. Antacids may be used in place of H2 blockers, but dasatinib should be given 2 hours before or after the antacid (Lexicomp).

Many small molecule inhibitors are metabolized by the CYP3A4 group of liver enzymes, which can be adversely influenced by certain medications and foods (see **Table 2**). Nurses should be aware that taking small molecule inhibitors with macrolide antibiotics, "-azole" antifungals, aprepitant, or grapefruit juice can result in increased drug levels of the small molecule inhibitor, which can result in increased toxicities. When small molecule inhibitors are taken with dexamethasone, barbiturates, carbamazepine, phenytoin, or topiramate, decreased efficacy of the drug may result. Careful review of all concurrent medications and foods is strongly

recommended during therapy with small molecule inhibitors, in order to minimize the risks of interactions that could affect the drug's effectiveness. A searchable list of potential CYP-related drug interactions can be found at drug-interactions.medicine.iu.edu/MainTable.aspx.

Table 2. Drugs That Can Alter Blood Levels of Small Molecule Inhibitors	
Drugs that may *decrease* blood levels of small molecule inhibitors (resulting in decreased efficacy of the small molecule inhibitor)	Drugs that may increase blood levels of small molecule inhibitors (resulting in increased toxicity of the small molecule inhibitor)
Barbiturates Echinacea Dexamethasone Green tea H2 antagonists Phenobarbital Proton pump inhibitors Rifampin St. John's wort Topiramate	Aprepitant Grapefruit juice Ketoconazole Posaconazole Voriconazole

Lexicomp provides information for extemporaneous preparations of some small molecule inhibitors listed in Table 2. These are additional recommendations for extemporaneous preparations:

- Extemporaneous preparations should be made one dose at a time by adding an intact (not crushed or broken) capsule or tablet to the recommended liquid and allowing it to dissolve over a recommended time period.

- Extemporaneous solutions should be administered as soon as possible after preparation. They develop a bitter taste the longer they stand.

- To ensure that the entire dose is given, add 30 mL of diluent (water or juice) to the container used to dissolve the tablet, rinse the container, and then give the rinse to the patient.

Safe Handling

Small molecule inhibitors are considered hazardous drugs according to a draft of updated guidelines from the National Institute for Occupational Safety and Health (NIOSH, [2020]). Although they may not be carcinogenic and may not be directly cytotoxic, many small molecule inhibitors meet the NIOSH criteria for hazardous drugs because the manufacturer's prescribing information has included special handling instructions to protect workers who are handling the drug. Some small molecule inhibitors are considered hazardous because they have the potential to cause adverse developmental or reproductive effects. A list of hazardous drugs can be found in the *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings 2016* (NIOSH, 2016).

APHON recommends using "safe handling procedures for any biotherapy agent labeled hazardous by the manufacturer or the Occupational Safety and Health Administration (e.g., interferon, bortezomib, brentuximab, inotuzumab, all tyrosine kinase inhibitors)" (Conley et al., 2019, p. 155).

Another set of standards has been set forth in the United States Pharmacopeia (USP) *General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings*, created by the United States Pharmacopeial Convention in December 2019. This document sets out standards and guidelines for safe practices and processes in handling hazardous drugs, in order to minimize damage to public health across the United States, especially through occupational exposure. USP <800> has provided recommendations for personal protective equipment (PPE) that should be worn by healthcare workers who handle hazardous drugs. **Table 3** briefly summarizes PPE requirements relevant to small molecule inhibitors.

Table 3. Appropriate Personal Protective Equipment According to Administration Route					
Form or Route of Administration	Double Gloves	Protective Gown	Eye Protection	Respiratory Protection	Engineering Control
Intact tablet or capsule	No, single pair of gloves	No	No	No	N/A
Tablet or capsule (manipulated)	Yes	Yes	Yes	Yes, if not done in control device	N/A
Oral liquid	Yes	Yes	Yes, if spitting up is potential	No	N/A

Subcutaneous	Yes	Yes	Yes, if liquid could splash	Yes, if inhalation is potential	Yes, sharps protection
Intravenous solution	Yes	Yes	Yes, if liquid could splash	Yes, if inhalation is potential	CSTD *recommended* (*required* by USP <800>)

Note. CSTD = closed-system transfer device; N/A = not applicable; USP <800> = U.S. Pharmacopeia General Chapter <800>.
Adapted from *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings 2016* (U.S. DHHS NIOSH Publication Number 2016-161), National Institute for Occupational Safety and Health, 2016, Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; *General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings,* U.S. Pharmacopeial Convention, 2016, uspnf.com/notices/general-chapter-hazardous-drugs-handling-healthcare-settings

Side Effects

Hypersensitivity reactions. These are not commonly seen with oral small molecule inhibitors but may occur with intravenous infusions of bortezomib or temsirolimus.

Emesis. Bosutinib (>400 mg/day), crizotinib, dabrafenib, and imatinib (>400 mg/day) are associated with moderate to high emetic risk. Most of the other small molecule inhibitors have minimal to low emetic risk (National Comprehensive Cancer Network [NCCN], 2021). Management of nausea and vomiting caused by small molecule inhibitors follows the same principles as those used for chemotherapy. A number of established antiemetic guidelines are available, and most now include biotherapy agents in the discussion. Nurses who administer these agents should be prepared to give scheduled antiemetics for agents listed as having low or moderate potential for emesis (see **Table 4**). Patients who receive oral agents listed as having minimal or low risk for emesis should be given antiemetics on an as-needed basis (NCCN, 2021).

Table 4. Emetogenic Potential of Small Molecule Inhibitors (including percentage of patients who will experience emesis in the absence of antiemetic therapy)	
Minimal to low (<30% frequency of emesis)	**Moderate to high** (≥30% frequency of emesis)
Axitinib	Bosutinib (>400 mg/day)
Bortezomib	Crizotinib
Bosutinib (<400 mg/day)	Dabrafenib
Dasatinib	Imatinib (>400 mg/day)
Erlotinib	
Everolimus	
Gefitinib	

Ibrutinib	
Imatinib ($\leq$400 mg/day)	
Larotrectinib	
Nilotinib	
Pazopanib	
Ruxolitinib	
Sorafenib	
Temsirolimus	
Vemurafenib	
Venetoclax	
Vismodegib	

Diarrhea. Many small molecule inhibitors are associated with diarrhea. Patients taking erlotinib, gefitinib, or other EGFR inhibitors can experience significant diarrhea in up to 25% of cases. The diarrhea associated with vascular endothelial growth factor (VEGF) inhibitors (sorafenib, sunitinib, pazopanib) is usually mild to moderate. But even mild diarrhea can have negative effects on a patient's well-being when it is caused by a medication that is taken daily for extended periods of time. The etiology of diarrhea caused by small molecule inhibitors may be related to EGF and VEGF receptors in the intestinal epithelium that are inadvertently targeted by the drug, resulting in inhibition of normal gut function. Inflammation, altered chloride secretion, and changes in the intestinal microflora may also play a role. Management generally involves supportive care to avoid dehydration and electrolyte imbalances. After evaluation to exclude other causes of the diarrhea, the use of medications such as loperamide or octreotide to treat prolonged mild or moderate diarrhea may be considered. Further research is needed to better define the pathophysiology of diarrhea caused by small molecule inhibitors, in order to identify specific medications that may prevent symptoms (Secombe et al., 2020).

Drug-induced liver injury (chemical hepatitis). Small molecule inhibitors that cause transient elevations in transaminases without hepatotoxicity include erlotinib, gefitinib, imatinib, pazopanib, and nilotinib (and probably others). Hepatic dysfunction caused by imatinib can lead to chronic hepatitis. Severe hepatotoxicity (grade 4 transaminitis) has been reported with crizotinib (Ricart, 2017). Management of hepatocellular injury involves monitoring transaminase and bilirubin levels and withholding the drug if significant elevations occur. Other steps would be to evaluate concurrent medications with hepatic side effects and to evaluation for viral illnesses.

Effects on skin and mucous membrane. Skin rashes are very common in patients who are taking small molecule inhibitors that target EGFR.

Cardiac effects. Tyrosine kinase inhibitors are associated with T prolongation.

Table 5 provides an overview of side effects commonly seen in patients who are receiving small molecule inhibitors, grouped according to their target.

Type	Agent (FDA-approved for pediatric use in bold print, with date of approval)	Pediatric Indications (FDA-approved pediatric indications in bold print)	Target	Common Side Effects by Target
Receptor tyrosine kinase (RTK) inhibitors *These agents target receptors on the surface of a cell.*	Crizotinib	Neuroblastoma Anaplastic large cell lymphoma	ALK, cMET	Nausea and vomiting Diarrhea Elevated liver enzymes
	Ensartinib		ALK, ROS1	Elevated liver enzymes Rashes
	Erlotinib (2015) Gefitinib	Recurrent or refractory ependymoma	EGFR	Skin rashes Mucositis
	Larotrectinib (2018) **Entrectinib** (2019)	Refractory solid tumors with NTRK mutations	NTRK	Cytopenia Elevated liver enzymes
Multikinase inhibitors *These agents can target cell surface receptors as well as signaling proteins inside a cell.*	Pazopanib	Sarcomas Relapsed and refractory solid or CNS tumors	VEGFR, PDGFR	Hypertension Fatigue Diarrhea Rashes Hypothyroidism
	Ponatinib	Ewing sarcoma	VEGFR, FLT3	
	Sorafenib	Acute myeloid leukemia	VEGFR, PDGFR, RAF, RET	
	Sunitinib (2019)	Refractory solid tumors	VEGF, PDGF, FLT3, cKIT	

Table 5: Small Molecule Inhibitors Currently Being Used or Investigated in Pediatric Oncology (the list is not all inclusive)

Nonreceptor tyrosine kinase inhibitors *These agents target signaling proteins on the inside surface of a cell membrane.*	**Imatinib** (2006, 2013)	Chronic myeloid leukemia (CML) Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL)	BCR-ABL, cKIT, stem cell factor	Cytopenia T prolongation Cardiomyopathies
	Dasatinib (2018, 2019)	CML Ph+ ALL	BCR-ABL, cKIT, PDGFR	
	Nilotinib (2018)	CML	BCR-ABL	
	Ibrutinib	Relapsed and refractory acute leukemia	BTK	
	Ruxolitinib (2017)	Relapsed or refractory leukemia T-cell leukemia	JAK	Cytopenia Fatigue Diarrhea
Cytoplasmic Inhibitors (also known as serine/threonine kinase inhibitors) *These agents target signaling proteins along pathways inside of a cell.*	Sorafenib Dabrafenib Vemurafenib	Relapsed or refractory solid tumors or leukemias	BRAF	Skin rashes Arthralgias Fatigue Elevated liver enzymes
		Langerhans cell histiocytosis Melanoma High-grade gliomas		
	Trametinib	High-grade gliomas	MEK	Skin rashes Diarrhea Fatigue
	Sirolimus	Relapsed or refractory solid tumors Complex vascular anomalies	mTOR, Pi3	Diarrhea Mucositis Elevated liver enzymes

	Everolimus (2012)	Subependymal giant cell astrocytoma in pediatric patients with tuberous sclerosis complex		
		Relapsed or refractory solid/ or CNS tumors		
	Temsirolimus	Relapsed or refractory solid tumors		
		High-risk hepatoblastoma		
		Lymphangiomatosis		
	Bortezomib	T-cell leukemia	NF-kB	Fever
		T-cell lymphoma		Nausea
				Diarrhea
				Neuropathies
	Alisertib	Neuroblastoma	AURKA	Cytopenia
BCL-2 inhibitors *These agents target proteins that regulate apoptosis*	Venetoclax	Relapsed or refractory acute leukemia	BCL-2	Cytopenia
				Electrolyte disturbances
				Diarrhea
				Nausea
	Navitoclax	Relapsed or refractory acute lymphoblastic leukemia or lymphoma		
Epigenic modulators Histone deacetylase (HDAC) inhibitors *These agents target enzymes within cells (HDACs) that are responsible for regulating gene expression*	Panobinostat	Multiple myeloma		
		Diffuse intrinsic pontine glioma		
	Vorinostat	Cutaneous T-cell lymphoma		Thrombocytopenia
		Relapsed or refractory solid tumors and CNS malignancies		Neutropenia
		Relapsed or refractory acute leukemia		
		High-grade gliomas		
		Neuroblastoma		
CNS = central nervous system; FDA = U.S. Food and Drug Administration.				

Late Effects

Acquired resistance is an important long-term concern related to the use of small molecule inhibitors. Acquired resistance can be categorized according to the presence or absence of symptoms derived from progressive disease, the kinetics of tumor growth, and the number of progressive metastases (Westover et al., 2018). In some cases, the tumor develops mutations that counteract the effect of the small molecule inhibitor. In other cases, the tumor cells develop alternate signaling pathways that bypass the target of the small molecule inhibitor. Because of potential resistance mechanisms, pharmacokinetics, selectivity, and tumor environment, single- and multi-kinase inhibitors have advantages and disadvantages (Kuhlen et al., 2019).

Small molecule inhibitors are only beginning to be prescribed, so not enough time has elapsed to allow researchers to obtain adequate long-term data on possible late effects. However, imatinib, the small molecule inhibitor that has been used the longest, has provided a glimpse into late effects of agents in this biotherapy category. The most prevalent late effect of imatinib is growth delay in children with chronic myeloid leukemia (Narayanan et al., 2013).

A few common late effects are starting to emerge. Kuhlen and colleagues (2019, p. 2). have observed that "attention should be paid to the various acute and long-term side effects of TKIs including gastrointestinal, cardiovascular, pulmonary, dermatologic, and—particularly in children—endocrine toxicities." Very little is known yet about most small molecule inhibitors, and only time will unveil their major long-term and acute side effects.

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